

Evaluating Cardiometabolic Risk Screening and Monitoring among Patients Prescribed Antipsychotic Drugs (ECRSMA study)

By

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A thesis submitted to the University of Birmingham for the degree of
DOCTOR OF PHILOSOPHY

School of Pharmacy
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01/07/2022

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"In the name of Allah, the Compassionate, the Merciful"

105. Say, "Act. Allah will see your actions, as will His Messenger and the believers. Then you will be returned to the Knower of secrets and declarations, and He will inform you of what you used to do."

-Quran; Surah al-Tawbah, Chapter 9-

"To be the voice of those who cannot speak for themselves"

-Ruba Azfr Ali-

Abstract

Background: Antipsychotics have been associated with cardiometabolic side effects despite their wide use and effectiveness. Routine cardiometabolic monitoring of patients prescribed antipsychotics is recommended by clinical guidelines, including the National Institute for Health and Care Excellence (NICE). However, the evidence indicated suboptimal monitoring practices. This PhD work aims to evaluate the level of cardiometabolic monitoring in patients prescribed antipsychotics in primary care according to the guidelines and factors associated with adherence to monitoring guidelines.

Methods: The programme of work presented in the thesis was conducted in two stages. A systematic literature review was conducted to i) understand the epidemiology of the cardiometabolic side effects of antipsychotics; the available interventions to mitigate these side effects, and ii) identify the barriers to effective monitoring of these side effects. A population-based, retrospective, observational and open-cohort study was then conducted to evaluate the extent of cardiometabolic monitoring in patients prescribed antipsychotics. The Health Improvement Network (THIN) database incorporating electronic medical records from general practices throughout the UK, representing ≈ 6% of UK general practice registrants, was used to identify a cohort of patients on chronic antipsychotic therapy for mental illnesses. The NICE guideline for Psychosis and Schizophrenia in adults [CG178] was used as the reference standard to assess monitoring practices. Also, the association between antipsychotic drugs prescribed at the study index and monitoring practices was investigated through regression modelling by measuring the odds of monitoring events at different time points.

Results: The review showed various but high prevalence of cardiometabolic side effects among antipsychotic users. Information on the cardiometabolic profile for individual

antipsychotics was scarce. Several interventions are available to counter these side effects. Some pharmacological and non-pharmacological interventions demonstrated promising effects to counteract some cardiometabolic side effects of antipsychotics mainly weight gain. The qualitative component of the review identified several intrinsic (e.g., mental health stigma) and extrinsic factors (e.g., fragmented healthcare) that can hinder the management and monitoring of cardiometabolic side effects of antipsychotics. The THIN study showed suboptimal cardiometabolic monitoring levels in primary care. A total of 11,435 records for adult patients with mental illness and prescribed antipsychotics were included. Of these patients, 9707 (85%) were prescribed second-generation antipsychotics. The majority (n=11,145, 97%) failed to receive complete monitoring for any of the study outcomes. 52% of the patients (n= 6,599) had evidence of any cardiometabolic monitoring for any of the study outcomes (e.g., BMI records) and the majority had at least one abnormal lab value at baseline (n=4,627, 97%). Additionally, waist circumference and blood glucose levels were the least recorded in the screened records (≈5% and <30%). Among different antipsychotics, the recorded monitoring frequency did not surpass 52% for any outcomes at any time point. The regression analysis showed that prescribing antipsychotics with high cardiometabolic risks (e.g., olanzapine) did not promote cardiometabolic monitoring (OR: 04–1.2, P>0.05).

Conclusions: In UK primary care, cardiometabolic monitoring practices in antipsychotic users remains suboptimal. Baseline and follow-up cardiometabolic monitoring was infrequent, irregular, and did not change in response to the use of high cardiometabolic risks antipsychotics. The barriers to optimum monitoring could be multifactorial. Pharmacists' participation in the monitoring process is essential to enforcing cardiometabolic monitoring guidelines for antipsychotic drugs.

Keywords: Antipsychotic, cardiometabolic, monitoring, primary care, observational study.

Thesis synopsis

This work aimed to evaluate the prevalence of cardiometabolic side effects of antipsychotic drugs- and the extent of monitoring of side effects and associated factors according to clinical guidelines in patients prescribed these drugs in primary care. The study comprised a systematic review and a retrospective cohort study using the Health Improvement Network (THIN) dataset.

The systematic review showed a consistently high prevalence of cardiometabolic side effects with clozapine and olanzapine, while relevant data for individual antipsychotics were limited. Selective pharmacological and non-pharmacological interventions can alleviate cardiometabolic side effects, but further studies are warranted. Also, barriers to cardiometabolic monitoring and management can be multifactorial including patient-level factors and system-level factors.

The cohort study demonstrated suboptimal monitoring of the cardiometabolic health of patients prescribed antipsychotics as nearly 2.0% received complete monitoring for certain outcomes. Although the majority of patinets were monitored for body mass index and blood pressure the minority had records for waist circumference and blood glucose were less recorded (≈5% and <30%). Prescribing antipsychotics with high cardiometabolic risks did not improve monitoring practices. This research highlights the need to promote guideline adherence to prevent adverse outcomes in antipsychotic-treated patients as cardiometabolic monitoring practices among this population remain suboptimal.

External output

Full reports

I. Azfr Ali. R, Jalal Z, Paudyal V. Guidelines versus practice in screening and monitoring of cardiometabolic risks in patients taking antipsychotic medications: where do we stand? General Psychiatry. 2021;34(4). DOI: 10.1136/gpsych-2021-100561

***Manuscript location in the thesis: Chapter 1; page 22

II. Azfr Ali. R, Jalal, Z. & Paudyal, V. Barriers to monitoring and management of cardiovascular and metabolic health of patients prescribed antipsychotic drugs: a systematic review. BMC Psychiatry.2020;20(1):1-5. DOI: 10.1136/gpsych-2021-100561

***Manuscript location in the thesis: Chapter 4 (Qualitative review); page 120

Permissions to incorporate the manuscripts into this thesis were granted from the publishers (BMC Psychiatry & General Psychiatry). In compliance with the university guidelines for thesis presentation, the numbering of headings, Tables, Figures and spacing were only adjusted for consistency with the current report.

Conference abstracts

I. Azfr Ali. R, Paudyal. V, Jalal. J. 'Guideline adherence among health professionals for cardiovascular and metabolic monitoring of patients prescribed antipsychotic medications: Evaluation of data from primary care'. The abstract is published in the December issue of the International Journal of Clinical Pharmacy. 49th ESCP virtual symposium on clinical pharmacy 19.10.2021–21.10.2021 Clinical pharmacy, working collaboratively in mental healthcare. Int J Clin Pharm 43**,** 1736–1801 (2021). DOI: 10.1007/s11096-021-01352-w

Oral presentations

I. Azfr Ali. R, Paudyal. V, Jalal. J. 'Guideline adherence among health professionals for cardiovascular and metabolic monitoring of patients prescribed antipsychotic medications: Evaluation of data from primary care': presented as an oral talk at the European Society of Clinical Pharmacy (ESCP) Symposium, 48th Symposium on Clinical Pharmacy: Mental Health; Online conference, United Kingdom, 19-21 October 2021**.**

II. Azfr Ali. R, Paudyal. V, Jalal. J. 2019, 'Prevalence and effective interventions to manage cardiovascular and metabolic side effects in patients using anti-depressants or antipsychotic medications: a systematic review': presented as an oral talk at the HSRPP Conference, Birmingham, United Kingdom, 8-9 April 2019.

Poster presentation

I. Azfr Ali. R, Paudyal. V, Jalal. J. 2019, 'Cardiovascular and metabolic Side Effects in Patients Using Anti-depressants or Antipsychotic Medications: A Systematic Review of Mixed-method. Presented as a poster at the 11th Medication safety conference, UAE, Abu Dhabi, 2-3 November 2018.

***Other manuscripts are being prepared for publication at the time of submitting this thesis.

Dedications

“In the name of ***Allah***, the Compassionate, the Merciful’’

127. “As Abraham raises the foundations of the House, together with Ishmael, “Our Lord, accept from us; You are the Hearer, the Knower’’. -Quran; Surah al-Baqarah, Chapter 2-

To whom words cannot express your greatness. To whom is the ultimate purpose of my life and existence. To whom the source of my strength whenever I am crumbled by life. To my mighty Lord, my Creator, my dear God (***Allah***).

Then…

To my parents, who ask so little, but give so much.

In the memories of my beloved mom, Fatima Palembang, who could not complete this journey with me. May we reunite in Heaven. All I can say at a moment like this is ‘’Life comes to end, but love never end’’.

To my dad, Saleh Azfr Ali, my guardian angel, my inspiration and my hero,

To my beloved siblings; my solid ground,

To my friends who encourage and support me,

To all the people in my life who touch my heart,

To my homeland Kingdom of Saudi Arabia, the warmest womb,

I dedicate this work to all who will read this thesis and hopefully make the best use of it.

Acknowledgements

I am grateful to Almighty God (Allah) for blessing me with the courage and strength to complete this research.

A PhD dissertation is, by definition, an individual's achievement. However, this work would never have reached the completion stage if it had not been for a number of highly supportive individuals, groups, organisations, and institutions.

First and foremost, I want to thank my family for their support during these last 4 years. I sincerely acknowledge the hard work and endurance they have invested in the course of my PhD journey, physically and mentally. Their presence has been an invaluable enrichment to my life and during my PhD programme. In addition, I would love to say a big thank you to my peer PhD researchers, whom I would call sisters.

Academically speaking, my most profound appreciation goes to my team (my supervisors) at the University of Birmingham, and I consider myself blessed to have known and worked with them. My primary supervisor, Dr Vibhu Paudyal, Associate Professor of Clinical Pharmacy, helped me uncover my potential. He guided me with patience, support and encouragement every time I needed it and even when I was not aware I needed it. My appreciation also goes to my co-supervisor, Dr Zahraa Jalal. Her support, guidance and encouragement have been a guiding star and a professional aspiration for me throughout my PhD project. I sincerely thank them both for being by my side during one of the darkest times in my life.

I would like to extend my profound gratitude to Mr Jaspal Johal, Pharmaceutical Consultant at Dudely CCG, for his dedication and commitment that enabled us to complete the observational work associated with local datasets. This work and my appreciation extend to Dr Malcolm Price, Lecturer in Biostatistics, who was my guidance during the data analysis.

Finally, I thank the Institute of Applied Health Research at the University of Birmingham, particularly Dr Joht Chandan and Dr Anuradhaa Subramanian, for their invaluable help in the data acquisition for the THIN study.

Furthermore, my appreciation is also directed towards the Royal Embassy of Saudi Arabia Cultural Bureau. I am indeed grateful for their support throughout my PhD journey in the UK. I also appreciate the support from Umm Al-Qura University for supporting my scholarship.

Thesis structure

This thesis was formatted using the 'Alternative Format' recommended by the University of Birmingham. This format allows a postgraduate researcher to incorporate published sections or in a format suitable for submission for publication in a peer-reviewed journal. The applied referencing style is Vancouver.

Originally, this PhD work involved several phases: a systematic review of the literature followed by two quantitative phases and a qualitative phase. Due to the COVID-19 pandemic, the proposed qualitative work with patients and healthcare professionals could not be conducted. Accordingly, the focus of this report was shifted entirely to systematic reviews **(Chapters 3&4)** and observational study **(Chapter 5)**. Methods describing the original phases of the work are available in the main study protocol (Appendix II-A). The following Table lists phases that were originally planned to be conducted during the PhD work.

Table. Overview of the original studies sequence in this research

Study stages	Systematic literature review (two systematic reviews; quantitative and qualitative review): ***Completed***	Quantitative stage (an observational study): ***Completed***	Qualitative: ***Not conducted due to the COVID-19 pandemic***
Aim/ objectives	a) To explore the prevalence of cardiometabolic side effects in antipsychotic users and interventions to manage these side effects. b) To identify the barriers to managing cardiometabolic side effects of antipsychotics.	To investigate the level of cardiometabolic monitoring in primary care for patients prescribed antipsychotic drugs	To investigate factors affecting the uptake of guidelines for monitoring and managing cardiometabolic side effects of antipsychotics.
Design	A mixed-method systematic review of quantitative and qualitative evidence	An observational cohort study through retrospective analysis of primary care patients' data from a national database	Semi-structured interviews with patients and primary care healthcare providers

Summary of chapters

Chapter 1 provides background information about the cardiometabolic side effects of antipsychotics. It also provides an overview of the available international clinical guidelines about monitoring practices. It outlines the research questions and the aims and objectives of this research project.

Chapter 2 presents the study design, rational for methods used in this research project, research reflexivity, validity and credibility of data, and, finally, it discusses the procedure used for data protection and ethical approval.

Chapter 3 presents the results of the quantitative review (First review). It provides a global evidence review of the main reported cardiometabolic side effects of antipsychotics.

Chapter 4 presents the results of the qualitative review (Second review). This chapter highlights factors influencing cardiometabolic monitoring and management among antipsychotic users.

Chapter 5 presents the methods used in the THIN study, detailing the process of cohort selection, data extraction and analysis. Also, it presents the findings and assesses their relevance to the current practice.

Chapter 6 addresses how studies conducted in this research have answered the research questions. It also discusses the limitations and strengths of the whole programme of work. Additionally, it provides recommendations and suggestions for future work.

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Key abbreviations

ADA: American Diabetes Association

APA: American Psychiatric Association

APs: Antipsychotic drugs

BMI: Body mass index

BP: Blood pressure

BD: Bipolar disorder

C: Credible

CATIE: The Clinical Antipsychotic Trials of Intervention Effectiveness

CATS: Documentation system, which was developed by the clinical analysis of the treatment of schizophrenia (CATS) study to assess the treatment practices of patients with schizophrenia using antipsychotic drugs

CCGs: Clinical Commissioning Groups

CERQual: The Confidence in the Evidence from Reviews of Qualitative research approach

CRD: Centre for Review and Dissemination

CrI: Credible Interval

CUtLASS: The Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study

CVDs: Cardiovascular diseases

ECG: Electrocardiogram

EPS: Extrapyramidal symptoms

FBG: Fasting blood glucose

FDA: Food and Drug Administration

FGAs: First-generation antipsychotics

HbA1c: Glycosylated haemoglobin

HDL: High-density lipoprotein

JBI-QARI: Joanna Briggs Institute Assessment and Review Instrument

MI: Mental illness

MS: Metabolic syndrome

NCEP ATP III: The US National Cholesterol Education Programme Adult Treatment Panel III

NICE: National Institute for Health and Care Excellence

Non-HDL: Non High-density lipoprotein

PRISMA: Preferred reporting items for systematic review and meta-analysis

PRISMA-P: Preferred reporting items for systematic review and meta-analysis- Protocol version

SCZ: Schizophrenia

SCZA: schizoactive disorder

SGAs: Second-generation antipsychotics

TGs: Triglycerides

THIN: The Health Improvement Network

U: Unequivocal

US: Unsupported

WC: Waist circumference

WHO: World Health Organisation

Chapter 1 Introduction

Summary of the chapter

This chapter introduces the PhD work. It presented background information regarding the morbidity and mortality burden associated with mental illness focusing on schizophrenia as a primary condition for antipsychotic drug prescribing. It also highlighted the clinical aspects of schizophrenia: disease pathology, clinical presentations and diagnosis. Also, concepts of antipsychotic effectiveness, safety, and prescribing were highlighted. It describes the nature of cardiometabolic side effects in general terms and the context of the use of antipsychotic therapy. It also summarises the recommendations from published guidelines around monitoring practices for patients prescribed antipsychotic drugs. Finally, the overall aims and objectives of the thesis are presented.

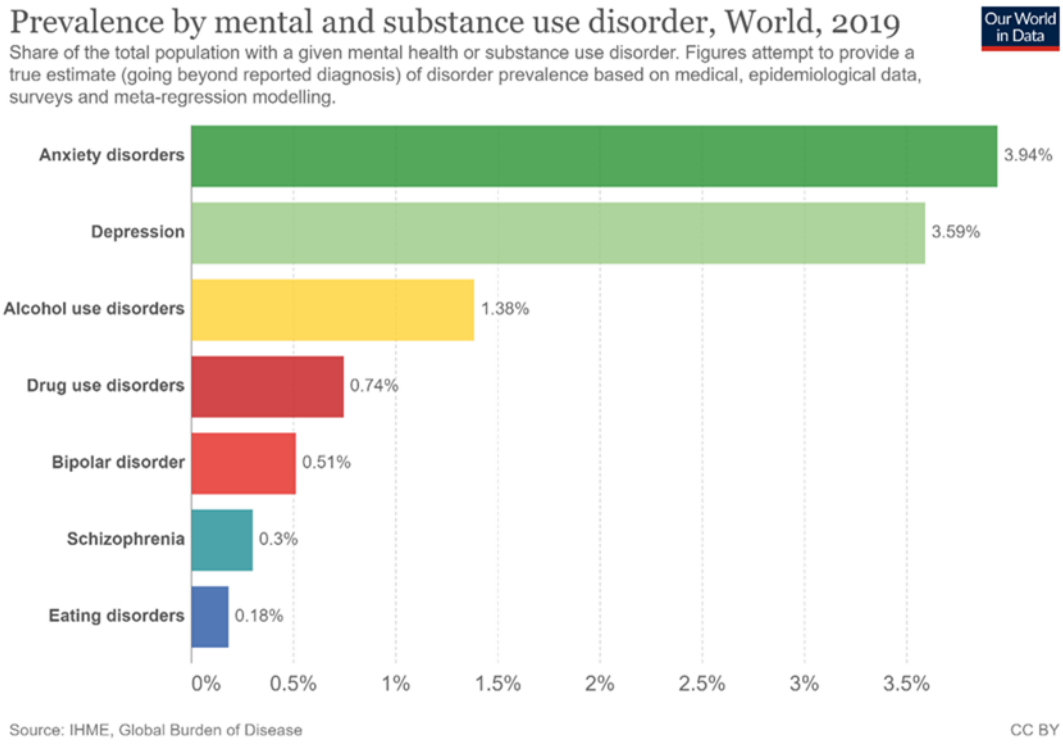
Part A: Background

1.A.1. Mortality and morbidity burden of mental illness

According to the World Health Organization (WHO), mental illnesses (MIs) are sets of diseases mainly characterized by abnormalities in thought, behaviour and emotion that may hinder people's effective interaction with others.(1) They are clinically diagnosable disorders that demonstrate recurrent patterns during the affected person's life and may continue for life. MIs include various disorders, with the most common being schizophrenia and its related spectrum disorders, bipolar and major depressive disorder.(2) Projection reports from the WHO estimated a global increase in the prevalence of people affected by Mis, where it was estimated that approximately 792 million people worldwide would develop mental illnesses by 2017.(3) It has been reported that the life expectancy of people with mental illness is reduced by 10–17.5 years compared to the general population, most likely due to the high mortality rate in this group.(2) Mental illnesses are reported to be

independently associated with a substantial excess in all-cause mortality risk (28% of the world's population) (Figure 1-1, A). The prevalence of various MIs and the global burden of mortality due to non-communicable disorders are illustrated in Figure 1-1.

(A)



(B)

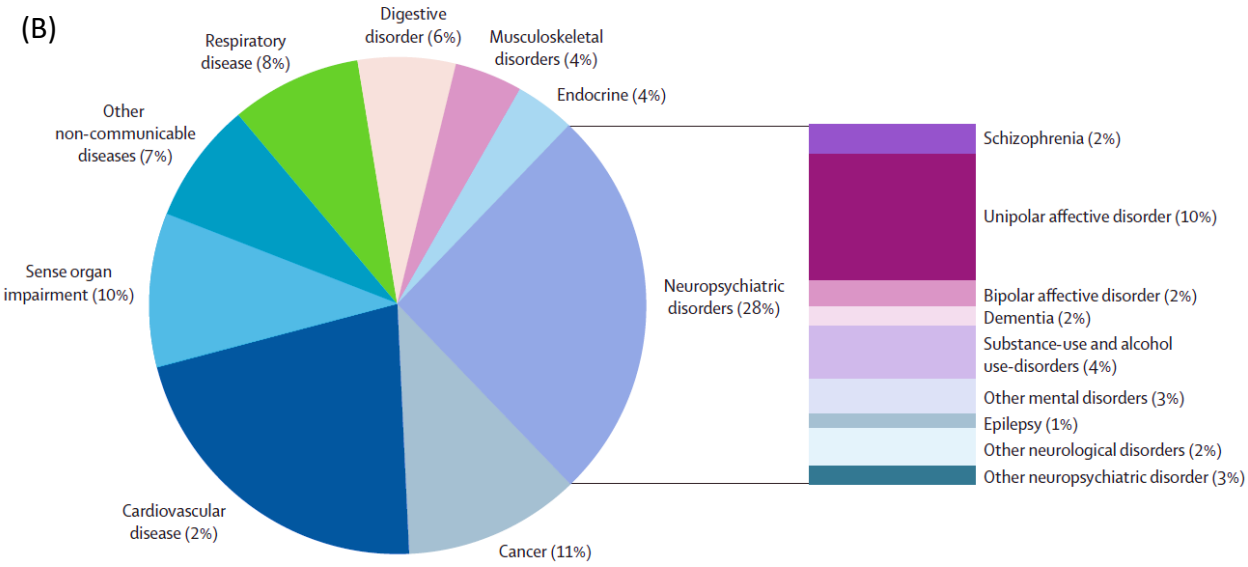


Figure 1-1. Prevalence of different mental illnesses (A) and the global mortality due to non-communicable conditions, including mental illness (B). Adapted from (3,4) with permission.

Although the predictive incidence of schizophrenia is relatively low (median value: 15.2 per 100,000 persons annually), the condition is considered a significant contributor to global mortality.(3) Various causes of mortality, excluding suicides, have been reported for schizophrenia (relative risk [RR] = 2.59, 95% CI 2.55–2.63), bipolar disorder (standardised mortality ratio [SMR] = 1.9 for men and 2.1 for women), and dementia (RR = 2.63, 95% CI 2.17–3.21).(4) Considering the increased mortality rate in patients with MIs, such as schizophrenia, physical conditions account for approximately 70% of the death cases.(5)

Cardiovascular diseases (CVDs) are a significant cause of death in patients with schizophrenia.(6,7) The aetiology of CVDs in this group is multidimensional, including several aspects, such as lifestyle factors, genetic factors, and cardiovascular risk factors. The high mortality is linked with the increased prevalence of modifiable cardiovascular risk factors in schizophrenia.(7) Traditional CVD risk factors include age, gender, CVD family history, smoking, hypertension, hyperglycaemia and dyslipidaemias. Additionally, new cardiovascular risk factors have been recognised, including, but not limited, to abdominal obesity (e.g., waist circumference), insulin resistance, inflammation cascades (e.g., high-sensitivity C-reactive protein, hsCRP), sedentary lifestyle, and psychosocial stress.(8) The term 'cardiometabolic' is a joint set of traditional and some new cardiovascular and metabolic risk factors that will be used throughout this thesis. Recent studies have indicated that modifiable cardiometabolic risk factors, such as central obesity, hypertension, dyslipidaemias, hyperglycaemia and insulin resistance (8), are highly prevalent in patients with MIs such as schizophrenia.(7,9) Although the exact cause of cardiometabolic complications in patients with schizophrenia is not well established (7), there is a growing body of evidence linking the increased incidence of CVDs and the associated cardiometabolic risks of antipsychotics.

1.A.2. Schizophrenia and psychosis (aetiology and pathophysiology)

Schizophrenia and related psychotic illnesses are traditionally referred to as “functional psychoses”. This term refers to an abnormality in brain function without corresponding structural problems.(10,11) Schizophrenia does not involve a “split personality,” as depicted in the media. Rather, it is a chronic illness that disrupts the patient’s thoughts and mood. The illness commonly interferes with a patient’s ability to effectively engage in social events and relationships.(12) Schizophrenia is considered the fourth leading cause of disability among adults, interfering with employment, marriage, and independent living.(12,13)

The aetiology of schizophrenia remains unknown.(13) Over the decades, many theories have been introduced that highlight neurotransmission abnormality in people with schizophrenia. Most theories centre on either an excess or a deficiency of neurotransmitters, including dopamine, serotonin and glutamate. The dopamine theory, which is the oldest pathophysiologic theory, proposes that psychosis is caused by excessive dopamine in the brain.(14) In a normal functioning brain, dopamine has four pathways (Figure 1-2).

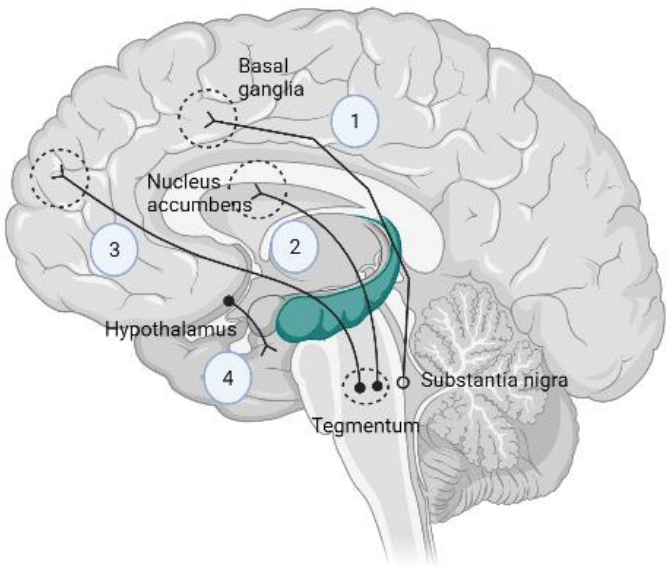


Figure 1-2. The four dopamine pathways in the brain. (15) i) The nigrostriatal pathway, ii) The mesolimbic pathway, iii) The mesocortical pathway, iv) The tuberoinfundibular pathway. Created with BioRender.com.(16)

It is postulated that the nigrostriatal pathway is responsible for movement regulation. The mesolimbic pathway in the midbrain connects to the nucleus accumbens, a part of the brain's limbic system that is thought to be responsible for the euphoria that is associated with drugs (drug abuse), delusions and hallucinations of psychosis. Another pathway is the mesocortical pathway, which is located in the midbrain ventral tegmental area. Projections of this pathway to the dorsolateral are thought to regulate cognition, executive functioning, emotions and distress. Another important dopamine pathway is the tuberoinfundibular pathway, which regulates prolactin secretion. It is believed that the mesolimbic and mesocortical pathways are involved in the pathophysiology of schizophrenia and psychosis. Hyperdopaminergic activity in the mesolimbic pathway contributes to the positive symptoms of psychosis. Nonetheless, dopamine theory alone failed to explain the cognitive deficits experienced by many patients. For example, some studies reported dopaminergic hypoactivity of the mesocortical pathway in the prefrontal cortex, in which the studied subjects demonstrated negative and cognitive symptoms.(13) This might explain the remarkable efficacy of the new antipsychotics against the negative symptoms, which were linked to their broad receptor affinities.

Another theory was introduced and involved glutamate activity, the major excitatory neurotransmitter in the brain. This theory was raised in response to the finding that phenylciclidine and ketamine, two non-competitive N-methyl-D-aspartate (NMDA) and glutamate antagonists, induce schizophrenia-like symptoms. Consequently, it is suggested that NMDA receptors are inactive in the normal regulation of mesocortical dopamine neurons, highlighting possible explanations for the negative, affective, and cognitive symptoms that are observed in some patients with schizophrenia.(13,15) Other theories

involve the role of aspartate, glycine and gamma-aminobutyric acid (GABA) neurotransmitters in the neurochemical imbalance of schizophrenia.(13) Experimental data revealed a low level of GABA in first-episode schizophrenia patients, suggesting reduced overall GABAergic neurotransmission in the brain of patients with psychosis.(17) Further evidence supports the implication of other neurotransmitter systems, including the serotonergic system (5-HT2A). Meanwhile, the exact mechanisms by which this system is involved in psychotic symptoms are unclear. However, the available evidence has shown that the enhanced effects of serotonin in the brain resulted in schizophrenia-like symptoms.(14)

1.A.3. Clinical presentations and diagnosis

The symptoms of schizophrenia encompass two dimensions: positive and negative symptoms.(18) The term positive symptoms refer to abnormal features that do not normally exist as part of human physiology or psychology. On the other hand, negative symptoms refer to defects in the normal psychosocial process. Commonly, these symptoms are accompanied by cognitive impairments. The cognitive symptoms are the newest classification in schizophrenia. These symptoms are nonspecific; therefore, they must be severe to be detected and diagnosed. Cognitive symptoms include disorganized speech, and thinking, defective attention, and impaired communication ability.(10,18) Different symptoms of Schizophrenia are illustrated in Figure 1-3.

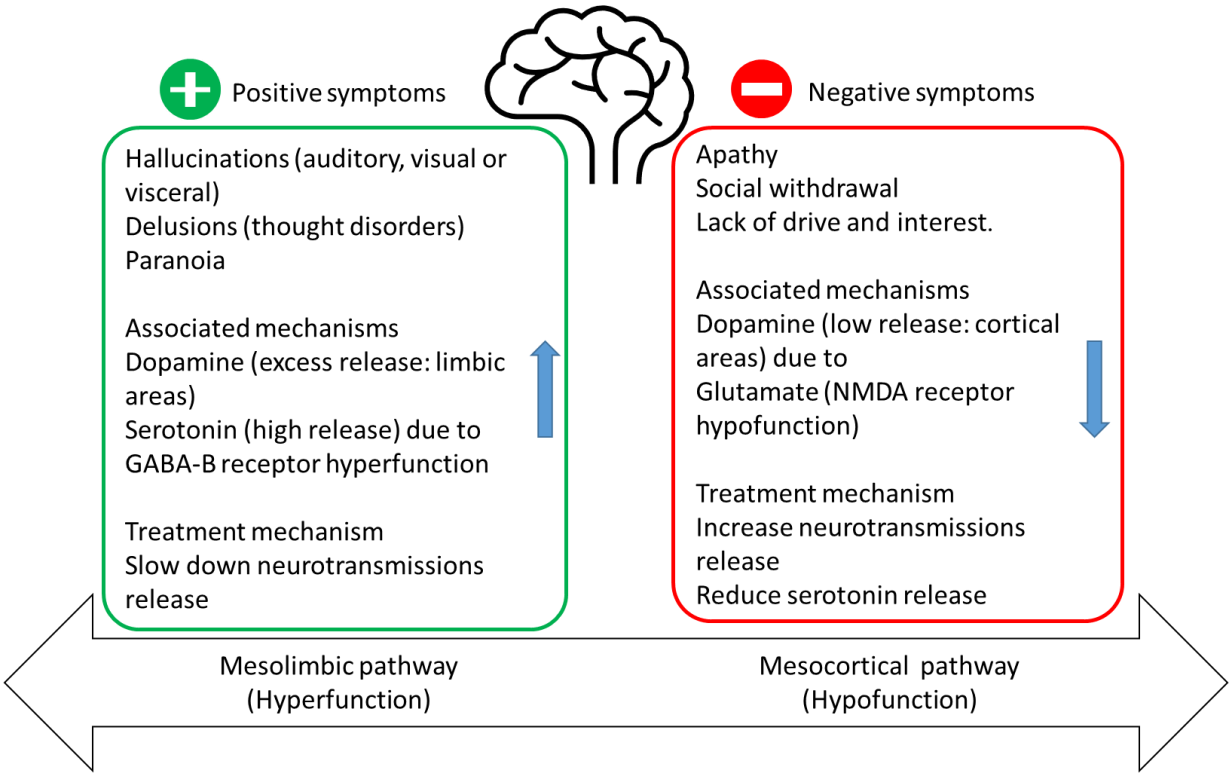


Figure 1-3. Symptoms and aetiology of Schizophrenia. (14,15); *the increased release of serotonin in the mesocortical area was associated with negative symptoms. GABA: gamma-aminobutyric acid; NMDA: N-methyl-D-aspartate.

The positive symptoms, mainly delusions and hallucinations, are often the main drive for patients and families to seek specialised aid.(14) However, the negative symptoms are clinically significant since they have been associated with severe social and vocational disabilities (19), and can impair patients' response to pharmacotherapy.(14,19) There is no definitive diagnostic test available for schizophrenia. Therefore, the diagnosis of schizophrenia is made clinically using operationally defined criteria.(10) The Diagnostic and Statistical Manual of Mental illness, 5th ed. (DSM-V-TR) criteria is a diagnostic tool used to diagnose schizophrenia.(10,20) Diagnostic criteria for schizophrenia are detailed in Figure 1-4.

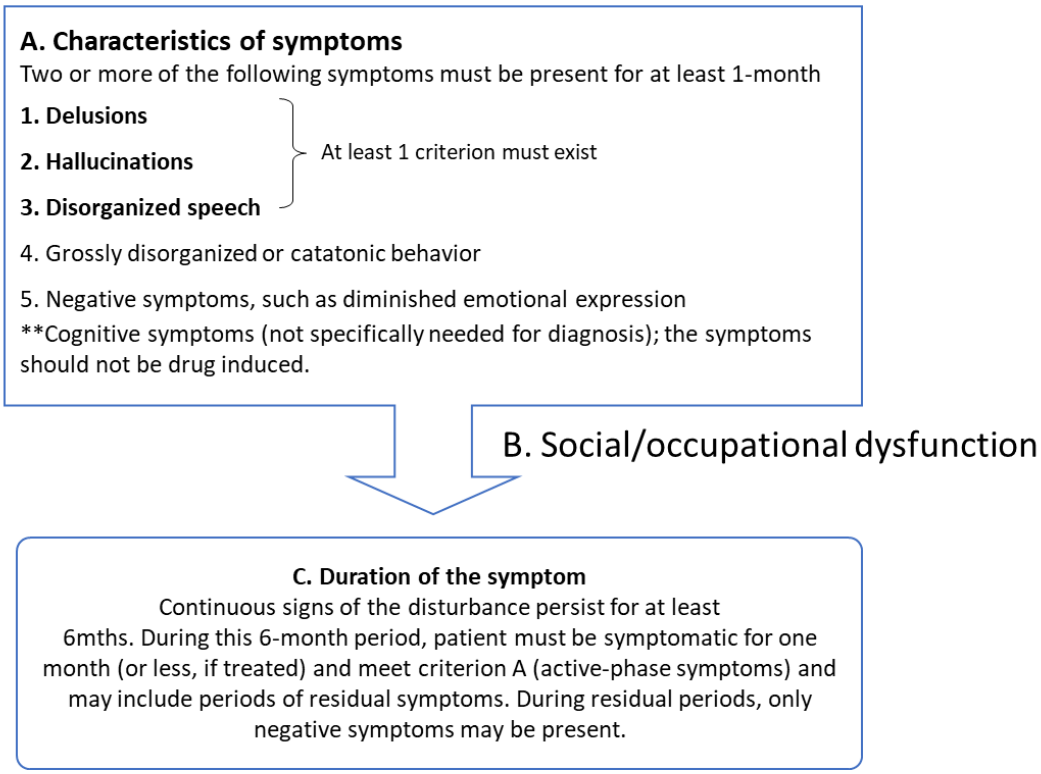


Figure 1-4. DSM-5 Criteria for Schizophrenia diagnosis. (10,19,20)

In order to differentiate schizophrenia from other mental conditions, such as major depressive disorder with psychotic symptoms, a comprehensive differential diagnosis is necessary. Differential diagnosis of schizophrenia can be achieved by investigating the duration, timing, and severity of symptoms such as hallucinations or delusions.(12) The intensity of positive and negative symptoms may vary throughout the illness course. For example, the positive symptoms tend to exacerbate during the acute phases of illness (e.g., relapse), which can be problematic. Nonetheless, during remission periods between acute attacks, the negative symptoms are more common, and patients at this phase are generally less responsive to antipsychotic therapy. Thus treatment with antipsychotic medications should begin as soon as psychotic symptoms are recognized.(13)

1.A.4. Antipsychotic therapy

Antipsychotic drugs are classified into two classes. The first class is known as the typical or first-generation antipsychotic drugs (FGAs), and the second class is the atypical or second-generation antipsychotics (SGAs). Antipsychotic drugs are mainly prescribed as the standard treatment for schizophrenia, psychotic-related disorders and bipolar disorders.(13) Evidence suggests that the clinical response induced by antipsychotic drugs depends mainly on the level of dopamine receptor blockage by the antipsychotic drugs. Clinical response is generally associated with 60% dopamine (D2) receptor blockade, while high blocking levels (70% and 80%) are primarily associated with motor side effects (e.g., extrapyramidal side effects) and hyperprolactinemia.(15)

The first-generation antipsychotic drugs are assumed to possess high-affinity D2-receptor antagonist activity. This group has been shown to relieve positive psychotic symptoms such as hallucinations effectively. However, they have been proven to be less effective against negative symptoms.(21) During the 1990s, SGAs began to replace FGAs as first-line therapy. SGAs may have different receptor-binding profiles contributing to their “atypicality” characteristics. This possibly includes but is not limited to great serotonin to i) dopamine antagonism; ii) dopamine antagonism with rapid dissociation; iii) partial dopamine antagonism; iv) serotonin1A (5-HT1A) partial agonism. The heterogeneous receptor binding may explain the variable activity among the different SGAs against psychosis.(13)

1.A.5. Clinical efficacy and choice of antipsychotic drugs in schizophrenia and psychosis

In MIs like schizophrenia, which comprises different symptoms, selecting the proper antipsychotic could be challenging. Therefore, caution should be considered when interpreting the efficacy between and within the antipsychotic class. Over the years, a

debate has been raised regarding the differences in the overall efficacy of the two classes of antipsychotics (SGAs vs FGAs).

Initially, claims were made that the SGAs are more effective than their counterparts (FGAs) against positive, negative and cognitive symptoms, in addition to their improved tolerability profile. Generally, as a class, SGAs showed superiority over first-generation antipsychotic drugs in relieving negative symptoms. This symptomatic improvement can enhance patients' therapeutic compliance, reducing the risks of frequent relapse.(10) Clozapine is the prototype SGA that is widely acknowledged as the gold standard antipsychotic and preserved for refractory schizophrenia due to its unusual side-effect.(22) Currently, 11 SGAs are licensed for use in the UK, which was modelled on the pharmacological profile of clozapine due to its low propensity to cause extrapyramidal side effects and superior effectiveness in refractory schizophrenia.(23)

The landmark study: The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)(24), examined the effectiveness of the SGAs against a mid-potency FGA, perphenazine. The study findings revealed no differences between the two classes (FGAs vs SGAs) concerning the primary outcomes of the study; rates of treatment discontinuation and improvement in psychotic symptoms or quality of life. Historically, SGAs have been more expensive than the FGAs; however, newer antipsychotic members are now available in generic formulations with more affordable prices, which makes them more accessible to patients. New evidence suggests that SGAs and FGAs (low dose) share similar efficacy profiles and hence do not favour certain antipsychotic drug classes (22) resulting in a modest rise in FGA use.

The available efficacy data do not favour a specific drug class regarding overall symptomatic relief. However, aside from clozapine, the effects vary across different

antipsychotic drugs. A recent network meta-analysis compared the tolerability and efficacy of oral antipsychotics (32 drugs) (25) and found some advantages for risperidone (mean difference from placebo: –0.55, 95% CrI –0.62 to –0.48) over other agents in easing the overall symptoms of psychosis.(25) Regarding individual efficacy among members of the same antipsychotic classes, aside from clozapine, other SGAs members specifically, olanzapine showed superiority over aripiprazole, risperidone, quetiapine, and ziprasidone.(26)

Furthermore, evidence showed various antipsychotic activity profiles against specific psychotic symptoms. For example, clozapine is more effective against negative symptoms than other agents. The reported mean differences from placebo between clozapine and iloperidone were –0.62 (95% CrI –0.84 to –0.39) vs –0.22 (95% CrI –0.33 to –0.11), respectively. Similarly, FGA antipsychotic (amisulpride) was better than risperidone (SGA) in reducing positive symptoms (mean difference from placebo: –0.69, 95% CrI –0.86 to –0.52). However, the study also reported a well-recognised difference in side effects between typical and atypical antipsychotics, indicating that differences in side-effects profiles are more profound.(25) In conclusion, the use of antipsychotic drugs is schizophrenia should be based on their clinical efficacy profile (positive vs negative symptoms), and the associated risk benefits.(27)

1.A.6. Antipsychotics in bipolar disorder

Bipolar disorder (BP), known as manic depression is a recurrent illness which is characterised by cycles of mood swings. The fluctuated mood episodes vary by i) the type of episode (mania, hypomania, or depression); ii) the duration of euthymic intervals; iii) the frequency of relapse; iv) the severity of episodes.(15) Generally, BP treatment aims to relieve symptoms, induce remission, prevent relapse, improve patient functioning, and minimize

drug side effects.(13) All of these activities are observed in some antipsychotic drugs (e.g., quetiapine and olanzapine).(27)

The mainstay of drug therapy has been mood-stabilising drugs. However, research on multiple treatments indicates antipsychotic drugs, both first-generation (FGAs) and second-generation (SGAs), may be more effective for acute mania.(13) Various antipsychotics have various properties consisting of sedative, anxiolytic, mood-stabilising, and antidepressant effects. Antipsychotics can be used alone or combined with conventional mood stabilisers. Antipsychotics have been reported to relieve manic and depressive symptoms during acute episodes. Furthermore, SGAs have been preferred over lithium in cases of acute mixed-episodes.(15)

Many SGAs have also demonstrated decent efficacy as maintenance therapy for BP. To date, agents including aripiprazole, olanzapine, quetiapine (adjunctive), risperidone, and ziprasidone (adjunctive) as the FDA-approved long-acting preparations as maintenance treatment of BD. However, evidence regarding the duration of antipsychotics in maintenance treatment is limited.(27) Additional concerns regarding the long-term cardiometabolic consequences of the SGAs require attention.

1.A.7. Prescribing trends of antipsychotics in the UK

The introduction of SGAs was thought to be a revolution in the treatment of schizophrenia leading to a progressive decline in the use of FGAs. Many countries have reported a noticeable rise in antipsychotic utilisation rates over recent years.(28) In the UK alone, evidence shows that overall antipsychotic prescribing has increased during the last two decades (2007-2016).(29–31) When comparing the prescribing patterns of antipsychotic drug classes in 2007 and 2014, SGAs, namely olanzapine (n=7094, 62%) and quetiapine (n=4824, 36%), were the most commonly prescribed drugs regardless of the indication.(30)

Further reports of antipsychotic prescribing patterns in the UK revealed an increasing trend in quetiapine prescribing in the last ten years. A study investigating prescribing patterns of antipsychotics in response to the changes in the NICE guidelines in 2007 found that the most significant increase in prescribing trend was seen with quetiapine between 2007 and 2014.(29) Comparable results were observed in another study investigating the prescribing practices of antipsychotics in patients with personality disorders where the most commonly prescribed antipsychotic was quetiapine (n=5819/15,562;37% of individuals receiving antipsychotics).(31)

It is unlikely that the increased use of quetiapine is due to the treatment of schizophrenia due to its relatively low clinical efficacy compared to other antipsychotics.(29) Despite the strong evidence supporting the high efficacy of clozapine, this drug only made up 0.1% of the atypical antipsychotics both in 2007 and 2014.(29) Furthermore, new SGAs such as depot paliperidone and lurasidone have been widely introduced over the last few years, providing more options for prescribers than clozapine.(29) Notably, specific antipsychotics like quetiapine possess a broad-spectrum psychoactive property, explaining its increased use.

Antipsychotics are also prescribed, but to a lesser degree, for other non-psychotic conditions, including depression, anxiety, insomnia, autism, and as an antiemetic in early pregnancy.(30) For example, some national guidelines recommend antipsychotics use for specific conditions of psychotic depression and treatment-resistant cases of severe depression and obsessive-compulsive disorder (OCD). UK data (2017) showed that antipsychotics are mainly prescribed for schizophrenia and related conditions.(30) Although the off-label utilisation of antipsychotics remains debatable, current evidence shows an increasing pattern of unlicensed antipsychotic prescribing.(30) Reports from 2017 found that up to 14% of patients were prescribed two antipsychotics simultaneously in the UK alone.

Among these patients, up to 18% of the prescribed antipsychotics were intended for off-label use.(30) Despite the increase in off-label prescribing of antipsychotics, some indications are not recommended by the clinical guidelines, such as antipsychotics in dementia (30) and personality disorders.(31) This increased utilisation of antipsychotics of high cardiometabolic liability (e.g., olanzapine and quetiapine) parallels the rising cardiometabolic mortality observed in the last years.(29)

1.A.8 Antipsychotic safety profile and side effects

Both therapeutic and side effects of antipsychotics can be explained by the neuroanatomy of neuronal dopamine pathways in the brain. In the treatment of schizophrenia, FGAs act on the dopaminergic system by blocking the dopamine type-2 (D2) receptors. However, SGAs demonstrated a different pattern of receptor binding, which involves other types of receptors, e.g., serotonin receptors (5-HT2a & 5-HT2c).(13) Also, the degree of binding affinity for a specific receptor is presumed to determine the nature of the side effects profile for an antipsychotic. For example, antipsychotics with high dopamine affinity tended to have fewer effects on other neurotransmitter systems.(15) Similarly, anticholinergic side effects are less predominant among FGAs of weak-anticholinergic binding, as well as with clozapine.(13)

Due to the broad receptor binding affinity of the new generation (SGAs), side-effect risks may vary between these agents. Antipsychotics can display a wide range of side effects ranging from relatively minor (e.g., mild sedation or dry mouth), to distressing side effects including constipation, acute dystonia and disfiguration including weight gain, tardive dyskinesia and even life-threatening events (e.g., myocarditis, agranulocytosis). Although some adverse effects can have a short-term clinical impact (e.g., serum lipid levels), they can

pose long-term medical complications.(32) Table 1-1 provides estimates for the relative liability of commonly used drugs to cause specific adverse effects.

Table 1-1. Side effect profiles of selected antipsychotic drugs

Adverse effects	AMI	ARI	CPZ	CLO	HAL	LUR	OLA	PAL	PER	QUE	RIS	SER	ZIP
Anticholinergic effects	0	0	++	+++	0	0	++	0	0/+	+/++	0	0	0
Acute parkinsonism	+	+	+	0	+++	+/++	0/+	++	++	0	++	0/+	+
Akathisia	+	++	+	+	+++	+/++	+	+	++	+	+	+	+/++
Tardive dyskinesia	0/+	0/+	++	0	++	0/+	0/+	0/+	++	0/+	0/+	0/+	0/+
Diabetes	0/+	0/+	+++	+++	0/+	0/+	+++	+	+	++	+	+	0/+
Weight gain	0/+	0/+	+++	+++	+	0/+	+++	++	++	++	++	++	0/+
Increased lipids	+	0/+	+++	++	0/+	0/+	+++	+	+	++	+	+	0/+
Sialorrhea	0	0	0	++	0	0	0	0	0	0	0	0	0
Neutropenia	0/+	0/+	0/+	+++	0/+	0/+	0/+	0/+	0/+	0/+	0/+	0/+	0/+
Orthostatic hypotension	0/+	0/+	++	++	0	0/+	+	+	+	++	+	++	0
Hyperprolactinemia	+++	0	+	+	++	+	+	+++	++	0	+++	+	+
Increased QTc interval	++	0/+	0/+	++	0+	0/+	0/+	+	+	+	+	++/+++	++
Sedation	0/+	0/+	++	+++	+	+/++	+/++	0/+	+	++ b	+	0/+	+
Seizures	0/+	0/+	0/+	++	0/+	0/+	0/+	0/+	0/+	0/+	0/+	0/+	0/+

Table keynotes: 0: none or equivocal, 0/+: minimal/rare, +: mild/sometimes occurs, ++: moderate/occurs frequently, +++: severe/occurs very often. Abbreviations: AMI: amisulpride; ARI: aripiprazole; CPZ: chlorpromazine; CLO: clozapine; HAL: haloperidol; LUR: lurasidone; OLA: olanzapine; PAL: paliperidone; PER: perphenazine; QUE: quetiapine; RIS: risperidone; SER : sertindole; ZIP: ziprasidone. Adapted from (32) with permission.

According to Table 1-1. the antipsychotic drugs' profiles do not adhere closely to the antipsychotic drug class.(32) Also, the incidence of the side effects diverges considerably across antipsychotic drugs. Some side effects are common in most antipsychotics, including weight gain, sedation, sexual dysfunction, and Hyperprolactinemia. Some side effects are predominant in specific drug classes. For example, akathisia and Parkinsonism are more common with older drugs (FGAs). Several side effects (e.g., seizures, neutropenia, sialorrhea) are unique to clozapine.(32)

1.A.9. General principles for antipsychotic prescribing in schizophrenia

The goal of antipsychotic use in psychotic patients is to alleviate acute psychotic attacks and prevent psychotic relapses with the minimum possible side effects.(13) Newer approaches

also focus on functional and social outcomes.(13) The basis of antipsychotic drug selection can be summarised in three words: effectiveness, safety, and tolerability.(33) Some fundamental principles were introduced to guide prescribers to attain optimal prescribing of antipsychotic medications.(27)

1.A.9.1. Target the symptoms, not diagnoses of mental illness

The NICE Clinical Guidelines 82(34) and the subsequent updated Clinical Guideline 178 (22) "Psychosis and schizophrenia in adults: prevention and management" strongly recommend that no preference should be given to a particular antipsychotic drug class in the treatment and management of schizophrenia.(22,35) Prescribing antipsychotics should only be made when a clear benefit is expected, but no other safe alternatives are feasible. Antipsychotic selection should be individualised considering the clinical status of the patients. Therefore, the decision regarding the proper antipsychotic should be guided by the nature of the predominant symptoms. Also, the NICE guideline for schizophrenia emphasises the importance of patient choice rather than specifically recommending a class or individual antipsychotic as a first-line treatment.(22)

Because the benefits of antipsychotics are sometimes obscured by their side effects and medical risks, risk-benefit assessments regarding antipsychotic drugs prescription should base on antipsychotic drug types (as opposed to "generation" or "class" of drug) and the specific situation (i.e., actual benefits and harms expected or experienced by an individual). As previously stated, each antipsychotic medication has a unique side effect profile, which affects individuals differently.(32) Also, response to antipsychotics may be distinctive in some population groups. For example, elderly patients are more vulnerable to specific adverse effects, like orthostatic hypotension.(32) Thus, avoiding medications causing orthostatic hypotension in the elderly is recommended.

1.A.9.2. Start low, then go slow

Dose selection must be individualised empirically. The minimum effective dose is recommended to be used as starting dose, followed by slow dose titration according to individual response.(27)

1.A.9.3. Use only one antipsychotic

Aside from clozapine augmentation, monotherapy is recommended over the combined antipsychotic regiment. Generally, combined antipsychotics are not recommended unless the therapeutic response to clozapine is lacking.(22) Furthermore, antipsychotics are not recommended to be used as pro re nata ('PRN', as required) tranquilisers for acutely disturbed patients. Instead, guidelines recommend prescribing a short course of general sedatives.(27)

1.A.9.4. Special practical considerations for patients on chronic depot formula

Patients on regular depot antipsychotic treatment should be closely monitored to stabilise antipsychotic plasma levels. Regular depot dosing results in a sustained rise in plasma levels (at least 6–12 weeks after initiation), even on a stable dose. However, evaluating plasma levels associated with increased dosing can be challenging. The preferred method is to establish the efficacy and tolerability of oral medication at a particular dose before administering the equivalent dose for the new formula (long-acting injectable) antipsychotic.(27)

1.A.9.5. Monitor efficacy and adverse reactions

Response to antipsychotic treatment should be assessed using standardised assessment tools.(32) Antipsychotic users should be regularly monitored for side effects. If side effects

were observed, prescribers are strongly advised to perform a risk-benefit analysis individually. The prescribers should discontinue the antipsychotic if no benefits were achieved or when the risks of antipsychotic side effects outweigh the benefits. Nonetheless, evidence suggests that adverse effects are not the main reason for the discontinuation of antipsychotics. Nevertheless, optimal monitoring of adverse effects will improve patients' quality of life and functional outcomes. Patients receiving antipsychotics should undergo close and regular monitoring of physical health, including cardiometabolic risk factors (body weight, blood pressure, plasma glucose and plasma lipids).(22,27,32) Basically, some of these critical principles are broadly applied. In some instances, monitoring recommendations are partially based on expert opinion.(21)

Summary of the background (part A)

The use of antipsychotics is a key to the pharmacological management of schizophrenia and affective mood disorders. Aside from clozapine, the efficacy of currently available antipsychotic agents in the treatment of schizophrenia is broadly similar, and individual patient responses may greatly vary. However, side effects are common and antipsychotics demonstrate various degrees of heterogeneity in terms of their side effects. Also, patients' tolerability to different side effects can vary. Accordingly, treatment with antipsychotics should be individualised considering aspects related to the current symptoms, side effects and patients' preferences. To optimise the use of antipsychotic medications, it is important that careful monitoring of side effects including the cardiometabolic side effects is frequently done. The following section (Part B) focuses on the cardiometabolic side effects of antipsychotics, the potential underlying mechanisms for these side effects, and the available recommendations for monitoring these side effects.

Manuscript number (1)

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Printed title of the Manuscript: Guideline vs practice in screening and monitoring of cardiometabolic risks in patients taking antipsychotic medications: where do we stand?

Status: published

Location in the thesis: page 22

Authors' contribution: Conceptualization: R.AA, VP, ZJ. Project administration: VP, ZJ. Writing original draft: R.AA. Review & editing: R.AA , VP, ZJ.

Title page

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Part B: Guideline vs practice in screening and monitoring of cardiometabolic risks in patients taking antipsychotic medications: where do we stand?

1.B.1. Introduction

Despite the known benefits of antipsychotic medications, they have associated with increased risks of cardiometabolic side effects. Antipsychotics-induced adverse cardiometabolic effects such as weight gain, high blood pressure, alterations in glucose metabolism, and lipid dysregulation are well-recognised risk factors for cardiovascular diseases (CVDs) and diabetes.(9) Clinical guidelines call for regular physical health assessments and laboratory monitoring as a means to prevent and detect adverse cardiometabolic effects of antipsychotic medications. However, recent evidence suggests that cardiovascular conditions remain the key cause of mortality amongst people using antipsychotic medications, suggesting suboptimal screening and monitoring practices. Suboptimal cardiometabolic screening among antipsychotic users can hinder the early detection of high-risk people and delay receiving proper management.(36)

1.B.2. Antipsychotic medications and adverse cardiometabolic effects

Although the pathophysiological pathway underlying cardiometabolic side effects of antipsychotic treatment is not fully understood, antipsychotics-induced cardiometabolic side effects are attributed to multiple functional pathways. This involves the activation of the dopaminergic pathway (D2), with multiple inhibitions of serotonergic (5HT2A), adrenergic (α1) and histamine (H1) pathways. These combined mechanisms suggest that cardiometabolic changes during antipsychotic treatment may be a net result of alterations in glucose and lipids regulations along with satiety signalling resulting in reduced energy expenditure.(9)

Notably, these cardiometabolic changes vary significantly across different antipsychotics. For example, clozapine and olanzapine, risperidone and quetiapine have been recognised as antipsychotics with the highest metabolic liability. Moreover, evidence suggests that some antipsychotics, mainly aripiprazole and ziprasidone, demonstrate neutral cardiometabolic effects. However, caution is advised even when dealing with such agents, as these side effects can be unpredictable.(9)

While the available literature focuses mainly on the magnitude of the antipsychotic-induced cardiometabolic effects, little is known about the onset or duration of these changes. Preclinical studies reported some variability in the onset of some cardiometabolic changes. For example, the onset of some metabolic side effects such as glucose and lipid abnormalities with antipsychotics can be rapid that occur earlier than the onset of weight gain(9), suggesting an independent relationship between the metabolic changes and weight gain. Besides, most records reported data from studies that were mostly conducted over a shorter duration and little is known about these cardiometabolic changes over the long-term.(37) It would be helpful to investigate such relationships, as it would enable appropriate monitoring of patients vulnerable to cardiometabolic changes.

Although monotherapy is preferred over multiple antipsychotic therapy, there is growing evidence for the use of augmented antipsychotic regimens, especially when there has been an inadequate response to clozapine. Though the augmenting agent should meet the NICE eligibility criteria for antipsychotic combined therapy, combined antipsychotic therapy may contribute to an increased risk of high mortality related to cardiometabolic issues.(22) With the increased use of augmented antipsychotic regimens, the risks of associated cardiometabolic problems require further attention.

1.B.3. Practical challenges in antipsychotic therapy and cardiometabolic monitoring

Improving the psychotic symptoms has been the ultimate goal since the introduction of antipsychotic medications. Issues associated with antipsychotic treatment, such as treatment failure, may shift the attention entirely towards the efficacy of the antipsychotics. In clinical practice, the dose and course of antipsychotic therapy vary between patients depending on patients' factors, including the acuity and course of the psychotic illness. Selecting antipsychotic medications can be challenging for many prescribers since the therapeutic response primarily drives the decision.(37) However, such a decision must balance the benefits and associated cardiometabolic risks. Selecting an initial agent with a favourable cardiometabolic profile is considered the best approach for those with or at higher risk of CVDs.(37) Guidelines recommend using new antipsychotics as initial therapy; though, such an option may be inconvenient for many patients. As the antipsychotic efficacy of both antipsychotic classes has shown to be comparable, routine clinical decisions should be based on the patients individual therapeutic response and tolerability, which can vary between individuals.(38)

The risk of relapse of psychotic illness represents an additional obstacle to dose or drug alteration. Likewise, resistance to antipsychotic therapy remains a significant issue that continues to provoke debate over its clinical management.(37) To date, clozapine is the only approved agent for refractory conditions, and the role of augmented antipsychotic therapy is less advocated as routine practice. Not surprisingly, these obstacles in antipsychotic therapy can often deviate clinical decisions away from the adverse outcomes profile as they direct the attention more toward treatment efficacy and less to treatment safety resulting in suboptimal monitoring for the side effects.

1.B.4. Importance of optimal monitoring

Regular monitoring for metabolic issues among high-risk individuals is considered a crucial first step in determining the treatment plan.(39) In the UK, the National Institute for Health and Care Excellence (NICE)/Royal College of Psychiatrists provide guidance for baseline and ongoing monitoring of people taking antipsychotic medications. Specifically, the recommendations include monitoring personal and family history; anthropometric measures and body compositions (weight, BMI, WC, BP); fasting plasma glucose (HBA1c) and lipid profile.(22) Similarly, international clinical guidelines recommend similar monitoring requirements.(22,27,38,40–43) (Table 1-2).

Table 1-2. Guidelines for cardiometabolic risk factor monitoring in patients treated with antipsychotic medications.

Guidelines	Origin	Focus of the guidelines	Recommended cardiometabolic components
The consensus statement of the American Psychiatric Association (APA)/American Diabetes Association (ADA), 2004.(40)	USA	Monitoring of metabolic adverse events associated with antipsychotics Focus mainly SGAs	Physical health monitoring: BP, weight (body weight and WC) Baseline Follow-up: 4-8 weeks, quarterly then annually Biochemical examination: fasting glucose and lipids Baseline Follow-up: quarterly then annually.
The Best Practice Advisory Centre (BPAC) guidelines, 2007.(41)	New Zealand	Monitoring of metabolic adverse events associated with antipsychotics	Physical health monitoring: BP, weight (body weight and WC) Biochemical examinations: fasting glucose and lipids Baseline Follow-up: quarterly then annually Frequency increase in high risk groups
Guidelines for Biological Treatment of Schizophrenia part 2, 2013.(42)	Global	Management of schizophrenia and related disorders General recommendations including general health monitoring.	Personal/Family history Physical health monitoring: BP, weight (body weight and WC) Biochemical examinations: fasting glucose and lipids Cardiovascular examination Baseline Follow-up: 4-8 weeks, quarterly then annually
The National Institute for Health and Care Excellence (NICE)/RCP, 2014.(22)	UK	Management of schizophrenia and related disorders Evidence-based recommendations for optimising treatment and prognosis. General recommendations including general health monitoring.	Personal/Family history Physical health monitoring: BP, weight (body weight and WC) Biochemical examination: fasting glucose and lipids Baseline Follow-up: 4-6 weeks, quarterly, then annually
The Royal Australian and New Zealand College of Psychiatrists (RANZCP), 2016.(43)	Australia and New Zealand	Management of schizophrenia and related disorders General recommendations including general health monitoring.	Physical health monitoring: BP, weight (body weight and WC) Management of comorbidities, particularly metabolic health

Guidelines	Origin	Focus of the guidelines	Recommended cardiometabolic components
		Focus mainly on SGAs	Biochemical examination: fasting glucose and lipids
The Maudsley prescribing guidelines in psychiatry, 13th edition, 2018.(27)	UK	Evidence-based recommendations for optimising treatment and prognosis. General recommendations including general health monitoring.	Physical health monitoring: BP, weight (body weight and WC) Baseline Follow-up: quarterly then annually Cardiovascular examination: ECG Biochemical examination: fasting glucose and lipids Early on treatment monitoring: during dose titration Follow-up: quarterly then annually
Scottish Intercollegiate Guidelines Network. SIGN: management of schizophrenia: a national clinical guideline, 2020.(38)	Scotland	Evidence-based recommendations for optimising treatment and prognosis. General recommendations including general health monitoring.	Physical health monitoring: BP, weight (body weight and WC) Pre-treatment screening. Baseline Follow-up: quarterly then annually Biochemical examination: fasting glucose and lipids Pre-treatment screening. Baseline Follow-up: quarterly then annually

Abbreviations: SGAs: second-generations antipsychotics; BMI: body mass index; WC: waist circumference; BP: blood pressure; ECG: electrocardiogram

It is important to note that not all guidelines provide explicit recommendations standards for adverse cardiometabolic effects monitoring of antipsychotics, yet they all proposed physical examination for people with severe mental illness (SMI). Available guidelines also differ in terms of timing and extent of monitoring and the scope of physical health domains that are to be monitored. In terms of monitoring indications, most guidelines recommend 'frequent' monitoring mainly in the presence of risk factors(27,38,40,41,43), while others state frequent monitoring after initiation or changing antipsychotic medications.(27,40)

Despite guidelines emphasising the importance of monitoring practices, albeit inconsistent, monitoring practices are reported to be suboptimal. This was parallel with the findings of a systematic review assessing metabolic screening practices among antipsychotic users, as the authors concluded the rate of metabolic monitoring were 'generally inadequate' except for body weight (76%) and blood pressure (75%).(36) Similarly, other studies showed significant variations in monitoring level of cardiometabolic outcomes in antipsychotics users, as some anthropometric variables, blood pressure was frequently measured in 56.1% of subjects, while waist circumference was rarely recorded.(44–46) Literature also demonstrate variations in monitoring practices as per patient demography. Certain patients' groups such as the older populations appeared to be more frequently tested for cardiovascular diseases in some studies. For example, the overall monitoring rate of different metabolic components in people with SMI attending primary care tended to be higher among older people.(44)

Currently, there are variations regarding what extent of monitoring can be called the 'optimal' level of monitoring. For example, one study defined adequate monitoring when 70% of the patients receive cardiometabolic monitoring for each outcome.(45) While the same definition was expressed in another study as comprehensive recording of all modifiable risks' factors at least once during the treatment period.(9) Collectively, these reports suggest there is room to improve the monitoring of patients receiving antipsychotic medication in primary care. Also, further research assessing the level of adherence to the available guidelines for cardiometabolic monitoring in patients with SMI using antipsychotics in primary care is highly recommended.

The inconsistent monitoring practices reported by the literature may be a consequence of 'hidden factors' that may affect the prescribed population from receiving comprehensive

cardiometabolic care. A recent review of qualitative evidence attempted to address barriers for cardiometabolic monitoring among people using antipsychotics. The review revealed numerous barriers, including lack of knowledge and understanding of the physical health issues; attitude of the patients and healthcare professionals; the nature of the psychotic disease; financial constraints; fragmentation of care; lack of specialised training, and limited resources to perform the monitoring (findings were explicitly described in Chapter 4 of this thesis).

Better liaison between different healthcare sectors is imperative. The transition in mental healthcare from secondary care to community-based care has been accompanied by some challenges that indirectly influence physical healthcare delivered to patients using antipsychotics (findings were explicitly described in Chapter 4 of this thesis). To resolve this, there is a need to establish the effects of this transition on the level and quality of care delivered to patients prescribed antipsychotic medications. Also, integrating other medical care into psychiatric teams, particularly those concerned with managing vulnerable groups such as those with cardiometabolic comorbidities, is paramount. There is a scope to develop a treatment algorithm to detect antipsychotic-induced weight gain and metabolic dysregulations and used as guidance for pre-treatment assessment for patients who recently start antipsychotic treatment. Such tools may allow rapid, comprehensive, systematic collection and assessment of these adverse outcomes if integrated as part of routine care.

1.B.5.The promising role of pharmacists

Pharmacists are in a unique position to enhance the quality of antipsychotic medications uses with the potentials to reduce drug-related outcomes that may cause harm. In the context of mental health, pharmacists can improve cardiometabolic monitoring by being an active part of the monitoring process. Preliminary previous study demonstrated pharmacists

ability to contribute to the cardiometabolic risks assessment and monitoring of patients prescribed antipsychotics.(46) In another study of pharmacists-led cardiovascular risk-reduction strategy in the US, pharmacists were able to identify patients with SMI at high risks for cardiovascular issues by closely reviewing their lab profile and making appropriate decisions, including starting medications and ordering relevant laboratory tests.(47) These findings revealed the capability of pharmacists in performing appropriate screening of patients with SMI as they demonstrated fair competency to make decisions and order laboratory tests for general comorbidities such as diabetes in patients with SMI when necessary. Additionally, the literature suggests that pharmacists can indirectly improve cardiometabolic monitoring by providing focused education on adverse cardiometabolic outcomes of psychotropic medications for patients and other healthcare professionals. Healthcare professionals including pharmacists should also offer advice and intervention to address other known modifiable risk factors related to cardiometabolic health when counselling patients in relation to antipsychotic medicines.

Also, pharmacists can function as the bridge that facilitates care transitions between acute and community-based care settings since they work closely with patients and other healthcare providers at different levels. Such roles can improve patients' clinical outcomes by allowing continuity of care; improving medication adherence; assessing therapeutic outcomes; optimising medication regimens, and ordering and evaluating monitoring parameters.(47) Further robust interventions using randomised controlled trials are necessary to investigate clinical outcomes following pharmacist interventions regarding monitoring adverse metabolic outcomes associated with antipsychotic use. It is also important to understand patients' perspectives regarding the services delivered by

pharmacists and the associated effects on their health outcomes. This can be achieved using qualitative study designs.

1.B.6. Conclusions

While guidelines have attempted to emphasise frequent monitoring for cardiometabolic risks in antipsychotic users, monitoring adverse outcomes in these patients remains suboptimal. There is a need to investigate potential factors influencing the adoption of monitoring guidelines. There is a need to develop and evaluate interventions aiming to incorporate the roles of other healthcare professionals such as pharmacists in the care of patients prescribed antipsychotic medications.

Contributors

Writing: RAA; reviewers: VP and ZJ.

Funding

This work was supported by the University of Birmingham, United Kingdom. RAA is supported for her PhD by the Royal Embassy of Saudi Arabia, London, United Kingdom. The funding body had no roles the preparation of this manuscript.

Competing interests

None declared.

Patient consent for publication

Not required.

Part C: Rational of this PhD work

For the present study, cardiometabolic risk management was defined according to the definition proposed by Schrijvers (48) for disease management, who stated:

'Disease management refers to the use of an explicit, systematic population-based approach to identify persons at risk, intervene with specific programs of care, and measure clinical outcomes'.

This definition includes early and regular screening and monitoring of cardiometabolic risk factors. The current doctoral work interests will be examining the extent of compliance to cardiometabolic monitoring guidelines among patients prescribed antipsychotics in primary care. For this purpose, reviewing the available guidelines for cardiometabolic monitoring practices for antipsychotic users is relevant. This would allow for assessing the concordance between different guidelines and linking guidelines to actual practice.

It is also essential to examine the commonly reported cardiometabolic side effects among patients prescribed antipsychotics and the available interventions designed to counteract them. Currently, there is a lack of systematic reviews addressing barriers to managing and monitoring cardiometabolic side effects in patients prescribed antipsychotic drugs. Synthesis of barriers identified from the literature will allow interventions to be developed to promote monitoring practices. Finally, in the UK, there is a lack of recent studies aiming to identify the extent of cardiometabolic monitoring, and this PhD work aims to fulfil these gaps.

1.C. Aims and objectives of this thesis

This PhD programme of work aims to examine the extent of screening and monitoring of cardiometabolic side effects in patients prescribed antipsychotic drugs and the potential influences on the uptake of recommended guidelines around monitoring cardiometabolic

side effects in practice. Objectives for the systematic review and observational studies are presented separately.

1.C.1.Objectives of the systematic review (Chapters 3&4)

I. To identify and summarise studies reporting the prevalence of cardiometabolic side effects in patients prescribed antipsychotic drugs.

II. To identify the nature of interventions around managing cardiometabolic side effects in patients prescribed antipsychotic drugs and the cardiometabolic outcomes measured by these interventions.

III. To explore the perspectives of healthcare providers regarding the assessment, screening, monitoring and management of cardiometabolic side effects in patients prescribed antipsychotic drugs as reported in the published literature.

IV. To explore patients' perspectives regarding the assessment, screening, monitoring and management of cardiometabolic side effects related to antipsychotic drugs as reported in the published literature.

The results of this review guided the design of the subsequent phases of this PhD programme.

1.C.2. Objectives of the observational study (Chapter 5)

I. To explore the prevalence of patients prescribed antipsychotic drugs with records of cardiometabolic outcomes in a large national primary care dataset; the Health Improvement Network (THIN) database.

II. To identify monitoring patterns for cardiometabolic outcomes among patients prescribed various antipsychotics.

The applied methodologies for the entire work are discussed in the next chapter.

Chapter 2 Methodology

Summary of the chapter

This chapter presents the proposed methodological approaches relevant to the PhD study. Aspects related to the philosophical underpinnings and paradigmatic basis of the research methods selected in this work have been described.

2.1. Paradigm positioning

According to Lincoln and Guba (1994), a research paradigm is 'the basic belief system or worldview'.(49) Researchers have their views on what constitutes truth and knowledge. Social scientists refer to these views as paradigms, which define their thinking, beliefs, and assumptions regarding themselves and society. Also, the paradigm reflects the world from the researchers' perspective.(50,51) Accordingly, the chosen strategy will depend on the researcher's views of the problem and how it can be studied so that the researcher and others in the same discipline can be confident in the conclusions. A paradigm comprises four elements: epistemology, ontology, methodology and axiology, which represent the researcher's view about the truth and reality (Figure 2-1)(49)

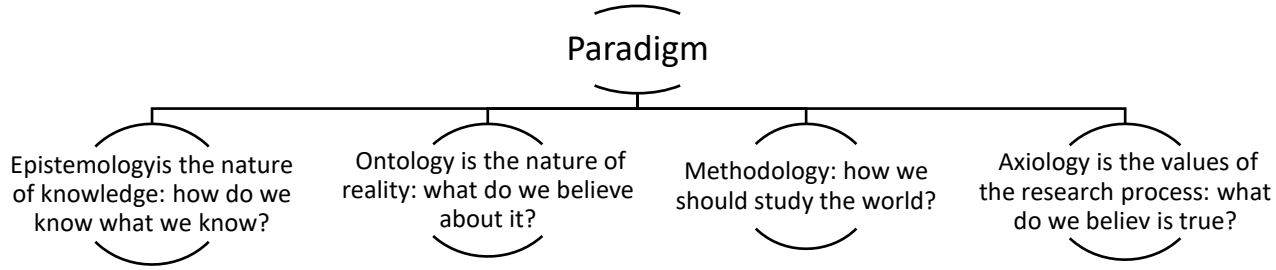


Figure 2-1. Basic beliefs and elements of a research paradigm. Reproduced from (49)

A paradigmatic stand greatly influences the evaluation of healthcare research. Therefore, it is crucial to understand how specific research methods and approaches to data collection have evolved from vastly different traditions in healthcare and how those approaches result

in different understandings of social reality. Before laying out the research design, it is necessary to understand the epistemological foundations and philosophical roots.

2.1.1. Application of positivism in healthcare research

This study aimed to determine and quantify patterns of cardiometabolic monitoring among patients prescribed antipsychotic drugs. To date, positive thinking still dominates modern clinical and basic science(52), and mental healthcare research is no exception. A positivist researcher believes knowledge is objective and can be acquired through rigorous scientific methodology. Positivism relies heavily on experiments where the measured observations can be quantified and statistically analysed to demonstrate knowledge. Therefore, positive research emphasizes experimentation, observations, controls, measurement, reliability, and validity, which implies a quantitative approach. Since most scientific research methods assume objectivity, neutrality, and generalisability of data, they fall firmly into the positivist paradigm. In addition, research types like longitudinal or cross-sectional studies are based on positivist assumptions.(52) These studies are used to chart out a variety of topics, including but not limited to i) prognosis (the expected course of a disease); ii) prevalence (the extent to which a problem is dominated within a population); iii) other factors that may affect health outcomes.(53) Given these assumptions, the positivism paradigm was chosen as the underpinning approach since the methodology can be guided by objective measurements, systematic inquiry, and hypothesis testing.

The research approach stems from the researcher's philosophical viewpoint, and it can be either deductive or inductive. Research involving a deductive approach involves testing a theoretical hypothesis using a research strategy specifically designed for the target hypothesis.(54) Positivism and the deductive model of science are aligned. The deductive method is a circular process that begins with a theory based on the literature to build

testable hypotheses to ultimately ends with a theory contributing to the literature ending, thereby the circular process. See Figure 2-2.

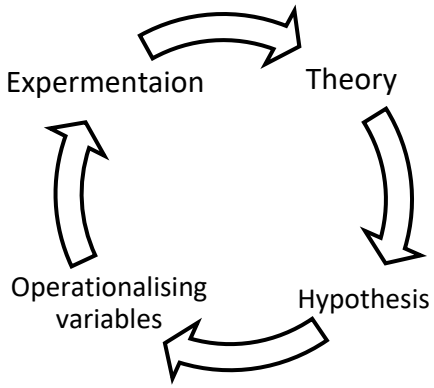


Figure 2-2. The hypothetico-deductive circle. Reproduced from (54)

2.2. Overall design of this PhD work

This project was conducted in several stages. The first stage involved a systematic review of literature assessing quantitative and qualitative evidence regarding the cardiometabolic side effects of antipsychotics. The quantitative component of the review focused on assessing the quantitative evidence to investigate the extent of the problem addressed in this PhD study, i.e.(the prevalence of cardiometabolic side effects among antipsychotic users). Also, it explored the available interventions designed to mitigate these side effects.

The qualitative part (qualitative review) targeted potential barriers to assessing, screening and monitoring cardiometabolic side effects in patients using antipsychotics. Fulfilling the review's objectives helped guide the study design of the observational phase. See relevant chapters for the detailed methods used for each review (**Chapters 3&4**).

The systematic reviews were followed by an observational study aiming to explore the level of guideline adherence concerning monitoring of the cardiometabolic side effects in patients prescribed antipsychotics in primary care. The study involved the analysis of anonymised electronic medical records extracted from a large database: the health

improvement network (THIN) database. The detailed methodology appears in the relevant chapter (**Chapter 5**). See Appendix II-B for the detailed study protocol.

2.3. Stage A: Methodology for the systematic literature reviews (Chapters 3&4)

2.3.1. Systematic review

Systematic reviews are the gold standard for gathering, analysing, interpreting, and synthesising the best available information about a particular clinical question.(55) Systematic review is a research approach that identifies, selects, synthesises, and appraises studies that meet pre-specified inclusion criteria to answer a research question. The process involves explicit methods, and the findings should be reproducible. Several basic steps must be taken when carrying out a systematic review.(56) The involved steps are graphically illustrated in Figure 2-3.

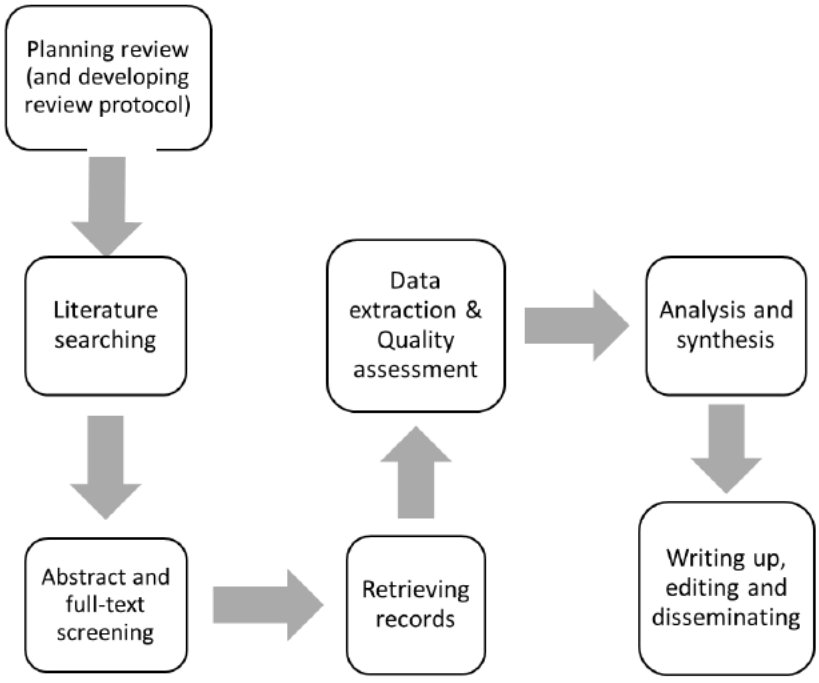


Figure 2-3.Key Steps for conducting a systematic review. Reproduced from (56)

Systematic reviews provide the most robust evidence base to support the development of trustworthy clinical guidelines (and their recommendations) and clinical decision-making.(55) However, one of the limitations of the traditional systematic review is the

restriction of studies for inclusion to a single study design, such as randomized controlled trials. This can limit the application of this methodology to providing insights about effectiveness rather than seeking answers to more complex search questions, for example, reasons for intervention failure.(57) In recent years, with the establishment of organizations such as the Cochrane Qualitative Methods Group (58) and the Joanna Briggs Institutions (JBI)(59), there has been a noticeable shift toward the inclusion of a broader range of study designs incorporating both quantitative, qualitative studies into a mixed-method design.

A mixed-method systematic review of literature design (MMSR) was utilised for this PhD work. This approach would allow answering questions of multiple dimensions by corroborating a wide range of data types from different sources in a single research.(59) The first review focused on the quantitative synthesis of evidence investigating the prevalence of cardiometabolic side effects of antipsychotic drugs. It also synthesised evidence focusing on the types and effectiveness of interventions targeting cardiometabolic side effects of antipsychotic drugs. The second review aimed to critically assess and synthesise qualitative evidence reporting barriers to cardiometabolic management and monitoring in antipsychotic users. Details for individual review methods are described in relevant chapters (**Chapters 3&4**). The approach used to join both reviews is described next.

2.3.2. Mixed-method systematic review as an approach to joining different reviews

The triangulations of findings from the two reviews offered the opportunity to call the work package relating to this study a 'mixed-method systematic review'.(59) The method applied to join the two reviews was done according to the conceptual framework developed by Joanna Briggs Institute for mixed-methods systematic reviews (MMSR).(59) (See Figure 2-4).

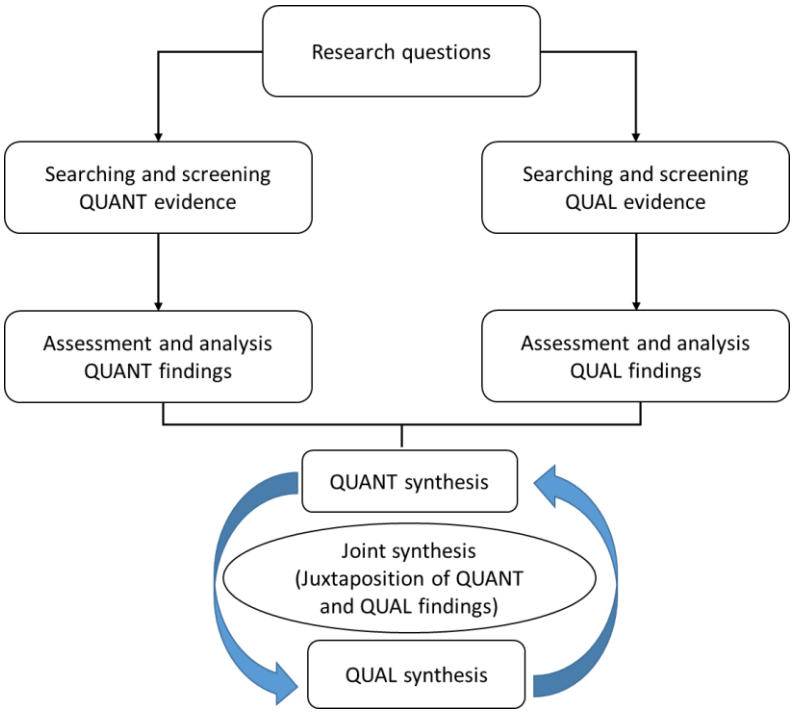


Figure 2-4.The convergent segregated approach is inspired by JBI approach for mixed-methods systematic review (MMSR); QUANT: Quantitative; QUAL: qualitative. Reproduced from (59)

In such a design, the data were first extracted, analysed and synthesised separately. Then the findings from both syntheses were merged for the purposes of comparison and complementarity (please see relevant chapters for each review for detailed analysis and synthesis; **Chapters 3&4**). Adding the qualitative to the quantitative synthesis increases the value of this integration. It helped analyse the reasons behind the heterogeneity of the quantitative findings and discover the gaps in the current research.(56)

The review method was pre-specified in a protocol, registered in the PROSPERO International Prospective Register of Systematic Reviews (registration number: CRD 42018106002), and accessible online: https://www.crd.york.ac.uk/PROSPEROFILES/106002_PROTOCOL_20180803.pdf.(60) The review was conducted as per the Cochrane guideline for systematic reviews (61) and Centre for Review and Dissemination (CRD) (62) and is reported following the Preferred Reporting Items for Systematic Reviews and Met-Analysis (PRISMA) statement and checklist.(55)

2.4. Stage B: Methodology for the observational studies (Chapters 5&6)

2.4.1. Observational study

Randomized controlled trials (RCTs) have long been recognized for their robustness in providing the most accurate estimates of comparative effectiveness. However, there may be discrepancies between the results of the experiments and what clinicians and patients observe in real-world practice.(63) Population-based studies, which are known as observational studies, play a significant role in identifying and addressing gaps in practice following the implementation of basic RCTs. Since this work aims to understand the current practice for antipsychotic therapy and how antipsychotic users are monitored for cardiometabolic side effects, observational studies are considered the proper methods to assess the practical relevance of evidence (monitoring guidelines) in a natural environment.(64)

Observational studies possess some features that make them superior to randomized controlled trials in exploring the functionality of intervention modules in a real-life setting.(63,65) Unlike RCTs, observational studies do not attempt to control participants or assign them to different interventions or environments.(64) Thus, observational studies directly observe individuals in their natural surroundings. Given the differences between patients recruited to trials and those seen in routine practice, samples derived from observational studies tend to be heterogeneous and provide various characterises that can be further addressed in RCTs. Also, observational designs can rapidly recruit large numbers of subjects using limited resources. Another advantage is the long follow-up periods, making examining long-term risks and benefits possible. Additionally, population-based studies provide information about toxicity associated with treatment, as drug side effects might be expected when the results of RCTs are applied to routine practice.(64) However,

observational studies impose important limitations that must be carefully weighed when evaluating treatment effectiveness. The disadvantages of cohort and cross-sectional designs are presented in Table 2.1.

Table 2-1. Limitations of the cohort and cross-sectional studies.

Limitations of each design	
Cohort study	**Cross-sectional**
Subjected to various bias types (e.g., recall bias: retrospective design)	
Difficulties in controlling confounders	Difficult to derive causal relationships.
It can be time-consuming and costly (prospective design)	The response rate is critical.
It may not be advantageous in case of rare outcomes.	Lack of randomisation
Loss of follow-up (prospective design)	

Reproduced from (66)

The most significant limitation of observational studies is the increased risk of bias. Also, it is difficult to distinguish between outcomes associated with new treatments and those resulting from unrecognized changes in the population. Data from administrative databases, medical chart reviews, or previous research studies are typical observational data sources.

2.4.4. Data source for this work

2.4.4.1. The use of real-world data in mental healthcare research

The increasing accessibility of digital health data, with the rising costs and recognized limitations of traditional trials, has renewed interest in using real-world data (RWD) to enhance the efficiency of research and bridge the evidentiary gap between clinical research and practice.(67) 'Real-world data' can be defined as data relating to patient health status or the delivery of healthcare routinely collected from various sources, such as electronic health data (EHR) and administrative data.(67) Real-world data are collected outside a clinical trial and used for healthcare decision-making.(68) Such data includes but is not limited to

electronic medical records from healthcare, administrative data, financial data (e.g., paying for care), and pharmacy data (e.g., prescriptions).(69)

2.4.4.2. Electronic health records (EHRs)

Electronic health records (EHRs) are an example of large secondary data commonly used in healthcare research.(70) Specific features of EHRs make them 'big data': i) their complexity (variety); ii) the number of patients and the amount of information recorded for each patient (volume); iii) the fact that they are collected for a multi-purposes (e.g., clinical care, auditing, and quality monitoring).(71) Considering the objective of this PhD work, using EHRs could significantly improve our understating of the healthcare delivery for patients with mental illness by enabling the development of a learning healthcare system that provides rapid feedback to providers and patients, allowing optimal treatment.

EHRs comprise structured and unstructured electronic data in which were collected during routine clinical care. Clinical data in structured EHRs is recorded using structured terminology systems, such as statistical classification systems (e.g., ICD-9-CM or ICD-10). Conversely, the unstructured data is stored as raw, unformatted clinical information (non-coded), such as medical histories, discharge summaries and handover notes.(67) Notably, the challenges of leveraging such diverse and large volume data are considerable. Several problems with EHRs data have been cited, including inaccurate or incomplete data or even missing which must be inferred. Also, the data may contain codes that classify patients for purposes other than clinical care, making meaningful interpretation difficult. Additionally, free-text notes often contain important information that must be interpreted.(71,72)

2.5. Importance of confounding factors and their adjustments in observational studies

Data from healthcare databases offer large sample sizes and a better representation of real-world populations. Thus, they provide an opportunity to improve patient care by

personalizing therapeutic decisions when evidence supports heterogeneous treatment effects (HTEs). Like other populations with chronic illnesses, patients with mental illness may inherit clinical heterogeneity. Optimizing the target population is affected by such heterogeneity since it impacts both the type of care likely to be delivered and the possible outcomes that could develop. This heterogeneity has been articulated as confounding.(73) Confounding refers to bias resulting from common exposures and outcomes. Thus, confounders can distort the observed exposure/outcome associations. To account for these variations in patient characteristics, research criteria must be adjusted for processes and outcomes. However, confounding control represents particular challenges in studies relying on healthcare databases, where data on many potential confounding factors is lacking, and the meaning of variables is unclear.(74) Notably, it would be helpful to utilise these patients inherited characteristics to our advantage to explore hidden factors that may have potential roles in the suboptimal effects of delivered treatment.

Confounding in observational research can be controlled using various techniques. However, excluding the effects of unmeasured residual confounders can be very challenging. Various types of regression modelling are available depending on the nature of the outcome variable. When the outcome variable can have only two categories (e.g., outcome present vs outcome absent), then binomial or binary logistic regression is considered the model of choice. If the outcome variable has more than two categories (e.g., drug A, drug B, and drug C) which are not ordered, then multinomial logistic regression is preferred.(72) For this research, univariate binary logistic regression modelling was applied to estimate the relationships between specific patient characteristics and the probability of any monitoring occurrence within the study period (baseline, 6 weeks, 12 weeks and 1 year). The binary logistic regression is used to express the relationship between an outcome variable and

predictor variables (factor variables) as a function of the natural logarithm of odds (logit)(75), which is presented in the following models:

$$logistic\ Yi = Ln\ \frac{\pi}{1-\pi}\ \beta_0 + \beta_1 X_1 \ldots.+ \beta_n X_n \quad (2\text{-}1)$$

The odds ratio can be calculated by the following formula,

$$OR = e^{\beta} \quad (2\text{-}2)$$

Where:

- π: is the probability of occurring the outcome
- Y: dependent binary variable under study
- π/(1−π): the odds of success; the ratio of the probability of occurring the outcome Y and the probability of not occurring the outcome Y.
- X: the covariate (independent) variable under study either continuous or dichotomous
- β_0 and βn: intercept and slope (regression coefficient) respectively.

For this study, antipsychotic exposure was selected as the independent variable, while the confounders were added to the model as a covariate. In addition, certain patients' factors were selected to be tested as predictor variables for the outcome variables. For example, the effect of using the antihypertensive treatment on the likelihood of a patient having blood pressure monitoring. By applying the previous equation to our study, we would like to investigate the likelihood of BMI monitoring in patients taking antipsychotic drugs. Furthermore, we planned to assess whether the type of antipsychotic prescribed and the participant's age may potentially influence BMI monitoring patterns. Accordingly, the outcome variable here is BMI monitoring status, whether a subject has records for BMI or not (1=yes, 0=no), and the two predictors are antipsychotic type (1= yes, 0=no) and age. Therefore, we can construct the model as:

$$logistic\ BMI\ monitoing = \beta_0 + \beta_1 * ATP\ type_1 + \beta_1 * age \quad (2\text{-}3)$$

2.6. Ethical considerations for this PhD work

The researcher invested extensive time and effort in ensuring that the study is conducted as per the highest ethical standards. A full NHS ethical approval as well as ethical approval within the sponsor organisation, i.e., the University of Birmingham, were obtained in the following dates:

- NHS Research Ethics Committee (REC): Approval request was submitted on 13th May 2020; decision received on 22nd of May 2020; final approval to commence the study was granted on 14th July 2020. See appendix II-C for the decision letter.
- University of Birmingham Research Ethics Committee: Research Governance (RG), reference number RG_19-187 (approved upon the REC approval; appendix II-C).
- THIN database study approval: Scientific Review Committee (SRC), reference Number: 19THIN070. Approval request was submitted on 19th October 2019; approved on the 11th November 2021. The decision letter is provided in appendix II-C of this thesis.

The research approval processes involved a considerable timeframe within this PhD study. Due to the disruptions resulting from the recent pandemic (COVID-19), the qualitative part of the study was not undertaken due to the inability of participating sites to contribute as planned in the protocol. Therefore, only the comments related to the observational studies were executed. See preliminary (Thesis structure) and study protocol (Appendix II-A) for details related to the original study plans. The approval processes and how they informed the study and the researcher's development have been described below, along with key comments raised by the ethics committees.

2.6.1. Comments raised by the health research authority (HRA) review

The comments raised mostly concerned adjusting research activities in the participating sites (GPs and community pharmacies) per the COVID-19 environment. These included queries associated with methods of transferring the anonymous data between the involved parties and how anonymised data would be communicated from hospital staff to the research team.

Upon the discussion between the research team and ethics committee, it was emphasised that patient confidentiality is paramount. Originally, the data extraction for the observational studies was planned to be conducted by staff with routine access to clinical records. Accordingly, the entire data extraction process was conducted remotely, including the planning, communication and data transmission between different parties. See appendix II-C and appendix II-D for the decision letter and research ethics queries.

No actual amendments related to this part were applied to the study protocol. According to the HRA COVID-19 research guide, the presented measures have been suggested as a non-substantial amendment and did not require a review. Please see the HRA guidance section on 'Changes to site monitoring arrangements or changes to administrative arrangements to reduce burden or physical contact with sites'. Available here: https://www.hra.nhs.uk/covid-19-research/covid-19-guidance-sponsors-sites-and-researchers/.

2.6.2. Comments raised by the University of Birmingham research committees

Concerns raised by the Clinical Research Compliance Team (CRCT) and Research Governance (RG) were mainly related to the consent process for research on anonymous data. Also, the committee highlighted the importance of the researcher's competency to carry on the study activities efficiently.

The current work involved using anonymised secondary data (data previously gathered for a purpose other than research). Thoughtful discussions were held to utilise the optimal methods to ensure patient confidentiality. The study was conducted ethically appropriate to the research questions and the participants involved, where a particular procedure for communication of anonymous data for research purposes was followed. Accordingly, the following recommendations were suggested:

- According to the HRA ethics guidelines, there was no need for individual patients' consent if the data were extracted and transferred by a delegated data abstractor from the participating site to the research team. Otherwise, further approval is required if an external researcher could access confidential patient information; the Confidentiality Advisory Group (CAG) consent. Nonetheless, gatekeeper consent was sought from the participating institutions. However, any identifiable information (e.g., MRA number) was omitted from the data set to maximise confidentiality.
- The researcher is a doctorate student at the UoB. Accordingly, the researcher obtained a research passport from the UoB and proper training (See Appendix II-D for this thesis).

2.6.3. THIN database study: Comments raised by the Scientific Review Committee (SRC)

Studies using the THIN database gained ethical approval from the UK National Health Service Southeast Multicentre Research Ethics Committee. The Scientific Review Committee (SRC) approved the study protocol (no. SRC 19THIN070). Comments raised by the committee were mainly related to clarity (e.g., outcome definition, study period etc.). As a result, the following actions were applied:

- Definitions for the study outcomes were refined upon the guidance of the data abstractors. Corresponding amendments were applied to the study protocol (See Appendix II-B of this thesis).

2.6.4. Comments raised by the ethics committees (HRA & University of Birmingham) that related to the qualitative study

The following are the comments raised by the ethics committee of the University of Birmingham (CRCT) and the HRA covering research activities that are related to the qualitative study of this work. Most concerns are related to the 'researcher-participant relationship'. Other queries were related to data use and management after the end of the study. The researcher is aware of the 'researcher-participant relationship' that is established between the researchers and participants in qualitative studies, which can raise various ethical concerns, such as respect for privacy, the establishment of honest, open interactions, and avoiding misrepresentations. Therefore, the following decisions were made to follow:

- According to the policy, participants should fully understand and agree to the university's terms to retain data for research purposes.
- Also, it was emphasised that the interview manuscript and all associated documents and records related to the interview would be destroyed immediately once participants decide to withdraw according to the university policies.

Relevant amendments and wording were added to the relevant documents, including the study protocol, IRAS form, PIC_NC agreement and the Participants Information Sheet (PIS) as per the HRA guidance on consent forms and participant information sheets, as well as the transparency wording from the University of Birmingham legal services.

*** All ethics submissions and accompanying forms and information sheets can be found in the Appendices of this thesis (Appendix II-E).

This chapter covered aspects related to the study design, the rational of the used method, and research reflexivity. It also presented the procedure used for data protection and ethical approval. The upcoming chapters will describe the results of the systematic review. The Results will be presented in two separate chapters: **Chapters 3 &4**

Chapter 3 Prevalence of Cardiometabolic Side Effects of Antipsychotic Drugs and Interventions to Mitigate them: Quantitative Systematic Review

Summary of the chapter

This chapter summarises the findings of the quantitative systematic review that aimed to identify and summarise studies reporting the prevalence of cardiometabolic side effects of antipsychotics and the available interventions to alleviate them. Methods for this review are described in Chapter 2.

3.1.Background

Epidemiological data showed a global increase in the prevalence of mental illness (MI), including schizophrenia, indicating a parallel rise in prescribing antipsychotic medications worldwide.(3) Patients with mental illnesses face several challenges, including healthcare inequality, social demerits, and the high prevalence of premature deaths. For example, a recent meta-analysis showed that schizophrenia is associated with a weighted average of 14.5 years of potential life loss.(76) Cardiovascular disorders, including coronary heart disease and cerebrovascular diseases, are reported to be the leading cause of death in patients with mental illness.(76,77) Multiple factors, including factors related to lifestyles and healthcare, can increase cardiometabolic risks in this group. Notably, antipsychotic treatment has been established to enhance CVD risks by altering body compositions, lipid, and glucose metabolism.(78)

To alleviate the cardiometabolic side effects of antipsychotic medications, representative epidemiological data are critical to exploring the prevalence of the common cardiometabolic side effects of antipsychotics reported in the literature. Also, it is essential to review the nature and effectiveness of interventions aimed at monitoring and managing the cardiometabolic side effects of these medicines. Doing this helps facilitate the successful management of cardiometabolic complications and improves patients' health prognosis.

3.2. Methods

3.2.1. Search strategy and eligibility criteria

A protocol was developed and registered on PROSPERO (CRD 42018106002).(60) Electronic search was performed for English language literature from 2003 until August 2018 using Medline, Embase, PsycINFO, and Cochrane Library database. This time frame was selected as it corresponds to the FDA warnings for risks of metabolic dysregulations associated with antipsychotic medicines.

A search strategy was developed based on keywords and medical subject headings. Terms that reflected the 'population' such as 'antipsychotics' and 'schizophrenia' were combined using the Boolean operator OR. Results of this search were combined with terms that represent the second domain; condition/context, which was defined by keywords reflecting cardiovascular or metabolic side effects such as 'obesity' and 'hyperglycemia'. To maximise the sensitivity and precision of the search, domains related to outcomes and interventions were not applied. Search terms and strategies appear in Appendix III-A. Cross-referencing of relevant papers including key articles and reviews was undertaken. The search was limited to the year 2003 and beyond and limited to articles published in the English language. To maximise the sensitivity and precision of the search strategy, domains related to outcomes and interventions were not applied. The search strategy and keywords used during the search were provided in the appendices of this thesis (Appendix III-A & Appendix III-B). Cross-referencing of relevant papers including key articles and reviews was undertaken. Years beyond 2003 and articles in the English language were applied as search limits.

The Cochrane and Centre for Review and Dissemination (CRD) guidelines (62) and the PRISMA statement (55) were followed in conducting and reporting the review. The inclusion criteria were formulated using traditional mnemonics for inclusion criteria (PICO). The

CoCoPop mnemonic (population, condition and context) for prevalence studies were applied for studies reporting prevalence data.(79) See Table 3-1.

Table 3-1. Inclusion criteria for the studies to be included in the quantitative systematic review

P	Populations	Adult patients (≥ 18 years) using one or more antipsychotics for mental health conditions.
I	Interventions	Studies focus on interventions meant to mitigate or reverse the cardiometabolic side effects of antipsychotic drugs. These interventions can be either drug therapy or specific programs, or both.
C	Condition	Prevalence of cardiometabolic side effects in patients using antipsychotic drugs.
O	Outcomes	- For studies reporting prevalence data, the outcomes were the percentage (%) of the reported prevalence of cardiovascular or metabolic causes. - For studies reported interventions, outcomes reflect improvements in the cardiovascular risk factors such as positive changing from baseline in clinical or biochemical parameters such as improvements of lipid panel and losing or maintaining weight.

3.2.2. Study identification and data extraction

First, title and abstracts were screened for eligibility then eligible records were screened for full-text. Two reviewers undertook the screening and reviewing process independently. Conflicts regarding the results were resolved by consensus or discussion with a third reviewer. The extracted data included: general information related to study characteristics (e.g., country of origin, study design, population, eligibility criteria, and setting (e.g., sample size). For studies reporting prevalence data, variables including time frame for data collection, the used diagnostic criteria, exposure characteristics and duration of treatment with the antipsychotic were extracted. For studies addressing interventions, information related to the applied interventions was extracted. These included details of intervention and control regimens, duration of the intervention, supportive management provided, mode of delivery, and details and characteristics of the people delivering the interventions.

3.2.2. **Quality assessment of the selected studies**

The quality assessment was done using Joanna Briggs Institute Assessment and Review Instrument (JBI-QARI) for prevalence and experimental studies.(80) The quality of the included studies was assessed using evaluation items of the quality assessment tools. These included sampling, condition measurements and data analysis which are considered potential sources of bias in observational and intervention studies. The study was considered to be at low risk of bias (good quality) if they fulfilled more than 6 positive scores (Yes). This included randomised sampling, using a large sample size, low attrition rate, long follow-up (more than one year), using a control group, and controlling confounders.

The methodological quality would be assigned 'fair' if the study scored between 4-6 (Yes). Conversely, the study would be considered of high risk for bias or low quality if it only fulfilled a maximum of three quality criteria as stated by the tool (0-3; Yes). Finally, an unclear risk of bias would be rated in the absence of the required information. However, if the study stated that randomisation was used but no information was provided, it would be considered to have a risk for allocation bias and hence the overall quality of the study would be graded down.

3.3. Results

The final search yielded 56 records that were included in the final synthesis. The studies were classified according to the review objectives into prevalence and intervention studies. The search process and reason for records exclusion are detailed in the PRISMA-P flow chart (Figure 3-1).

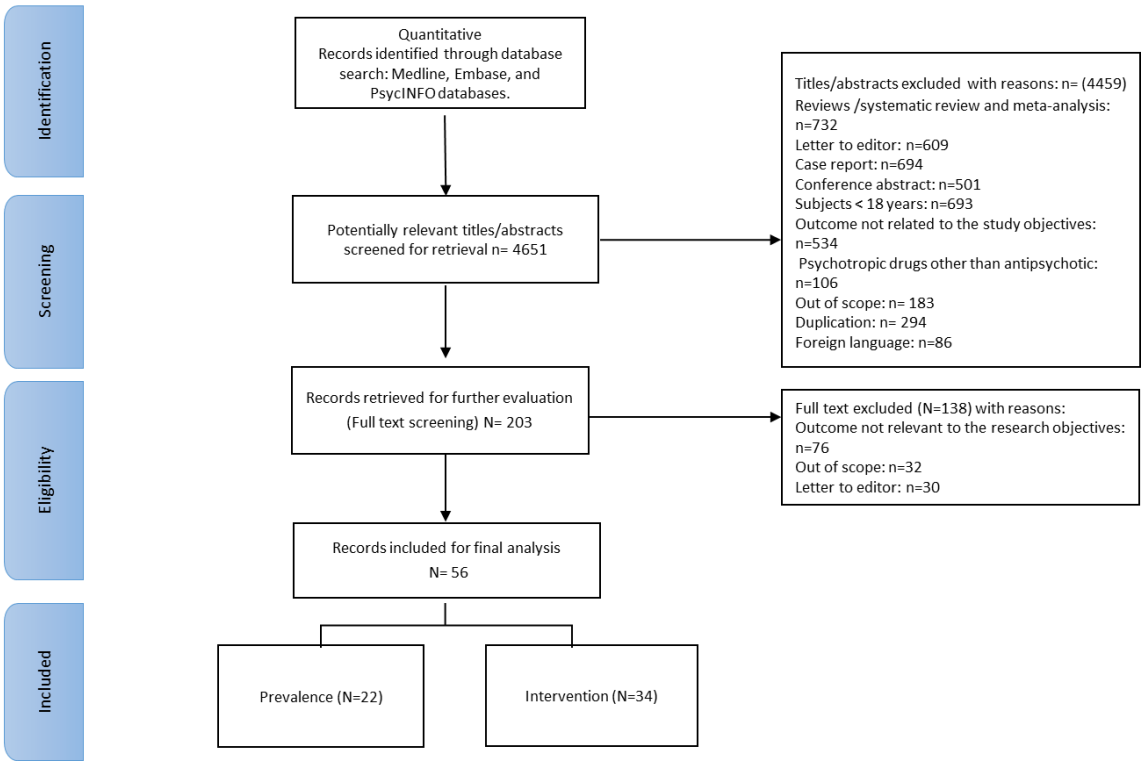


Figure 3-1: PRISMA-flow chart of literature searching.

3.3.1 Quality of the included studies

Studies reported prevalence data were assessed against the three unique items of the following domains 'population and setting', 'condition measurement', and 'Statistics' stated by the JBI assessment tool for prevalence studies (Appendix III-C). In addition, items that reflected 'Condition measurement' was covered in all studies. Most studies described items related to 'Population and setting' except for two studies that did not specify the data source. Even though the majority of studies were based on chart abstraction, they did not provide sufficient information regarding the data collection process. Also, not all studies addressed confounders related to patients, such as age, gender, the severity of the mental illness and antipsychotic treatment status (exposure status). Factors such as race, comorbidities, and medicines for other conditions like antidiabetic agents were less consistently adjusted. Additionally, the majority of the studies recruited small sample sizes.

Studies reporting intervention data were assessed against the domains specified by the JBI tools (Appendix III-C) for RCTs and non-RCTs studies. Information related to 'Population & setting' and 'Condition measurement' were presented for all studies. However, most studies did not adequately address unique items related to 'Randomisation & blinding', including allocation concealment. All studies did not adequately assess statistical aspects related to sample size estimation. Also, some critical aspects related to specific domains, such as the representativeness of the sample and appropriate measurement of condition, were not adequately reported across the studies. For the randomised controlled studies, details reflecting blinding were less consistently described. In addition, most studies did not analyse the outcomes on an intention-to-treat (ITT) basis. Also, many studies did not assess the confounding associated with treatment withdrawal. The quality appraisal for the studies included in the review was provided in Appendix III-D of this thesis.

3.4. Studies reporting prevalence data

3.4.1. Characteristics of the included studies

Twenty-two studies reported the prevalence of cardiometabolic abnormalities in people using antipsychotic drugs.(81-102) The majority's focus was on epidemiological interest. However, few studies had different aims, but the prevalence of cardiometabolic effects was reported. The studies were heterogeneous regarding the sample size, recruitment and data collection methods. Study general characteristics are provided in the appendices of the thesis. Almost in all studies, samples were driven from targeted practices such as psychiatric departments in general care facilities or specialised mental health clinics. The number of participants was enormously diverse across the studies, ranging from 100 to 1452 recruits.

Regarding the data collection methods, most studies obtained data by clinical and laboratory assessment (14/22) of participants. Few studies used other methods such as questionnaires filled by participants at the study site (3/22), medical history gathered from patients' records review (5/22), specific tools (1/22) and (1/22) recruited patients by contacting their cares. This is likely due to the challenges of collecting laboratory samples. Most studies did not report the status of diagnosed mental illness. The characteristics of participants of the studies reporting prevalence data are shown in Table Table 3-2 and Table. 3-3.

Table 3-2. Summary characteristics of the studies reported prevalence data

Study ID	Country	Sample			Methods			
		Aim	No. of participants	Age	Identification and recruitment	Data collection	Outcomes measures	Quality Rating
Hyun Kang. et al, 2015	Korea	Evaluation of metabolic among patients with schizophrenia treated with three different antipsychotic drugs.	957	18–65 years	Inpatients and outpatients visiting the psychiatric department at a general care hospital; primary data (patients)	Clinical and laboratory assessment along with medical history at the study site.	Different components of metabolic syndrome	Low
Vinberg et at,2012.	Denmark	To investigate the prevalence in a naturalistic cohort of the patient treated at a Mood Disorder Clinic	143	> 18 years	Outpatients visiting the mood disorder clinic at the psychiatric centre; primary data(patients)	Clinical and laboratory assessment along with current drug assessment obtained from patients' medical records.	Different components of metabolic syndrome	Low
Misawa et al, 2011.	Japan	Investigation of the relationships between antipsychotic polypharmacy and metabolic syndrome in outpatients with schizophrenia, with adjustment for the effects of lifestyle	399	> 18 years	Outpatients patients visiting general care hospital; primary data(patients)	A questionnaire filled by the participants	Different components of metabolic syndrome	Low
Yang et al, 2016.	Taiwan	to explore the prevalence of metabolic syndrome among patients with chronic schizophrenia	357	20 and 65 years	Inpatients from psychiatric rehabilitation units; primary data(patients)	Clinical and laboratory assessment at study site.	Biochemical Analysis Anthropometric Measurement Blood Pressure Measurement	Low

Study ID	Country	Sample			Methods			
		Aim	No. of participants	Age	Identification and recruitment	Data collection	Outcomes measures	Quality Rating
Coakley et al, 2012.	USA	Unclear	125	18-64 years	Patients information gathered by medical chart review; secondary data	Specific data tool was used to organize the collection of patient's relevant data that obtained from the medical records.	unclear	Low
Y. K. Ko et al, 2013.	Korea	To examine the prevalence of metabolic syndrome and its risk factors in a large group of schizophrenic patients.	1,103	18-65 years	Outpatients and inpatients attending national general healthcare hospital; primary data(patients)	Clinical and laboratory assessment at study site.	The prevalence of metabolic syndrome	Low
Shakeri et al, 2016	Iran	To determine the prevalence of metabolic syndrome in patients with schizophrenia	280	20-40 years	Patients referred to a general hospital; primary data(patients)	Questionnaire to be filled by participants along with clinical assessment	The prevalence of diabetes and hyperglycaemia	Low
Lamberti et al, 2006.	Not reported	To compare the prevalence of the metabolic syndrome in outpatients with schizophrenia and schizoaffective disorder treated with clozapine	93	25-70 years	Outpatients attending the medical centre at department of psychiatry; secondary data(patients records)	Clinical assessment and drug history was gathered from medical records	The prevalence of metabolic syndrome	Low
Chukwuma et al)	UK	To estimate the prevalence of metabolic syndrome in adults with serious mental disease treated with olanzapine or clozapine	815	19-44 years	Outpatients and inpatients from community sittings and long stay rehabilitation centres; secondary data(patients' medical records)	Survey	The prevalence of anthropometric measurement and blood testing in	Low

Study ID	Country	Sample			Methods			
		Aim	No. of participants	Age	Identification and recruitment	Data collection	Outcomes measures	Quality Rating
							patients taking antipsychotics	
Said et al, 2012.	Malaysia	To determine the prevalence of metabolic syndrome in patients with schizophrenia receiving antipsychotics	270	18–65 years	Outpatients from different sittings; 4 mental health centres, 2 military hospital and 2 general practice hospital; primary data(patients)	Clinical and laboratory assessment at the study sites.	Prevalence of patients with metabolic syndrome	Low
Bell et al, 2009.	USA	To identify and assess risk of metabolic along with exploring intervention options.	819	≥ 18 years	Patients from 15 community mental health centres; primary data(patients)	Clinical and laboratory assessment	Prevalence of patients metabolic syndrome	Low
Kim et al,2010.	Korea	To assess the prevalence and predominant factors of metabolic syndrome among psychiatric patients.	225	≥ 18 years	Patients from specialised psychiatric hospital; primary data (patients)	Clinical and laboratory assessment	Prevalence of patients with obesity, diabetes and hypertension	Low
Hägg et al,2006.	Sweden	To investigate the prevalence of MS	269	20–69 years	Outpatients and inpatients from a psychiatric clinic; primary data(patients)	Clinical assessment at the research department	Prevalence of patients metabolic syndrome	Low
Gardner-Sood et al, 2015.	UK	(1)To determine the prevalence of cardio-metabolic risks factors according to the International Diabetes Federation (IDF) criteria for the MS.	450	18 - 65 years	Outpatients from 5 community mental health centres; primary data (patients' medical records)	Patients recruited through their care-coordinator	Prevalence of pateints with metabolic syndrome elements	Low

Study ID	Country	Sample			Methods			
		Aim	No. of participants	Age	Identification and recruitment	Data collection	Outcomes measures	Quality Rating
		(2) To identify lifestyle factors that associated with risk of the MS. (3) To investigate association between illness severity and presence of the metabolic syndrome						
Arango et al, 2008.	Spain	To compare clinical, laboratory, lifestyle, and sociodemographic parameters and cardiac risk in antipsychotic-treated patients with and without metabolic syndrome	1452	18–74 years	Outpatients from different psychiatric centres ;primary data (patients)	Clinical and laboratory assessment	Prevalence of pateitns with metabolic syndrome elements	Good
Pallava et al, 2012.	India	Assess the prevalence of MS in schizophrenia and related disorders and its correlation with various demographic, clinical and treatment variables	100	18 – 40 years	Outpatients attending a psychiatric community centre ;primary data(patients)	Clinical and laboratory assessment at the study site	Prevalence rate of patients with cardiometabolic risks factors	Low
Grover et al, 2012.	India	To estimating the prevalence and predictors of metabolic syndrome in patients with schizophrenia	458	≥ 18 years	Inpatient and outpatient form a psychiatry clinic at multi-specialty tertiary-care hospital; primary data(patients)	Clinical and laboratory assessment at the study site.	Prevalence of metabolic syndrome	Low

Study ID	Country	Sample			Methods			
		Aim	No. of participants	Age	Identification and recruitment	Data collection	Outcomes measures	Quality Rating
Owusu–Ansah et al, 2018.	Australia	To determine the prevalence of MS in patients with schizophrenia	348	≥ 18 years	Outpatients from psychiatric department at general care hospital; primary data (patients)	Clinical and laboratory assessment at the research department.	The prevalence of patients with metabolic syndrome	Low
Miller et al, 2005.	USA	To compare the prevalence of diabetes mellitus/hyperglycaemia between patients receiving treatment with clozapine and patients receiving treatment with depot neuroleptics.	Clozapine (n=24) and patients receiving treatment with depot (n=27) neuroleptics	27-59 years	Participants information from medical records of patients attending a Veterans Affairs mental health clinic; secondary data (patients records)	Medical record review	Prevalence of patients with diabetes	Fair
Argo et al, 2011	USA	To estimate prevalence of T2DM	192 participants	≥ 18 years	Outpatients from an Adult Psychiatry Clinic at University of Iowa Healthcare; primary data (patients)	Clinical and laboratory assessment at the research department.	Prevalence of patients with cardiovascular risk factors	Low
Zhang et al, 2011.	China	To examine the prevalence and correlates of diabetes in a large sample of Chinese patients with schizophrenia on long-term clozapine treatment	206 patients	25-70 years	Not reported	Patients medical records	Prevalence of patients with metabolic syndrome	Low
Deuschle et al, 2013.	Germany	To analyse screening for metabolic disorders in German patients with schizophrenia spectrum	674 patients	≥ 18 years	Not reported	Patients electronic health records		Low

Study ID	Country	Sample			Methods			
		Aim	No. of participants	Age	Identification and recruitment	Data collection	Outcomes measures	Quality Rating
		disorders in routine psychiatric care						

Table.3-3. Clinical characteristics of the participants among studies included in the prevalence synthesis.

Study ID	Quality rating	Diagnosed mental illness	The course of mental illness	Prescribed psychotropic drugs	Duration of antipsychotic use	Treatment regimen
Owusu–Ansah et al, 2018.(81)	Low	Not specific	Severe and persistent mental illness	APs (non specified)	Drug naïve Chronic users: < 3 months 23(10%) 3 -8 months 44(19%) 9 – 12 months 48(20%) >12 months 121 (51%)	NR
Shakeri et al, 2016. (82)	Low	SCZ	NR	APs (non specified)	NR	NR
Yang et al, 2016 .(83)	Low	SCZ	NR	APs (non specified)	NR	NR
Gardner-Sood et al, 2015.(84)	Low	SCZ,SCZA ,BPAD	NR	APs (non specified)	NR	Combined antipsychotics
Hyun Kang. et al, 2015. (85)	Low	SCZ,SCZA	NR	SGAs	NR	Monotherapy
Deuschle et al, 2013. (86)	Low	SCZ	NR	APs (non specified)	NR	NR
Y. K. Ko et al, 2013. (87)	Low	SCZ	NR	Olanzapine & quetiapine	Current antipsychotic users	Monotherapy and combined therapy
Coakley et al, 2012. (88)	Low	SCZ	NR	APs (non specified)	NR	NR
Grover et al, 2012.(89)	Low	SCZ	NR	APs (non specified)	NR	Monotherapy and combined therapy
Said et al, 2012.(90)	Low	SCZ	NR	Olanzapine & quetiapine	Treatment for at least one year	Monotherapy
Pallava et al, 2012.(91)	Low	SCZ	NR	APs (non specified)	NR	NR
Vinberg et at,2012.(92)	Low	SCZ	NR	APs (non specified)	NR	Monotherapy and combined therapy

Study ID	Quality rating	Diagnosed mental illness	The course of mental illness	Prescribed psychotropic drugs	Duration of antipsychotic use	Treatment regimen
Argo et al, 2011. (93)	Low	SCZ	Current diagnosis of schizophrenia	SGAs	NR	NR
Zhang et al, 2011 .(94)*	Low	SCZ	Chronic ≥ 5 years	Clozapine	Chronic use of clozapine ≥ 12months	NR
Misawa et al, 2011.(95)	Low	SCZ	NR	APs (non specified)	NR	Monotherapy and combined therapy
Kim et al,2010.(96)	Low	SCZ	NR	APs (non specified)	≥ 3 months	NR
Bell et al, 2009.(97)	Low	SCZ	NR	SGAs	NR	NR
Arango et al, 2008.(98)	Good	SCZ	NR	APs (non specified)	136.4 weeks ± 210.1 ≈ 34.1 months: > 12 months	Monotherapy
Chukwuma et al,2008.(99)	Low	SCZ	Serious mental illness	Quetiapine Aripiprazole Amisulpride Paliperidone Olanzapine Risperidone Haloperidol Clozapine	NR	Monotherapy and combined therapy
Hägg et al,2006.(100)	Low	SCZ	NR	Clozapine	NR	Monotherapy and combined therapy
Lamberti et al, 2006.(101)	Low	SCZ	NR	Clozapine	NR	NR
Miller et al, 2005.(102)	Fair	SCZ	NR	Clozapine: 24 Depot haloperidol decanoate: 9 Fluphenazine decanoate:18	11-105 months. Average duration of depot use: 98 months.	Monotherapy

Keynotes: *study did not assess metabolic syndrome. Abbreviations: SCZ: schizophrenia, SCZA: schizoactive disorder, SGAs: Second-generation antipsychotic drugs, APs: antipsychotic drugs, NR: not reported.

In general, it was difficult to estimate the prevalence rate of cardiovascular and metabolic side effects caused by different antipsychotic agents across the studies. As most studies did not provide sufficient information regarding the prevalence rate of cardiometabolic abnormalities associated with each drug. Some studies investigated the prevalence of cardiometabolic side effects among certain antipsychotic drugs, namely, clozapine (94,100–102) and olanzapine.(87,90)

The nature of the treatment regimen was not clearly defined in 54% of the studies. The remaining studies provided information regarding the antipsychotic regimens (84,85,102,87,89,90,92,95,98–100); however, only one study reported the prevalence of metabolic side effects between different antipsychotic regimens (monotherapy against combined therapy).(95) Several studies attempted to isolate the effects of different antipsychotic drugs by recruiting patients treated with only one antipsychotic drug. (87,90,94,99–102)

3.4.2. Prevalence of metabolic syndrome (MS) associated with antipsychotic medications

Nearly all the included studies reported the prevalence of metabolic syndrome (MS).(81,82,95,96,98–101,83–86,89–92) The assessment of metabolic syndrome components was performed using different diagnostic criteria (Appendix III-F), mostly according to the Adult Treatment Panel (ATP)-III criteria for metabolic syndrome. The reported prevalence of MS across the studies is described in Table 3-4.

Table 3-4. Summary results for the prevalence estimates of subjects who fulfilled the criteria of metabolic syndrome by antipsychotics (number of studies=18).

Study ID	Total sample: n	Antipsychotic	Prevalence of metabolic syndrome (MS)	
			Defining criteria	n (%)
Hyun Kang. et al, 2015.(85)	Total: 174	CLZ/OLZ/ QUET:61	ATP-III	CLZ/OLZ/ QUET :35(57%)
		RIS:89		RIS : 24(27%)
		ARIP/ZIPR:24		ARIP/ZIPR :6(25%)
Deuschle et al, 2013. (86)	674 Male:387 Female: 287	APs (non specified)	ATP-III	Male: 151 (39%) Female:181 (63%)
Vinberg et at,2012.(92)	100	APs (non specified)	ATP III	27(27%)
Misawa et al, 2011.(95)	Total: 334	APs monotherapy (non specified) APs polypharmacy:167 (non specified)	The Japanese Committee of the Metabolic Syndrome Diagnostic Criteria	APs monotherapy:74(22%) Polypharmacy: 39(57%)
Yang et al, 2016.(83)	357	APs (non specified)	ATP-III	135(38%)
Coakley et al, 2012.(88)	125	APs (non specified)	ATP-III	21(17%)
Y. K. Ko et al, 2013.(87)	1,103	APs (non specified)	ATP-III IDF	ATP-III: 485 (44%) IDF: 441 (40%)
Shakeri et al, 2016.(82)	280	SGAs Olanzapine Risperidone Quetiapine	ATP-III	Total prevalence: 85(30%) 45 (17%) 9(3%) 31(11%)
Lamberti et al, 2006.(101)		Clozapine	ATP-III	95(53%)
Chukwuma et al,2008.(99)	815	AP monotherapy: 376 Quetiapine: 16 Aripiprazole: 41 Amisulpride :18 Paliperidone: 39 Olanzapine: 46 Risperidone :100 Haloperidol: 32 Clozapine: 46	ATP-III	Total prevalence: 307 (37%) quetiapine:3(18%). Aripiprazole: 9 (22%) Amisulpride: 6(33%) Paliperidone: 13(33%) Olanzapine: 16(34%) Risperidone: 35(35%) Haloperidol: 12(39%) Clozapine:21 (45%)
Said et al, 2012.(90)	270	APs (non specified)	ATP-III	126 (47%)
Kim et al,2010.(96)	225	APs (non specified)	ATP-III	77 (34%)
Hägg et al,2006.(100)	269	APs (non specified)	ATP-III	94 (35%)
Gardner-Sood et al, 2015.(84)	450	APs (non specified)	IDF & ATP-III	Total prevalence: 308 IDF :175 (57%) ATP-III :173 (56%)
Arango et al, 2008.(98)	1,452	APs (non specified)	ATP-III	357(24%)
Pallava et al, 2012.(91)	100	APs naïve (control) APs users (treatment)	ATP-III	Control: 13 (26%) Treatment: 25 (50%)

Study ID	Total sample: n	Antipsychotic	Prevalence of metabolic syndrome (MS)	
			Defining criteria	n (%)
Grover et al, 2012.(89)	227	APs (non specified)	ATP-III IDF	ATP-III: 101 (45%) IDF: 98 (43%)
Owusu–Ansah et al, 2018.(81)	Total: 348	APs users (treatment) APs naïve (control)	ATP-III WHO IDF	**Treatment group:** ATP-III: 42(18%) WHO: 62(26%) IDF: 71(30%) **Control group:** ATP III:7(6%) WHO :9 (8%) IDF: 11(10%)
		SGAs group FGAs group	ATP-III WHO IDF	**SGAs group** ATP-III: (17%) WHO: (30%) IDF: (44%) **FGAs group** ATP-III: (11%) WHO: (26%) IDF: (19%)

Abbreviations: APs: antipsychotic drugs; SGAs: second-generation antipsychotic drugs; IDF: International Diabetes Federation; NCEP ATP III: The US National Cholesterol Education Programme Adult Treatment Panel III; WHO: World health organisation; NR: not reported; GP: group, n: the absolute number of patients reported by each study.

Most of the identified studies that reported the prevalence of cardiometabolic side effects of antipsychotics aimed to identify the prevalence of patients who fulfilled the criteria of MS. Yet, the study by Misawa (95) reported that nearly 20% (n=61/334) of the patients fulfilled two criteria of MS, which were defined as pre-metabolic syndrome group. The prevalence of diagnosed metabolic syndrome in individuals with SMI varied according to the classification criteria used for MS in the included studies. The overall prevalence of MS in the studies ranged from 10.9 to 86.7%, but seems to far exceed that of the general population.(81,91) The prevalence of MS was also higher among chronically treated antipsychotics (18%-50%) compared to the drug naïve users (6%-26%). Notably, these studies did not provide clear information regarding the adequacy of the used sample size in reference to the outcome measures. Small samples are likely to exaggerate the effect estimates of the outcomes. However, the relatively small samples used in these studies can be justified by the data collection strategy used in the studies, as both studies used primary patients' data, which can have a limited sample size. Although primary data is characterised

by accuracy and reliability, collecting primary data can be time-consuming, which yields a small sample. Besides, the lack of details related to the quality elements such as details related to data collection and participant recruitment may affect the representativeness of the study sample and hence the study validity (Appendix III-D).

Few studies compared the prevalence of MS and its components between individual antipsychotic drugs.(82,85,99,101) Yet only one study provided head-to-head comparisons among the SGAs.(85) Among the reported antipsychotics, clozapine and olanzapine were commonly associated with a high prevalence of metabolic syndrome regardless of the used definition. The overall quality of the studies reporting MS prevalence across different antipsychotics was low with major methodological concerns related to the study sampling (e.g., small size and lack of sample representativeness). Although the studies used primary patients' data and measured their outcomes using standardised techniques, none of the studies provided sufficient information regarding the power of the sample size. The small sizes in these studies are likely to exaggerate the estimated prevalence.

One study (95) that was assessed to be of low methodological quality (due to issues relating to sample representativeness) reported the effect of antipsychotic polypharmacy on the rate of prevalence of metabolic syndrome. The prevalence of MS was higher in the polypharmacy compared to the monotherapy group regardless of the used definition (57% vs 22%) respectively. However, the small size used by the authors and the data collection technique limits the generalisability of the findings.

3.4.3. Individual cardiometabolic side effects of antipsychotic drugs reported across the studies

Most studies reported the diagnostic features of metabolic syndrome including weight gain(85-89,92-95), dyslipidaemias(82,85-88,92,93), glucose disturbances (82,86-88,92-94)

,and elevated blood pressure.(82,85-88,92,93) Few studies addressed the prevalence rate of cardiometabolic side effects across different antipsychotics. Estimating the prevalence rate of cardiometabolic side effects caused by different antipsychotic agents was difficult due to the variations in the sample sizes across the studies. The reported variations in the cardiometabolic prevalence may have resulted from the differences in the diagnostic criteria for MS applied by different studies.

3.4.3.1. Studies reporting the prevalence of obesity (number of studies=13)

Increased body weight was the most reported.(82,83,94,95,99,85–90,92,93) The data related to weight gain and obesity were heterogeneous. Obesity was mostly reported as central obesity (82,83,85–88,92,93,95), while few studies reported changes in BMI in antipsychotic users.(89,90,94,99) The overall prevalence of weight gain reported across the studies ranged from 8-65% for central obesity and 13-76% for elevated BMI scores. This apparent inconsistency of the reported weight gain prevalence was mostly related to the differences in the patients and the measurements of outcomes across the studies.

In this review, most studies reporting the prevalence of cardiometabolic side effects utilised the ATP-III as the defining criteria to measure the prevalence of MS, which defines the diagnosis of MS based on the presence of central obesity. Similarly, the definition of obesity varied across the studies. For example, one study (85) did not specify the reported obesity element despite it aimed to assess the prevalence of MS. Another study reported the prevalence of central obesity as the number of patients experiencing a raise waist-to-hip ratio.(93) In the studies that compared the prevalence across different antipsychotics, the prevalence of central obesity was high among patients treated with second-generation antipsychotics with high metabolic risks such as clozapine and olanzapine and

quetiapine.(85) The confounding effects of associated cardiometabolic risks among different antipsychotics in the studied samples were less clearly described.

In general, the methodological quality of the studies reporting obesity outcomes (high BMI and WC) was low (Appendix III-C1). Study quality was compromised based on study sampling, in particular, a small sample size. Considering the small size, except for few studies (86,94,99), all studies relied on primary data (the information on drug exposure and outcomes are collected directly by the researchers as a data source). Although the data gathered from primary sources are more accurate and reliable, collecting such data can be demanding and time-consuming, which can limit the obtained sample size. However, the studies that used primary data failed to provide transparent sample size calculations. The studies also failed to provide information reflecting the recruitment process and participants' response rate, which can further mask details regarding the appropriateness of the used sample size, limiting the precision and the external validity of the findings.

Also, few studies provided stratified samples (89,90), in which the prevalence of obesity was reported in samples of different obesity levels, however, no statistical attempts were made to adjust the associated risks of bias. Additionally, the estimated prevalence was not reported along with their corresponding confidence intervals, which raises concerns regarding the precision and representativeness of the findings. Furthermore, it is worth noting that most studies did not compare the prevalence of cardiometabolic side effects against a control group (comparator). Even where a comparator was used, sample sizes were generally small across the studies. The results of these studies are summarised in Table 3-5.

Table 3-5. Summary results of the weight gain associated with antipsychotic drugs reported across the studies (number of studies=13)

The reported prevalence of central obesity (WC)			
Study ID	**Variable reflecting weight gain**	**Total sample size: n**	**Prevalence of central obesity:n (%)**
Shakeri et al, 2016.(82)	Elevated WC	280	30 (11%)
Yang et al, 2016.(83)	Elevated WC	357	222 (62%)
Hyun Kang et al, 2015.(85)	Obesity (nonspecific)	Total: 174 CLZ/OLZ/QUIT:61	CLZ/OLZ/QUIT:8 (13%)
		RIS:8	RIS: 9(10%)
		ARIP/ZIPR:24	ARIP/ZIPR: 2(8%)
Deuschle et al, 2013.(86)	Elevated WC	674 Male: 387 Female: 287	Male:143(37%) Female:178(62%)
Y. K. Ko et al, 2013.(87)	Elevated WC*	1,103	713(65%)
Coakley et al, 2012.(88)	Elevated WC	125	36(29%)
Vinberg et at,2012.(92)	Elevated WC	100	55 (55%)
Argo et al, 2011.(93)**	Waist-to-hip ratio >1.0	192	48 (25%)
Misawa et al, 2011.(95)	Elevated WC	Total: 399 AP polypharmacy:167	176 (53%) AP polypharmacy: 25(61%)
The reported prevalence of elevated body mass index (BMI) score			
Study ID	**Variable reflecting weight gain**	**Total sample size: n**	**Prevalence of elevated BMI: n (%)**
Grover et al, 2012.(89)	Elevated BMI score	458	BMI ≥25:70(74%) BMI≥30 :22(22%)
Said et al, 2012.(90)	Elevated BMI score	270	126 BMI ≥25: 50(40%) BMI≥30: 51(41%)
Zhang et al, 2011.(94)	Elevated BMI score	Test: 206 Control: 615	
		BMI 24–28 Test: 71 Control: 230	Test: 16 (23%) Control: 14(6%)
		BMI>28: Test: 52 Control:134	Test:19 (37%) Control: 15(11%)
Chukwuma et al,2008.(99)	Elevated BMI score	842	417 (50%)

Table keynotes: Elevated WC: WC ≥ 102 cm (40 in.) for men, 88 cm (35 in.) for women;* (Asian cut-off) WC ≥90 cm in males; ≥80 cm in females. ** the study did not assess metabolic syndrome. Abbreviations: BMI: body mass index, WC: waist circumference, AP: antipsychotic drugs, NR: not reported, CLZ/OLZ/QUIT: Clozapine/olanzapine/ Quetiapine, RIS: Risperidone, ARIP/ZIPR: Aripiprazole/ziprasidone, n: the absolute number of patients reported by each study.

3.4.3.2. Prevalence of disturbed glucose haemostasis across the studies (number of studies=12)

Twelve studies (82,83,99,102,85–88,92–95) reported the prevalence of glucose abnormalities, including diabetes, in antipsychotic users. The Overall prevalence of glucose disturbance varied across the studies. The observed variations might have resulted from the differences in the applied definition of glucose disturbance and the presence of diabetes among study subjects.(87,93,102) Also, some of the studies compared the prevalence of hyperglycaemia across different antipsychotics. The comparisons were made mostly between antipsychotic agents with known metabolic risks. For example, among the antipsychotics evaluated, clozapine, olanzapine and risperidone were reported with the highest rate of glucose level abnormalities.(85,93) One study provided a stratified sample in which subjects were classified by age group.(94) Also, one study investigated the prevalence of diabetes in clozapine users using two different antipsychotic formulas.(102)

It is worth noting that the outcome definition for hyperglycemia varied across the studies. Most of the identified studies defined hyperglycemia as an existing diagnosis of hyperglycemia or diabetes, except for the study by Y. K. Ko (87) which reported the prevalence of patients who experienced elevated blood glucose during antipsychotic use. Also, the study by Miller (102), explored the prevalence of new cases of hyperglycemia among patients using clozapine and depot formula, where 5% of the clozapine users developed diabetes. Measuring the incidences of cardiometabolic side effects after starting the antipsychotic therapy would be more informative.

While the majority of studies included patients as young as 18 years old, one study (94) reported the prevalence across different age groups. According to Zhang (94) (low-quality study), older people (>55 years) were reported to have a higher prevalence of hyperglycemia

(27%-62%) compared to younger people (19%). It is worth noting the sample size used for this study was small (n=209) and no information regarding the appropriateness of the sample size was available, which was critical since a sub-group analysis was conducted by the study. The prevalence of diabetes or impaired glucose level associated with antipsychotic drugs can be found in Table 3-6.

Table 3-6. Summary results of the prevalence of impaired glucose level reported across the studies (number of studies=12)

Study ID	Variables reflecting disturbed blood glucose level	Total sample	Prevalence of hyperglycemia; n (%)
Shakeri et al, 2016.(82)	Elevated FBG*	280	26 (9%)
Yang et al, 2016 .(83)	Elevated FBG*	357	101 (28%)
Hyun Kang. et al 2015. (85)	Hyperglycaemia	Total: 174 CLZ/OLZ/QUIT:61 RIS:89 ARIP/ZIPR:24	CLZ/OLZ/QUIT *:19(32%) RIS: 10(11%) ARIP/ZIPR:4(16%)
Y.K.Ko et al, 2013. (87)	Elevated FBG*	1,103	271(25%)
	New cases DM		116 (11%)
Deuschle et al, 2013. (86)	Elevated FBG*	674 Male: 387 Female: 287	 Male (23%) Female (31%)
Coakley et al, 2012.(88)	Elevated FBG*	125	34 (27%)
Vinberg et at,2012. (92)	Elevated FBG*	100	20 (20%)
Argo et al, 2011. (93)	Random glucose >120 mg/dl	192	50 (26%)
	New cases of DM		22 (12%)
Misawa et al, 2011.(95)	Elevated BG (non-specific)	Total: 334 APs polypharmacy:167 (50%)	92 (28%) APs Polypharmacy:55(33%)
Zhang et al, 2011.(94)	Elevated FBG*	Test: 206 Control: 615	
		35–44 years Test:43 Control: 121	 Test: 8 (19%) Control: 2(12%)
		45–54 years Test:80 Control: 254	 Teat: 15 (19%) Control: 19 (8%)
		55–64 years Test:55 Control:141	 Test: 15 (27%) Control:13 (9%)
		>65 years Test:13 Control:48	 Test: 8 (62%) Control:4 (8%)
Chukwuma et al,2008.(99)	Elevated FBG*	815	295 (35%)
Miller et al, 2005.(102)	New cases of hyperglycemia/DM	Clozapine group: 18 Patients on depot neuroleptic: 21	New cases of hyperglycemia/diabetes in clozapine group: 5(28%) New cases of hyperglycemia/diabetes in depot group: 0

Table keynotes* Elevated FBG: (≥100 mg/dl or current ongoing treatment). Abbreviations: FBG: fasting blood glucose, DM: diabetes mellitus, CLZ/OLZ/QUIT: Clozapine/olanzapine/ Quetiapine, RIS: Risperidone, ARIP/ZIPR: Aripiprazole/ziprasidone, n: the absolute number of patients reported by each study.

3.4.3.3. Prevalence of dyslipidaemias reported across the studies (number of studies=10)

Ten studies (82,83,85–88,92,93,95,99) reported the prevalence of abnormal lipid profiles. The outcome measures for dyslipidaemia varied across the included studies. Despite the various definitions used, disturbed lipid profile was prevalent among antipsychotic users. Table 3-7 shows the prevalence of abnormal lipid profiles across the studies.

Table 3-7. Summary results for the prevalence of dyslipidaemias reported across the studies (number of studies=10)

Study ID	Variables reflecting dyslipidaemias	Total sample	Prevalence of dyslipidaemias; n (%)
Shakeri et al, 2016. (82)	Low HDL (< 50 mg/dl) TGs > 110(mg/dl)	280	121(43%) 71(25%)
Yang et al, 2016.(83)	TGs ≥ 150 mg/dl or on lipid-lowering medication	357	120 (34%)
	low HDL level**		170 (48%)
Hyun Kang et al,2015.(85)	TGs ≥ 150 mg/dl (1.69 mmol/L) or on lipid-lowering medication	Total: 174 CLZ/OLZ/QUIT:61 RIS:89 ARIP/ZIPR:24	CLZ/OLZ/QUIT:32(52%) RIS: 21(24%) ARIP/ZIPR:6(25%)
	Low HDL level**	Total: 174 CLZ/OLZ/QUIT:61 RIS:89 ARIP/ZIPR:24	CLZ/OLZ/QUIT:31 (51%) RIS:35 (39%) ARIP/ZIPR:5 (21%)
Deuschleet al, 2013.(86)	TGs ≥ 150 mg/dl (1.69 mmol/L) or on lipid-lowering medication	674 Male: 387 Female: 287	Male (41%) Female (34%)
	Low HDL level < 50 mg/dl	674 Male: 387 Female: 287	Male (38%) Female (35%)
Y. K. Ko et al, 2013. (87)	Existing diagnosis of dyslipidaemia	1,103	673(61%)
	Low HDL level **		534(48%)
	TGs ≥ 150 mg/dl (1.69 mmol/L) or on lipid-lowering medication		486(44%)
Coakley et al, 2012. (88)	Low HDL level **	125	44(35%)
	TGs ≥ 150 mg/dl (1.69 mmol/L) or on lipid-lowering medication		46(37%)
Vinberg et at,2012. (92)	TGs ≥ 150 mg/dl or on lipid-lowering medication	100	40(40%)
	Low HDL level **		24(24%)
Argo et al, 2011. (93)	Hyperlipidaemia (non-specific)	192	50 (26%)
Misawa et al, 2011.(95)	Hyperlipidaemia (non-specific)	Total: 334 AP polypharmacy:167 (50%)	138 (41%) AP polypharmacy (NR)
Chukwuma et al,2008.(99)	TGs ≥ 150 mg/dl or on lipid-lowering medication Low HDL level **	815	320 (38%) 357 (42%)

Table keynotes: ** Low HDL level < 40 mg/dl (1.04 mmol/L) men, < 50 mg/dl (1.29 mmol/L) women. Abbreviations: HDL: High-density lipoprotein, LDL: low-density lipoprotein; TGs: triglycerides; CLZ/OLZ/QUIT: Clozapine/olanzapine/ Quetiapine, RIS: Risperidone, ARIP/ZIPR: Aripiprazole/ziprasidone, AP: antipsychotics, NR: not reported; n: the absolute number of patients reported by each study.

Most of these studies reported a reduced level of high-density lipoprotein (HDL) and increased triglycerides (TGs) levels.(82,85-88,92) However, it would be challenging to determine if the reported prevalence was increasing or decreasing due to the significant variations in the study sizes and none of the studies provided information regarding the adequacy of the used samples. One study reported differences in the negative changes in lipid profiles among the users of different antipsychotic drugs.(85) The study results reported that subjects treated with clozapine or olanzapine or quetiapine experienced a significant increase in serum lipids. In contrast, the lowest prevalence range of dyslipidaemia was observed among subjects treated with aripiprazole or ziprasidone (N=6, 25%). However, the quality of that study was considerably low since the major quality features related to the study sample such as the appropriateness of the sample size and the suitability of the data collection and analysis were not properly described. Also, the small sample size used in the study (total size=174) may be associated with an overestimation of the reported cardiometabolic prevalence among the different antipsychotics leading to uncertainty of the estimated prevalence and the generalisability of the findings.

3.4.3.4. Prevalence of elevated blood pressure reported across the studies (number of studies=10)

Ten studies documented elevated blood pressure in subjects treated with antipsychotic medications. (82,83,85–88,92,93,95,99) The reported range varied across the studies, with a rate as low as 19% (88) among psychiatric patients to a high rate of 52% (85) among patients treated mainly with clozapine and quetiapine. Some studies (86,92) reported the prevalence of hypertension and gender differences when treated with antipsychotic drugs, where the prevalence rate of hypertension tended to be higher among males than females. Almost in all studies, the type of antipsychotic medications used was not specified, except for a few

studies. A head-to-head comparison of the prevalence of elevated blood pressure among different antipsychotics was reported in one study.(85) Elevated blood pressure was more prevalent in subjects treated with clozapine or olanzapine, or quetiapine.(85) Among the studies reporting clustered results (85,86,92) (low-quality study), the sample size used by the different studies was relatively small while lacking information related to the adequacy of the used samples which led to a compromised validity of the estimated prevalence. The prevalence of antipsychotic-induced hypertension is presented in Table 3-8.

Table 3-8. Prevalence of elevated blood pressure was reported across the studies (number of studies= 10)

Study ID	**Variable**	**Total sample: n**	**Prevalence of elevated blood pressure; n (%)**
Deuschle et al, 2013. (86)	Hypertension**	674 Male: 387 Female: 287	 Male (35%) Female (21%)
Vinberg et at, 2012. (92)	Hypertension**	100	41(41%)
Shakeri et al, 2016. (82)	Hypertension**	280 Male: 193 Female: 87	28(10%)
Yang et al, 2016.(83)	Hypertension**	357	144 (40%)
Hyun Kang et al,2015.(85)	Hypertension**	Total: 174 CLZ/OLZ/ QUET:61 RISP:89 ARIR/ZIPR:24	 CLZ/OLZ/QUET: 31(51%) RISP: 32(36%) ARIR/ZIPR:7 (29%)
Y. K. Ko et al, 2013.(87)	Hypertension**	1,103	441(40%)
Coakley et al, 2012.(88)	Hypertension**	125	9(19%)
Argo et al, 2011.(93)	Hypertension**	192	45(23%)
Misawa et al, 2011.(95)	Hypertension**	334 AP polypharmacy:167 (50%)	105 (37%) AP polypharmacy: 43 (26%)
Chukwuma et al,2008.(99)	Hypertension**	815	321 (38%)

Table keynotes: ** (SBP ≥130 mmHg, DPB ≥85 mmHg, or current ongoing treatment). Abbreviations: CLZ/OLZ/QUIT: Clozapine/olanzapine/ Quetiapine, RIS: Risperidone, ARIP/ZIPR: Aripiprazole/ziprasidone, AP: antipsychotics, n: the absolute number of patients reported by each study.

3.4.4. Studies reporting cardiometabolic side effects and polypharmacy

Only one identified study attempted to address the effect of polypharmacy antipsychotic use on the prevalence rate of metabolic syndrome.(95) Misawa and colleagues (95) reported that the prevalence of metabolic syndrome elements was higher among subjects treated with multiple antipsychotic drug regimens compared to subjects treated with a single agent except for the criteria of elevated blood pressure. The poor quality of the study (95), which was mainly due to the small sample size used limits the confidence to make a definitive conclusion regarding the prevalence of cardiometabolic side effects associated with antipsychotic polypharmacy. In addition, the study relied on self-reported patient outcomes using a questionnaire completed by the patients which compromised the validity of the findings.

3.5. Studies reporting interventions targeting cardiometabolic side effects of antipsychotic drugs

Of the 55 articles reporting quantitative evidence, 34 investigated interventions to mitigate cardiometabolic side effects among people using antipsychotic drugs. The studies were classified into pharmacological (103-122) and non-pharmacologic approaches.(123-135) Two studies (136,137) investigated the combined approaches (pharmacological and non-pharmacological approaches). The aim of the interventions was not clearly stated across the studies, yet few aimed to either treat or prevent antipsychotic-induced weight gain.

3.5.1. Studies reporting pharmacological approaches (N=21)

In total, ten different pharmacological agents were identified. Pharmacological approaches involve drugs that affect certain metabolic elements such as lipid profiles or body compositions. The drugs were divided according to their metabolic regulating effects into five categories: metabolic modulators and antidiabetic agents, weight-losing drugs,

psychotic drugs and miscellaneous agents. Most pharmacological agents were used as monotherapy or adjunctive treatment to existing antipsychotic therapy.

The majority of the studies were undertaken amongst clozapine and olanzapine users and one study (111) investigated the effects of the intervention among risperidone users. The cardiometabolic side effects of these drugs may differ and hence the outcomes of the interventions. Similarly, some strategies aimed to prevent cardiometabolic-induced antipsychotics in patients with the first episode of psychosis. Other studies investigated the treatment of cardiometabolic-induced antipsychotics. The response may be different in these two groups.

Most studies targeted weight gain among people using antipsychotic drugs, however; findings related to changes in body compositions differed widely across studies, but the majority measured changes in body weight and BMI. Measurements for central obesity (e.g., WC) were commonly reported with the BMI but no study focused solely on central obesity. Some studies defined the cut-off point of weight loss as ≥ 5% changes in body weight, and others defined it as a≥ 7% reduction. In addition, other cardiometabolic outcomes were assessed, like glucose haemostasis and plasma lipids. A detailed summary and description of the identified pharmacological interventions are provided in the additional files (Appendix III-E &F).

3.5.1.1. Summary of studies reporting the effectiveness of pharmacologic interventions

The overall reported effect size was relatively small across the studies. Few studies reported clinically relevant weight loss, which was defined differently. Registered agents such as metformin(103–108), orlistat (109,110), mifepristone (111), liraglutide (112) and antipsychotic drugs with neutral cardiometabolic mainly, aripiprazole (113–115), ziprasidone

(113,116), amisulpride (117), atomoxetine (118), and modafinil (119) demonstrated various effect on the different cardiometabolic outcomes.

a. Metabolic modulators and antidiabetic agents (N=6)

Among the identified drugs, metformin was the most investigated agent.(103–108) All the studies on metformin were conducted on patients prescribed clozapine or olanzapine, yet the treatment course was not clearly defined except in one study (103) which recruited participants on chronic clozapine therapy (≥ 3 months). Mostly, metformin showed some effectiveness against antipsychotic-inducing weight gain (Table 3-9).

Table 3-9. Reported outcomes in studies assessed the effect of pharmacologic interventions on cardiometabolic side effects of antipsychotic drugs; metformin (number of studies=6). Data are presented as mean ±SD unless otherwise stated. Values in bold represent significant results

Study ID	Metformin (low dose: 500 mg/day vs high dose: 1000mg/day)					
	Quality rating	**Variable**	**Intervention**	**Duration**	**Change from baseline/ Δ**	**% analysed**
Chiu, et al 2016.(103)	Fair State double-blinded but no information about the assessor nor care provider blinding.	Body weight (kg)	Metformin	12 weeks	**Low Dose** Baseline: 62.8 ±9.7 Endpoint: **62.1±10.7** **High Dose** Baseline: 69.7 ±9.4 Endpoint**: 68.7±8.9***	100%
			Placebo		**Baseline:** 71.1 ±10.4* **Endpoint:** 71.0 ±10.8	
		BMI score	Metformin		**Low Dose** Baseline: 24.6 ±3.5 Endpoint: **23.9±3.6*** **High Dose** Baseline: 26.6 ±3.2 Endpoint: **26.1±3.0***	
			Placebo		**Baseline:** 26.7 ±3.8 **Endpoint:** 26.4 ±3.7	
		WC (cm)	Metformin		**Low Dose** Baseline: 88.7 ±9.3 Endpoint: 87.5 ±10.0 **High Dose** Baseline: 93.6 ±8.6 Endpoint: 91.4 ±10.6	
			Placebo		**Baseline:** 94.4 ±8.2 **Endpoint:** 93.3 ±8.5	
		TGs(mg/dl)	Metformin		**Low Dose** Baseline: 127.1±99.9 Endpoint: 123.5±76 **High Dose**	

					Baseline: 131.4±73.8 Endpoint**:** 140.6 ±70.4	
			Placebo		**Baseline:** 148.1 ±82.0 **Endpoint:** 145.3 ±66.8	
		HDL (mg/dl)	Metformin		**Low Dose** Baseline: 51.7±12.9 Endpoint: 48.3±10.1 **High Dose** Baseline: 53.9±15.1 Endpoint**:** 52.6±19.2	
			Placebo		Baseline: 43.9±12.4 Endpoint: 43.0±10.7	
		FPG,(mg/dl)	Metformin		**Low Dose** Baseline: 104.4±10.6 Endpoint: 103.4±7.5 **High Dose** Baseline: 106.4 ±11.7 Endpoint**:** 105.1±13.5	
			Placebo		**Baseline:** 44.9 ±12.4 **Endpoint:** 43.0 ±10.7	
Study ID	**Metformin**					
Wang, et al 2012. (104)	**Quality rating**	**variable**	**intervention**	**duration**	**change from baseline/ Δ**	**% analysed**
	Low No information about the randomisation and concealment process	Body weight (kg)	Metformin	8 weeks	Baseline: 65.2 ±5.5 Endpoint: **62.1±10.7**	66/72 (92%)
			Placebo		Baseline: 64.4 ±4.9 Endpoint: 66.9 ±5.1	
		BMI score (kg/m2)	Metformin		Baseline: 24.7 ±1.0 Endpoint: **23.5 ±1.3**	
			Placebo		Baseline: 24.3 ±1.2 Endpoint: 25.2 ±1.2	
		FBG (mmol/L)	Metformin		**Baseline:** 5.2± 0.4 **Endpoint:** 4.9 ±0.6	

			Placebo		**baseline:** 5.1 ±0.4 **endpoint:** 5.1 ± 0.4	
Study ID	**Metformin (extended-release; 500 -1000 mg/daily)**					
Carrizo, et al 2009. (105)	**Quality rating**	**variable**	**intervention**	**duration**	**change from baseline/ Δ**	**% analysed**
	Fair No information about the study power calculation	Body weight (kg)	Metformin	12 weeks	**Δ** : −1.87 ± 2.9	54/61=89%
			Placebo		**Δ** : +0.16 ± 2.9	
		BMI score (kg/m2)	Metformin		**Δ** : − 0.68 ± 1.0	
			Placebo		**Δ** : +0.05 ± 0.9	
		WC (cm)	Metformin		**Δ** : − 1.4 ± 3.5	
			Placebo		**Δ** : +0.2 ± 3.6	
		Glucose (mg/dl)	Metformin		**Δ** : − 0.1 ± 18.4	
			Placebo		**Δ** : −2.2 ± 18.3	
		HbA1c (%)	Metformin		**Δ** : +0.13 ± 0.2	
			Placebo		**Δ** : +0.23 ± 0.14	
		HDL (mg/dl)	Metformin		**Δ** : +3.8 ± 7.5	
			Placebo		**Δ** : −1.8 ± 3.7	
		Non-HDL (mg/dl)	Metformin		**Δ** : − 12.9 ± 30.8	
			Placebo		**Δ** : −10.7 ± 36.9	
		TGs (md/dl)	Metformin		**Δ** : − 4.1 ± 80.0	
			Placebo		**Δ** : +2.9 ± 82.4	
Study ID	**Metformin plus sibutramine**					
Baptista, et al 2008. (106)	**Quality rating**	**variable**	**intervention**	**duration**	**change from baseline/Δ**	**% analysed**
	Low No information about the randomisation and concealment process; the study stated double-blinded	Body weight (kg)	Metformin	12 weeks	**Δ** : - 2.8 ± 3.2	Unclear
			Placebo		**Δ** : -1.4 ± 2.6	
		BMI score (kg/m2)	Metformin		**Δ** : -1.1 ± 1.2	
			Placebo		**Δ** : -0.59 ± 1.2	
		Glucose (mg/dl)	Metformin		**Δ** : - 5.2 ± 8.9	
			Placebo		**Δ** : - 11.2 ± 9.0	
		Hb1c (%)	Metformin		**Δ** : - 0.07 ± 1.6	
			Placebo		**Δ** : - 0.5 ± 0.7	
		TC (mg/dl)	Metformin		**Δ** : - 58.2 ± 37.4	

	but no information about the assessor or care provider blinding.		Placebo		**Δ** : - 29.5 ± 46.9	
		LDL (mg/dl)	Metformin		**Δ:** – 59.4 ± 35.4	
			Placebo		**Δ** : - 34.6 ± 54.0	
		HDL (mg/dl)	Metformin		**Δ** : - 0.4 ± 11.2	
			Placebo		**Δ** : - 3.2 ± 10.1	
		TG (mg/dl)	Metformin		**Δ** : +5.0 ± 40.0	
			Placebo		**Δ** : +41.8 ± 32.1	
Study ID	**Metformin**					
Chen, et al 2008. (107)	**Quality rating**	**variable**	**intervention**	**duration**	**change from baseline/ Δ**	**% analysed**
	Low Open-label information about assessors or care provider blinding not provided No control	Body weight (kg)	Metformin	24 weeks	Baseline: 71.6 ± 9.5 Endpoint: 69.4 ± 8.9	Unclear
		BMI score (kg/m2)	Metformin		Baseline: 25.8 ± 4.0 Endpoint: 24.9 ± 4.2	
		FBG (mg/dl)	Metformin		Baseline: 97.8 ± 10.4 Endpoint: 93.8 ± 8.9	
		TGs (mg/dl)	Metformin		Baseline: 177.7 ± 79.5 Endpoint: 139.6 ± 67.6	
		TC (mg/dl)	Metformin		Baseline: 151.5 ± 21.7 Endpoint: 168.0 ± 24.7	
		HDL (mg/dl)	Metformin		Baseline: 40.7 ± 13.8 Endpoint: 41.6 ± 12.3	
		LDL (mg/dl)	Metformin		Baseline: 96.0 ± 19.4 Endpoint: 94.8 ± 19.0	
Study ID	**Metformin**					
Baptista, et al 2007. (108)	**Quality rating**	**variable**	**intervention**	**duration**	**change from baseline/ Δ**	**% analysed**
	Fair Allocation concealment unclear Double blinding was applied, yet no information	Body weight (kg)	Metformin	12 weeks	**Δ** : −1.40 ± 3.2	100%
			Placebo		**Δ** : −0.18 ± 2.8	
		BMI (kg/m2)	Metformin		**Δ** : −0.47 ± 1.2	
			Placebo		**Δ** : −0.07 ± 1.1	

Table keynotes: * data presented as mean ±SD; ** data presented as mean (95% IC); †data presented as the mean difference between control and intervention, Δ data presented as mean change from baseline; values in bold represent significant results. Abbreviations: BMI: body mass index; WC: waist circumference; FBG: fasting blood glucose; HbA1c: glycosylated haemoglobin; HDL: high-density lipoprotein; LDL: low-density lipoprotein; VLDL: very low-density lipoprotein, TGs: triglycerides; TC: total cholesterol.

The average weight reduction induced by metformin ranged from 1.0 to 3.3 kg. (103,104,107,108) Furthermore, metformin showed to be effective in improving other elements of body composition such as BMI (110,122,124) but not for waist circumference. (103,108) In a study by Wu and colleagues including 128 individuals with schizophrenia who experienced >10% rise in their body weight during antipsychotic use, metformin was shown to have yielded significant weight loss (−3.2 kg) compared to placebo (+3.1 kg) or a lifestyle intervention (−1.4 kg).(120) Similarly, in a study of olanzapine users in which prior weight gain was not required for inclusion, metformin resulted in significant weight loss from baseline (−1.4kg) compared to placebo (−0.2kg).(108) Another study by Wang (104) undertaken amongst olanzapine users that did not set a requirement for prior weight gain, reported that metformin resulted in significant weight loss (body weight: −3.3 kg and BMI: −1.2kg/m^2) compared to placebo (body weight: +2.5 kg and BMI: +0.9kg/m^2). Further positive findings were reported by a study (106) that investigated the effect of combining metformin with sibutramine among patients treated with olanzapine for 12 weeks. The combination of sibutramine and metformin for 12 weeks showed no difference from the placebo (2.8 vs. 1.4 kg). It is worth noting that both drugs (metformin and sibutramine) exhibited neutral activity on the glycaemic and lipid profile of the treated subjects (106). Sibutramine has been withdrawn from the U.S., Canadian, European, and Australian markets (121) after a clinical trial demonstrated an increased risk of cardiovascular outcomes. This study was mainly included as it assessed the efficacy of metformin in reducing antipsychotic-induced weight.(106)

When considering the quality of different studies, it was clear that the methodological quality differed across the studies reporting significant effects of metformin in alleviating cardiometabolic side effects in antipsychotic users. Most of the studies were considered of

fair methodological quality (103–105,108) as these studies used randomised controlled designs (Appendix-III). Yet, the main issue among the study with fair quality concerned inadequate information about the randomisation and concealment such as in the study by Baptista (108), which lacked information about the randomisation process leading to an increase in the risks of bias. In addition, the magnitude of the effect change in weight was notably small in the studies with fair quality (103,105,108) compared to the studies of low quality (104,106,107) studies where randomisation and data assessor blinding were unclear. Such information is critical particularly for measurements that rely on scaling systems such as body weight and BMI, which can result in performance bias.

When separately considering the effects of different doses of metformin, there were no clear benefits of using high dosing regimen (1000-2550mg/day) when compared to low doses of metformin (500mg/day). Less consistent results with metformin have been reported regarding its effect on antipsychotic-induced glycaemic and lipid dysregulations despite being indicated originally for diabetes.(104,107,108)

Other metabolic modulators, mainly orlistat (109,110) and mifepristone (111) were evaluated for their effectiveness in reducing or preventing weight gain in patients treated with SGAs (Table 3-10).

Table 3-10. Reported outcomes in studies assessed the effect of pharmacologic interventions on cardiometabolic side effects of antipsychotic drugs: orlistat (109,110) and mifepristone. (111) Data are presented as mean ±SD unless otherwise stated. Values in bold represent significant results.

Study ID	**Orlistat**					
Joffe, et al 2008. (109)	**Quality rating**	**Variable**	**Intervention**	**Duration**	**Change from baseline/ Δ**	**% analysed**
	Good	Body weight (kg)	Orlistat	16 weeks	**Δ** : -2.36±2.9	Unclear
			Placebo		**Δ** : +0.62±4.10	
		TC (mg/dl)	Orlistat		**Δ** : -0.15±0.8	
			Placebo		**Δ** : -0.17±0.4	
		LDL (mg/dl)	Orlistat		**Δ** : -0.37±0.7	
			Placebo		**Δ** : -0.13±0.6	
		HDL (mg/dl)	Orlistat		**Δ** : +0.2±0.16	
			Placebo		**Δ** : +0.02±0.12	
		FBG (mmol/L)	Orlistat		**Δ** : -0.14±1.18	
			Placebo		**Δ** : +0.16±1.05	
Study ID	**Orlistat short duration (open phase only 16 weeks)**					
Tchoukhine, et al 2011. (110)	**Quality rating**	**Variable**	**Intervention**	**Duration**	**Change from baseline/ Δ**	**% analysed**
	Fair Open-label	Body weight (kg)	Orlistat	16 weeks	**Δ : -1.69±2.5**	Unclear
		TC (mmol/L)	Orlistat		**Δ** : -2.10±2.78	
		LDL (mmol/L)	Orlistat		**Δ** : -0.09±0.76	
		TGs (mmol/L)	Orlistat		**Δ** : +0.2±0.48	
		FBG (mmol/L)	Orlistat		**Δ** : -0.34±1.06	
	Orlistat long duration (both phases; double-blind PLUS open-label phase: 32 weeks)					
Tchoukhine, et al 2011. (110)	**Quality rating**	**Variable**	**Intervention**	**Duration**	**Change from baseline/ Δ**	**% analysed**

		Body weight(kg)	Orlistat	32 weeks	**Δ** : -2.13±7.14	Unclear
		TC (mmol/L)	Orlistat		**Δ** : -0.25±0.74	
		LDL (mmol/L)	Orlistat		**Δ** : +0.03±0.71	
		TGs (mmol/L)	Orlistat		**Δ** : +0.18±0.77	
		FBG (mmol/L)	Orlistat		**Δ** : -0.14±0.38	
Study ID	**Mifepristone**					
Gross, et al 2010. (111)	**Quality rating**	**Variable**	**Intervention**	**Duration**	**Change from baseline/ Δ**	**% analysed**
	Fair Stated double-blinded but no details	Body weight (kg)	Risperidone PLUS placebo	28 days	**+4.2 ± 0.3 (3.6–4.9)****	100%
			Risperidone PLUS mifepristone		**+2.3 ± 0.3 (1.7–2.9)****	
			Mifepristone PLUS placebo		**+2.9 ± 0.4 (2.0–3.7)****	
		TGs (mg/dl)	Risperidone PLUS placebo		**Δ : +29.4 ±5.8**	
			Risperidone PLUS mifepristone		**Δ : +5.2 ±5.9**	
			Mifepristone PLUS placebo		**Δ : +9.9 ±8.0**	

Table keynotes: * data presented as mean ±SD; ** data presented as mean (95% IC); †data presented as the mean difference between control and intervention at the endpoint, Δ data presented as mean change from baseline; Values in bold represent significant results. Abbreviations: BMI: body mass index; WC: waist circumference; FBG: fasting blood glucose; HbA1c: glycosylated haemoglobin; HDL: high-density lipoprotein; LDL: low-density lipoprotein; VLDL: very low-density lipoprotein, TGs: triglycerides; TC: total cholesterol.

Only two trials assessed the use of orlistat for antipsychotic-induced metabolic dysregulation.(109,110) Orlistat failed to show significant results in a study of overweight or obese (BMI ≥30kg/m2) patients with serious mental illness taking olanzapine or clozapine. For example, in a double-blinded short-period study (109) orlistat showed positive reductions in body weight and other metabolic outcomes compared to placebo, yet it did not reach significant levels. Furthermore, the effects of orlistat on antipsychotic-induced cardiometabolic abnormalities were tested in two studies for different treatment duration (16 weeks vs 32 weeks). Notably, the extended phase in the group taking orlistat showed a significant reduction in body weight from baseline. Since the subjects treated with orlistat for a longer duration (32 weeks) (110) demonstrated significant body weight reduction during the extended period (−1.7kg), this extended phase was considered as an open phase, in which neither a control group nor blinding was used.

Mifepristone was assessed for preventing weight gain induced by risperidone in male subjects with normal body weight in a fair-quality study. Gross (111) reported that administering mifepristone as adjunctive therapy with risperidone significantly alleviated further weight gain associated with risperidone; body weight gain in the mifepristone arm was 2.3kg at the endpoint compared to 4kg weight gain from the baseline observed in the risperidone arm ($p<0.001$) (Table 3-10). Notably, the study lacked sufficient information about the adequacy of the used sample (n=76), particularly since the sample was classified into three groups along with the uneven distribution of the studied groups: risperidone alone (n = 30), risperidone plus mifepristone (n = 30) or mifepristone alone (n = 16). Failure to consider the minimum sample size increases the chance of false positive assumptions and thus limits the extrapolation of the results to the overall population.

b. Psychotropic drugs

Antipsychotics with neutral cardiometabolic profiles, mainly aripiprazole (113–115), ziprasidone (113,116) and amisulpride(117) were evaluated for their effectiveness in preventing weight gain among clozapine users. Antipsychotics were used either as a replacement (113) or adjunctive treatment (114,115) to reduce metabolic dysregulations caused by clozapine. Few studies assessed the effect of adding aripiprazole or ziprasidone to a clozapine-based regimen in schizophrenic patients who experienced weight gain after initiating clozapine.(114–116,122) The efficacy of aripiprazole as adjunctive therapy to a clozapine-based regimen was generally inconclusive (Table 3-11).

Table 3-11. Reported outcomes in studies assessed the effect of pharmacologic interventions on cardiometabolic side effects of antipsychotic drugs (psychotropic drugs). Data are presented as mean ±SD unless otherwise stated. Values in bold represent significant results.

Study ID	**Ziprasidone (antipsychotic switching: partial switch vs complete switch)**					
	Quality rating	**Variable**	**Intervention**	**Duration**	**Change from baseline/ Δ**	**% analysed**
Li Ch, et al 2013.(122)	Fair No control	Body weight (kg)	Ziprasidone complete switch	14 weeks	Baseline: 23.7 ± 2.9 Endpoint: 21.96 ± 2.2	194/ 213=91%
			Ziprasidone partial switch		Baseline: 23.34 ± 2.34 Endpoint: 22.10 ± 3.13	
		FBG (mmol/L)	Ziprasidone complete switch		Baseline: 5.9 ± 0.8 Endpoint: 5.83 ± 0.9	
			Ziprasidone partial switch		Baseline: 5.83 ± 0.95 Endpoint: 5.82 ± 0.89	
		HDL (mmol/L)	Ziprasidone complete switch		Baseline: 0.9 ± 0.3 Endpoint: 1.12± 0.4	
			Ziprasidone partial switch		Baseline: 0.95 ± 0.26 Endpoint: 0.96 ± 0.64	
		TGs (mmol/L)	Ziprasidone complete switch		Baseline: 1.6 ± 0.3 Endpoint: 1.52 ± 0.6	
			Ziprasidone partial switch		Baseline:1.69 ± 0.28 Endpoint: 1.54 ± 0.63	
Study ID	**Antipsychotic switching (aripiprazole vs ziprasidone)**					
Chen, et al 2012.(113)	**Quality rating**	**Variable**	**Intervention**	**Duration**	**Change from baseline/ Δ**	**% analysed**
	Fair No control High attrition rate	BMI score (kg/m^2)	Switch to aripiprazole	24 weeks	Baseline: 35.1 ±0.4 Endpoint: 34.9 ±0.6	27/52= 51.9%
			Switch to ziprasidone		Baseline: 35.1±0.4 Endpoint: 32.8 ±0.5	
		Body weight (lb)	Switch to aripiprazole		Baseline: 217.1 ±2.3 Endpoint: 215.6 ±3.2	
			Switch to ziprasidone		Baseline: 217.0 ±2.2 Endpoint: 203.1 ±2.8	

		TGs (mg/dl)	Switch to aripiprazole		Baseline: 302.5 ±25.5 Endpoint: 175.8 ±36.7	
			Switch to ziprasidone		Baseline: 299.7 ±22.5 Endpoint: 186.5 ±30.6	
		HDL (mg/dl)	Switch to aripiprazole		Baseline: 40.0 ±1.8 Endpoint: 42.7 ±2.6	
			Switch to ziprasidone		Baseline: 39.1 ±1.7 Endpoint: 40.7 ±2.2	
		TC (mg/dl)	Switch to aripiprazole		Baseline: 212.8 ±8.3 Endpoint: 200.6 ±12.9	
			Switch to ziprasidone		Baseline: 214.8 ±7.6 Endpoint: 180.0 ±10.2	
		HgbA1c (%)	Switch to aripiprazole		Baseline: 6.3 ±0.1 Endpoint: 5.7 ±0.2	
			Switch to ziprasidone		Baseline: 6.3 ±0.1 Endpoint: 6.2 ±0.2	
Study ID	**Antipsychotic switching (switching from atypical antipsychotics to amisulpride)**					
Lin ,et al 2009.(117)	**Quality rating**	**Variable**	**Intervention**	**Duration**	**Change from baseline/ Δ**	**% analysed**
	Low Open-label design No information about randomisation, concealment or blinding Attrition rate unclear	Body weight (kg)	SGA switch to amisulpride	12 months	**Δ : –7.8 ±6.7†**	Unclear
		BMI score (kg/m2)	SGA switch to amisulpride		**Δ : –3.1 ±2.6†**	
		WC (cm)	SGA switch to amisulpride		**Δ : –9.2±8.8†**	
		Waist-hip ratio	SGA switch to amisulpride		**Δ : –0.03±0.07†**	
		TG (mg/dl)	SGA switch to amisulpride		**Δ : –52.9±78.4†**	
		TC(mg/dl)	SGA switch to amisulpride		Δ : –12.8±29.7†	
		HDL (mg/dl)	SGA switch to amisulpride		Δ : +8.6 ±10.1†	
		Glucose level (mg/dl)	SGA switch to amisulpride		**Δ : –9.2 ±26.3†**	

Study ID	Aripiprazole (adjunctive therapy: clozapine PLUS aripiprazole)					
Fleischhacker, et al 2010. (114)	**Quality rating**	**Variable**	**Intervention**	**Duration**	**Change from baseline/ Δ**	**% analysed**
	Good Double blinding was applied, and no details were provided	Body weight (kg)	Clozapine PLUS aripiprazole	16-weeks treatment phase, then extension phase 12-weeks	**Δ** : −1.74 kg	167/207=81%
			Clozapine PLUS placebo		**Δ** : −0.47 kg	
		Glucose (%)	Clozapine PLUS aripiprazole		**Δ** : +0.6±1.9	
			Clozapine PLUS placebo		**Δ** : +1.2±2.0	
		TGs (mg/dl)	Clozapine PLUS aripiprazole		**Δ** : −5.5±3.7	
			Clozapine PLUS placebo		**Δ** : −0.7±4.1	
		TC (mg/dl)	Clozapine PLUS aripiprazole		**Δ** : −6.9±1.2	
			Clozapine PLUS placebo		**Δ** : −1.2±1.4	
		HDL (mg/dl)	Clozapine PLUS aripiprazole		**Δ** : −3.9±1.4	
			Clozapine PLUS placebo		**Δ** : −1.9±1.5	
		LDL (mg/dl)	Clozapine PLUS aripiprazole		**Δ** : −10.3±2.2	
			Clozapine PLUS placebo		**Δ** : +0.0±2.6	
Study ID	**Ziprasidone adjunctive therapy**					
Henderson, et al 2009. (116)	**Quality rating**	**Variable**	**Intervention**	**Duration**	**Change from baseline/ Δ**	**% analysed**
	Low Open-label design No information about randomisation, concealment or blinding	Body weight (lb)	Clozapine PLUS ziprasidone	6 weeks	Baseline: 230.1±40.8 Endpoint: 231.4±40.8	100%
			Olanzapine PLUS ziprasidone		Baseline: 229.2±29.4 Endpoint: 227.0±29.0	
		BMI (kg/m2)	Clozapine PLUS ziprasidone		Baseline: 36.1±3.7 Endpoint: 36.3±3.7	
			Olanzapine PLUS ziprasidone		Baseline: 33.4±4.0 Endpoint: 33.1±3.9	
		WC (cm)	Clozapine PLUS ziprasidone		Baseline: 112.6±9.5 Endpoint: 113.1±6.3	
			Olanzapine PLUS ziprasidone		Baseline: 103.9±22.6 Endpoint: 111.0±8.0	

		FBG (mg/dl)	Clozapine PLUS ziprasidone		Baseline: 125±43 Endpoint: 130 ±46	
			Olanzapine PLUS ziprasidone		Baseline: 121±61 Endpoint: 116.5 ±51.9	
		HBA1C (%)	Clozapine PLUS ziprasidone		Baseline: 6.9±1.21 Endpoint:7.0±1.0	
			Olanzapine PLUS ziprasidone		Baseline: 6.2±1.2 Endpoint: 6.2±0.9	
		TC (mg/dl)	Clozapine PLUS ziprasidone		Baseline: 183±29.3 Endpoint: 178±3	
			Olanzapine PLUS ziprasidone		Baseline: 189±516 Endpoint: 193±3	
		TGs (mg/dl)	Clozapine PLUS ziprasidone		Baseline: 293±183.0 Endpoint: 273±129.0	
			Olanzapine PLUS ziprasidone		Baseline: 207±110.0 Endpoint: 173±96.0	
		HDL (mg/dl)	Clozapine PLUS ziprasidone		Baseline: 42±13.0 Endpoint: 42±9.0	
			Olanzapine PLUS ziprasidone		Baseline: 45±8.0 Endpoint: 47±9.0	
		LDL (mg/dl)	Clozapine PLUS ziprasidone		Baseline: 95±23.0 Endpoint: 89±23.0	
			Olanzapine PLUS ziprasidone		Baseline: 114±28.0 Endpoint: 114±26.0	
Study ID	**Aripiprazole adjunctive therapy (Clozapine PLUS aripiprazole)**					
Henderson, et al 2006.(115)	**Quality rating**	**Variable**	**Intervention**	**Duration**	**Change from baseline/ Δ**	**% analysed**
	Low No control	Body weight (kg)	Clozapine PLUS aripiprazole	6-weeks	Baseline: 99.8 ±18.2 Endpoint: 97.1 ±17.6	10/13=77%
		BMI (kg/m2)	Clozapine PLUS aripiprazole		Baseline: 33.1 ± 6.4 Endpoint: 32.1 ± 6.0	
		TC (mg/dl)	Clozapine PLUS aripiprazole		Baseline: 211.0 ± 26.9 Endpoint: 184.4 ± 26.9	

		TGs (mg/dl)	Clozapine PLUS aripiprazole		Baseline: 274.2 ± 228.7 Endpoint: 176.1 ±106.0	
		Glucose (mg/dl)	Clozapine PLUS aripiprazole		Baseline:121.8 ±69.2 Endpoint: 130.2 ±69.9	
Study ID	**Atomoxetine**					
Ball, et al 2011.(118)	**Quality rating**	**Variable**	**Intervention**	**Duration**	**Change from baseline/ Δ**	**% analysed**
	Fair Randomisation & allocation concealment unclear	LDL (mg/dl)	Atomoxetine	24 weeks	Baseline: 101.9±40.6 Endpoint: 97.9±35.3	Total: 26/37=70% atomoxetine:14/20 placebo: 12/17
			Placebo		Baseline: 95.3±34.5 Endpoint: 88.3±29.3	
		HDL (mg/dl)	Atomoxetine		Baseline: 45.9±12.5 Endpoint: 48.1±13.3	
			Placebo		Baseline: 47.3±13.1 Endpoint: 44.1±10.5	
		TGs (mg/dl)	Atomoxetine		Baseline: 168.6±94.2 Endpoint: 134.3±64.9	
			Placebo		Baseline: 227.7±134.0 Endpoint: 236.8±178.3	
		VLDL (mg/dl)	Atomoxetine		Baseline: 29.7±13.3 Endpoint: 27.0±12.8	
			Placebo		Baseline: 37.4±18.7 Endpoint: 31.9±17.6	
		Glucose (mg/dl)	Atomoxetine		Baseline: 107.9±27.3 Endpoint: 99.6±12.8	
			Placebo		Baseline: 102.8±12.2 Endpoint: 94.1±12.7	
Study ID	**Modafinil**					
Henderson, et al 2011.(119)	**Quality rating**	**Variable**	**Intervention**	**Duration**	**Change from baseline/ Δ**	**% analysed**
	Fair	Body weight (kg)	Modafinil	8 weeks	−0.29†	35/37=95%
			Placebo			

	Double blinding was applied, and no details were provided Concealment unclear	BMI (kg/m2)	Modafinil		−0.10†	
			Placebo			
		TC (mg/dl)	Modafinil		+1.18†	
			Placebo			
		Non-HDL (mg/dl)	Modafinil		+1.05†	
			Placebo			
		HDL (mg/dl)	Modafinil		+0.09†	
			Placebo			
		TGs (mg/dl)	Modafinil		+8.17†	
			Placebo			
		Glucose (mg/dl)	Modafinil		+0.39†	
			Placebo			

Table keynotes: * data presented as mean ±SD; ** data presented as mean (95% IC); †data presented as the mean difference between control and intervention at endpoint, Δ data presented as mean change from baseline; values in bold represent significant results. Abbreviations: BT: behavioural therapy, BMI: body mass index, WC: waist circumference, FBG: fasting blood glucose, HbA1c: glycosylated haemoglobin, HDL: high-density lipoprotein, LDL: low-density lipoprotein, VLDL: very low-density lipoprotein, TGs: triglycerides, TC: total cholesterol

Two studies with different methodological quality; good (114) and low quality (115) examined adjunctive treatment with aripiprazole in clozapine-treated patients, where both studies showed positive effects associated with aripiprazole use. A clinical trial (good quality study) on aripiprazole administered to psychotic patients, receiving a stable dose of clozapine, led to more weight loss compared to the placebo group (aripiprazole: −2kg versus placebo: −0.4 kg) over 16 weeks. In addition to weight loss, patients who were randomised to receive the aripiprazole treatment had significant reductions in total and low-density lipoprotein cholesterol.(114) The other study (122) of low quality reported a significant reduction in BMI score in the treatment group from the baseline compared to the placebo group when adding aripiprazole to the clozapine regimen. The reduction in BMI score reached up to 2.7 kg/m^2. Yet, the study did not compare the effects of aripiprazole against a control group.

Ziprasidone was also investigated as adjunctive therapy with clozapine or olanzapine.(116) Adding ziprasidone to established clozapine or olanzapine therapy had no significant benefits in terms of reducing weight gain nor improving metabolic dysregulations associated with clozapine or olanzapine use.

Three studies (113,117,122) assessed the effect of switching clozapine with an antipsychotic with a favourable cardiometabolic profile: aripiprazole, ziprasidone or amisulpride antipsychotic. Two studies compared the effects of switching to aripiprazole or ziprasidone on improving metabolic profile among clozapine users.(113,122) Switching to aripiprazole, or did not show benefits in weight loss among patients using SGAs.

Amisulpride on the other hand showed some advantages in reducing weight and improving other metabolic profiles in obese psychiatric patients who were treated with

other SGAs in a small (n= 46) open-label 12 months study (low quality).(117) It is worth noting that the effects observed with amisulpride switching on the cardiometabolic outcomes were relatively larger than the effects observed with aripiprazole and ziprasidone (113,122), knowing that the former study (117) was of low quality and maybe indirectly influenced by the lack of randomisation and blinding along with the small size range (46-194 participants) used across these studies. Similarly, information related to sampling power and the attrition associated with antipsychotic switching was not clear across the studies. This was particularly essential as the applied design (non-randomised design) may require a large sample size compared to the randomised designs to compensate for issues related to confounding, withdrawals, missing data, and loss of follow-up.

Other psychotropic drugs were investigated as appetite suppressors to treat or prevent SGAs-induced weight gain, such as atomoxetine (118) and modafinil.(119) The results of the studies showed that treatment with atomoxetine or modafinil did not significantly improve metabolic or anthropometric parameters in the test group (Table 3-11).

c. Weight loss drugs and miscellaneous drugs

Few appetite suppressors, including liraglutide (112) and nizatidine (123) have also been studied for the treatment of SGA-associated weight gain. In a 16-week randomized double-blinded study, the effect of glucagon-like peptide-1 receptor agonist (liraglutide) was investigated among schizophrenia subjects treated with clozapine or olanzapine for its effects on body weight and metabolic variables.(112) Liraglutide has been shown to be effective in improving weight loss (-4.7kg, $p<0.001$) and HbA1C reduction from the baseline (−0.2kg, $p<0.001$).(112) The main adverse effect reported among study participants was gastrointestinal upset.

Also, the effect of nizatidine in reducing antipsychotic-induced weight gain was evaluated in one double-blind randomized placebo-controlled study that was conducted over 12 weeks of olanzapine-medicated subjects.(123) However, adjunctive treatment for weight gain with nizatidine did not seem effective in controlling weight in obese patients treated with a stable dose of olanzapine. The findings from the study reported that the study subjects treated with nizatidine experienced noticeable weight gain from the baseline (12%; 1.1 kg, p = 0.9) and no significant difference in other metabolic measures was observed at the endpoint (Table 3-12).

Table 3-12. Reported outcomes for studies assessing effects of weight loss drugs and miscellaneous drugs: liraglutide (104), Nizatidine (120) and Bergamot Polyphenolic Fraction (BPF) (121). Data are presented as mean ±SD unless otherwise stated. Values in bold represent significant results.

Study ID	**liraglutide**					
Larsen, et al 2017. (112)	**Quality rating**	**variable**	**intervention**	**duration**	**change from baseline/ Δ**	**% analysed**
	Fair Allocation concealment was unclear, yet the study stated that random sampling was used but no details were provided. Small sample size (n=96)	Waist-to-hip ratio	liraglutide	16 weeks	0.0±0.1 (0.0 to 0.0)**	97/103=94%
			Placebo		0.0±0.1(−0.1 to 0.0)**	
		Body weight (kg)	liraglutide		**Δ : −4.7 ±0.5**	
			Placebo		**Δ** : +0.5 ±0.7	
		WC (cm)	liraglutide		**Δ** : −4.0 ±0.6	
			Placebo		**Δ** : +0.5 ±0.7	
		BMI score (kg/m2)	liraglutide		**Δ** : −1.6 ±1.2	
			Placebo		**Δ** : +0.08 ±0.2	
		Impaired glucose tolerance	liraglutide		**Δ : −28 ±37.8**	
			Placebo		**Δ** : −6 ±12.5	
		FPG(mg/dl)***	liraglutide		**Δ : +0.90**	
			Placebo		**Δ** : +0.99	
		HbA1c %	liraglutide		**Δ : −0.2 ±0.04**	
			Placebo		**Δ** : +0.06 ±0.04	
		Visceral fat (mean SD)	liraglutide		**Δ : −315.8 ±75.3**	
			Placebo		**Δ** : −24.0 ±41.7	
		LDL (mg/dl)***	liraglutide		**Δ : −15.4 ±3.1**	
			Placebo		**Δ** : −2.3 ±1.9	
		HDL (mg/dl)***	liraglutide		**Δ** : +I0.95	
			Placebo		**Δ** : +0.99	
		VLDL (mg/dl)***	liraglutide		**Δ** : +0.94	
			Placebo		**Δ** : +0.94	
		TGs (mg/dl)***	liraglutide		**Δ** : +0.88	
			Placebo		**Δ** : +0.97	
Study ID	**Nizatidine**					

Assunção, et al 2006. (123)	**Quality rating**	**variable**	**intervention**	**duration**	**change from baseline/ Δ**	**% analysed**
	Fair Allocation concealment was unclear Small sample size(n=45)	Body weight (kg)	Nizatidine	12 weeks	**Δ** : +7.8±4.2	45/54=83%
			Placebo		**Δ** : +8.7±3.8	
Study ID	**Bergamot Polyphenolic Fraction (BPF)**					
Bruno, et al 2017. (124)	**Quality rating**	**Variable**	**Intervention**	**Duration**	**Change from baseline/ Δ**	**% analysed**
	Low (some elements were not fulfilled due to the design) No control & small sample size (n=13)	BMI score (kg/m^2)	BPF	12 weeks	Baseline: 35.0±5.2 endpoint: **34.4±5.2**	100%
		Glucose (mg/dl)	BPF		Baseline: 97.8±12.9 endpoint: 101.9±12.2	
		HbA1c (%)	BPF		Baseline: 5.7±0.46 endpoint: 5.7±0.48	
		TGs (mg/dl)	BPF		Baseline:198.9±90.5 endpoint:183.0±59.6	
		TC (mg/dl)	BPF		Baseline: 203.5±31.8 endpoint: 204.2±38.4	
		HDL (mg/dl)	BPF		Baseline: 47.8±12.3 endpoint: 43.4±10.8	
		LDL (mg/dl)	BPF		Baseline:120.8±26.8 endpoint: 125.2±24.7	

Table keynotes: ** data presented as mean (95% IC), Δ data presented as mean change from baseline. Abbreviations: BT: behavioural therapy, BMI: body mass index, WC: waist circumference, FBG: fasting blood glucose, HbA1c: glycosylated haemoglobin, HDL: high-density lipoprotein, LDL: low-density lipoprotein, VLDL: very low-density lipoprotein, TGs: triglycerides, TC: total cholesterol.

One study (low quality) investigated the effects of a herbal compound (Bergamot Polyphenolic Fraction) for its efficacy and safety as adjunctive therapy for reducing weight and metabolic side effects of antipsychotic drugs.(124) BPF was reported to be effective only in reducing body weight (-1.71kg, p=0.005) and BMI score (-0.57kg, p=0.004). Nevertheless, the extremely small size would not allow the extrapolation of the findings to a larger population.

3.5.2. Studies reporting non-pharmacological approaches (N=13)

Non-pharmacological interventions consisted of behavioural changes, dietary interventions, and exercise-based interventions. The most common type of non-pharmacological interventions were the ones that targeted individual behavioural changes (N=13). Dietary interventions based on modified dietary content included restricted calorie intake and healthy food. Finally, exercise-based interventions were prescribed mainly with other intervention modalities such as dietary and psychological interventions.

All non-pharmacological interventions were delivered in person, mostly by group interaction. The duration of the interventions varied from 6 to 12 months, with only few studies conducting a follow-up period.(123,125-127,129) As for the applied comparators, (10 studies) (122,124,127-133) evaluated the effects of the applied interventions against usual care. The professional background of staff delivering the intervention varied widely across the studies. In most studies, the interventionists were healthcare providers from different fields, including mental health, yet the interventions received specialised training at the beginning of the study. Only two studies recruited expert trainers to deliver the interventions. Further details regarding the non-pharmacologic interventions applied in the different studies are provided in the additional file (Appendix III-F).

3.5.2.1. Summary of studies reporting the effectiveness of non-pharmacologic interventions

The purpose of most non-pharmacological approaches was mainly to promote weight loss. The overall reported effect size was relatively small across the studies.

a. Exercise and modified dietary-based interventions (N=6)

The effect of exercise was investigated alone (125) or combined with other non-pharmacological modalities, mainly diet (e.g., calories restricted and Mediterranean diet) and behavioural change.(126–130) The effect of exercise was mostly observed on body weight. The observed weight loss at endpoints ranged from 3.1kg to 4.2kg. Interventions that included physical exercise showed conflicting results. The effects of exercise-based approaches are presented in Table 3-13.

Table 3-13.Reported outcomes for studies assessing exercise and modified dietary-based interventions (N=6); results reported in mean difference estimate (standard deviation) unless otherwise stated. Values in bold represent significant results

Study ID	**Physical activity and modified diet**					
Looijmans, et al 2017.(130)	**Quality rating**	**Variable**	**Intervention**	**Duration**	**Change from baseline/ Δ**	**% analysed**
	Low Allocation concealment was unclear Small size (61 patients)	BMI score (kg/m2)	Physical activity and diet	12 months	0.44 (-2.22 to 3.09) *†	736/814=90% Test:316/400 Control:320/414
			Usual care			
		WC (cm)	Physical activity and diet		−0.60(-1.56 to 0.36) *†	
			Usual care			
		Metabolic syndrome z-score	Physical activity and diet		−0.04 (-0.22 to 0.15) *†	
			Usual care			
Study ID	**Physical activity and modified diet**					
Hansen et al, 2016.(129)	**Quality rating**	**variable**	**intervention**	**duration**	**change from baseline/ Δ**	**% analysed**
	Low Open-label & no control No information about sample power.	Body weight (kg)	Physical activity and modified diet	12 months treatment phase 12 months extension phase	**−1.4 (−2.0 to −0.7)***	Unclear
		BMI score (kg/m2)	Physical activity and modified diet		**−0.5 (−0.8 to −0.3)***	
		WC (cm)	Physical activity and modified diet		0.1 (−0.5 to 0.7)*	
		FBG (mg/dl)	Physical activity and modified diet		**−10.8 (−16.2 to −7.2)***	
Study ID	**Physical activity and modified diet**					

Giannopoulou, et al 2014.(128)	**Quality rating**	**Variable**	**Intervention**	**Duration**	**Change from baseline/ Δ**	**% analysed**
	Low (some elements were not fulfilled due to the design) No control Randomisation & concealment unclear No information about sample power.	Body weight (kg)	Physical activity and modified diet		Baseline: 91.72 ± 2.84 endpoint: **86.85 ± 2.70**	Unclear
		BMI score (kg/m2)	Physical activity and modified diet		Baseline: 33.61 ± 0.91 endpoint: **31.82 ± 0.85**	
		WC (cm)	Physical activity and modified diet		Baseline: 103.62 ± 2.09 endpoint: **99.40 ± 2.06**	
		Body fat (%)	Physical activity and modified diet		Baseline: 43.09 ± 1.07 endpoint: **39.81 ± 1.12**	
		Fat-free mass (%)	Physical activity and modified diet		Baseline: 56.94 ± 1.01 endpoint: **60.10 ± 1.06**	
Study ID	**Physical activity**					
Bartels, et al 2013. (125)	**Quality rating**	**variable**	**intervention**	**duration**	**change from baseline/ Δ**	**% analysed**
	Fair Randomisation & concealment unclear Small sample size (133) No information about sample power.	Weight loss of ≥5% body weight	SHAPE programm	12 months	**30%**	Test: 45/67=68% control: 46/66=69%
			Usual care		**33%**	
Study ID	**Behaviour changes and physical exercise**					
Poulin, et al 2007.(126)	**Quality rating**	**variable**	**intervention**	**duration**	**change from baseline/ Δ**	**% analysed**

	Fair Open-label design Participants differed at baseline in terms of their age and LDL level. No information about sample power.	Body weight (kg)	Behaviour changes and physical exercise	18 weeks	**Δ : –3.1**	85% Test:59/70 Control:51/60
			Usual care		**Δ : +3.6**	
		BMI score	Behaviour changes and physical exercise		**Δ : –1.4**	
			Usual care		**Δ : +1.8**	
		WC (cm)	Behaviour changes and physical exercise		**Δ : –4.8**	
			Usual care		**Δ : +4.5**	
		Cholesterol (mmol/L)	Behaviour changes and physical exercise		**Δ : –0.65**	
			Usual care		**Δ** : +0.35	
		LDL(mmol/L)	Behaviour changes and physical exercise		**Δ : –0.46**	
			Usual care		**Δ : +0.56**	
		HDL(mmol/L)	Behaviour changes and physical exercise		**Δ : +0.28**	
			Usual care		**Δ** : –0.05	
		TG(mmol/L)	Behaviour changes and physical exercise		**Δ : –0.58**	
			Usual care		**Δ : +0.3**	
		Glucose(mmol/L)	Behaviour changes and physical exercise		**Δ : –0.76**	
			Usual care		**Δ** : +0.03	

Study ID	Physical activity and diet					
WU, et al 2007. (127)	**Quality rating**	**variable**	**intervention**	**duration**	**change from baseline/ Δ**	**% analysed**
	Fair Double blinding was applied, and no details were provided Small sample size (53) No information about sample power.	BMI score (kg/m2)	Physical activity and diet	14 weeks	**Δ : –1.59 ±1.7**	100%
			Treatment as usual (TAU)		**Δ** : +0.35± 1.3	
		Body weight (kg)	Physical activity and diet		**Δ : –4.2 ±4.4**	
			Treatment as usual (TAU)		**Δ** : +1.0 ±3.4	
		WC (cm)	Physical activity and diet		**Δ** : –3.32 ± 4.2	
			Treatment as usual (TAU)		**Δ** : +1.02 ± 4.3	
		Hip circumference (cm)	Physical activity and diet		**Δ** : –3.3 ± 4.5	
			Treatment as usual (TAU)		**Δ** : +0.3 ± 2.7	
		Waist-to-hip ratio	Physical activity and diet		**Δ** : –0.01 ± 0.004	
			Treatment as usual (TAU)		**Δ** : +0.01 ± .03	
		Body fat (%)	Physical activity and diet		**Δ** : –1.3 ± 6.4	
			Treatment as usual (TAU)		**Δ** : +1.3 ± 4.2	

Table keynotes: †differences in changes from baseline between the intervention and control at endpoints, * results reported in mean difference estimate (95% CI),** Fitness Improvement was defined as >50-m increase on the six-minute walk test values in bold represent significant results. Abbreviations: BT: behavioural therapy, BMI: body mass index, WC: waist circumference, FBG: fasting blood glucose, HbA1c: glycosylated haemoglobin, HDL: high-density lipoprotein, LDL: low-density lipoprotein, VLDL: very low-density lipoprotein, TGs: triglycerides, TC: total cholesterol.

Most studies reported significant weight loss among the intervention group. (125–129) For example, a study assessing the effectiveness of two different exercise programs to enhance cardiometabolic fitness in patients with mental illness (125) reported that both groups (intervention and control) achieved a significant reduction in body weight (> 5% reduction from baseline).

Furthermore, combining exercise with other strategies such as a calorie-restricted diet showed conflicting results regarding alleviating weight gain caused by olanzapine among obese users.(107,129) For example, the use of a calorie-restricted diet and regular exercise in 53 obese schizophrenic subjects treated with olanzapine helped reduce body weight and BMI by –4.2 ±4.4 kg and –1.59 ±1.7 kg/m^2, respectively.(127) Similarly, exercise reduced BMI score and WC among antipsychotic users when combined with diet as the intervention led to weight loss of up to 4kg.(127,128) Another study (126), in which exercise was delivered in combination with behavioural changes, showed a significant reduction from baseline in LDL cholesterol (–0.46 mmol/L), TGs (–0.58 mmol/L), total cholesterol (–0.65 mmol/L), and fasting glucose level (–0.76 mmol/L) of the test group compared to the control group. Nonetheless, a study by Looijmans (130) demonstrated a reduction in waist circumference at the study endpoint (after 12 months) in the test group, yet it did not reach a significant level. It is of interest to note that the methodological quality varied from fair (125–127) to low (128–130) across the studies reporting significant improvements in body weight. Among the studies that used an open-label design, the effect changes induced by the interventions were higher compared with the effects that were observed in the randomised studies. This was likely because the open design studies are more subjected to bias due to the lack of blinding or unclear allocation concealment.

b. Behavioural and psychological interventions (N=7)

The effect of behavioural interventions on cardiometabolic side effects caused by antipsychotic drugs was inconclusive. Most studies focused on weight management in clozapine users.(132–135) Five studies focused solely on behavioural modifications that promote weight loss, including adopting a healthy lifestyle, motivational interviewing interventions, group counselling and barriers identifications for self-care. According to the findings of the studies, behavioural interventions resulted in mixed outcomes, leading to inconclusive results regarding the effects of behavioural modifications on metabolic abnormalities caused by antipsychotics.

Some studies reported significant improvements in body weight and BMI scores.(126,133,136) A study (135) found that an intervention based on education and rehabilitation training for 24 weeks resulted in a significant reduction in body weight from baseline (−5.1 kg) in schizophrenic patients. Similar findings were observed in another study (136) where 25% of the patients achieved the target weight reduction at the baseline (> 5% reduction in body weight from baseline as defined by the author). Both studies were of fair quality, however, the risks of allocation bias and detection bias were high due to the lack of randomisation and concealment, which may have caused an overestimation in the results. Also, information about assessor blinding was unavailable. The remaining studies (132,134,136,137) reported a non-significant reduction in body weight among the intervention group compared to the control group (Table 3-14).

Table 3-14. Reported outcomes in studies assessed the effect of non-pharmacologic interventions on cardiometabolic side effects of antipsychotic drugs (Behavioural and psychological interventions (N=7)

Study ID	**Psychoeducational intervention**					
Littrell, et al 2003.(138)	**Quality rating**	**variable**	**intervention**	**duration**	**change from baseline/ Δ**	**% analysed**
	Good Open-label design Assessor or care delivery is not known if they were blinded: risk for detection bias	Body weight (kg)	Psychoeducational intervention	16 weeks	**Δ** : −0.06 ± 9.43	100%
			Standard care		**Δ : +9.57 ± 12.98**	
		BMI score (kg/m2)	Psychoeducational intervention		**Δ** : +0.01 ± 1.37	
			Standard care		**Δ: +1.37 ± 1.96**	
Study ID	**Behaviour change**					
Osborn, et al 2018. (132)	**Quality rating**	**variable**	**intervention**	**duration**	**change from baseline/Δ**	**% analysed**
	Good Open-label design Assessor was blinded	BMI score (kg/m2)	Behaviour change	12 months	−0·44 (−1·18 to 0·30) †*	88% Test: 152/172 Control: 137/155 for intention to treat
			Treatment as usual			
		WC (cm)	Behaviour change		−0·55 (−2·33 to 1·23) †*	
			Treatment as usual			
		Cholesterol (mmol/L)	Behaviour change		+0·03 (−0·22 to 0·29) †*	
			Treatment as usual			
		HDL (mmol/L)	Behaviour change		−0·01 (−0·07 to 0·05) †*	
			Treatment as usual			
		HbA1c (mmol/mol)	Behaviour change		+0·14 (−1·36 to 1·65) †*	
			Treatment as usual			
Study ID	**Behaviour change**					
Kilbourne, et al 2017.(133)	**Quality rating**	**variable**	**intervention**	**duration**	**change from baseline/Δ**	**% analysed**
	Fair Allocation concealment was unclear: risk of allocation bias	% Body weight reduction	Behaviour change	24 months	**8.5% $**	245/293=83%
		BMI score (kg/m2)	Behaviour change		**−0.50 (−1.05 to 0.05)***	
		WC (cm)	Behaviour change		**−0.02 (−0.78 to 0.74)***	
		TC (mmol/L)	Behaviour change		−6.53 (−17.0 to 3.99) *	

		HDL (mmol/L)	Behaviour change		+0.72 (−1.54-2.98) *	
		LDL (mmol/L)	Behaviour change		**−8.77 (−17.25 to −0.29) ***	
Study ID	**Cognitive/behaviour treatment (CB)**					
Khazaal, et al 2007. (137)	**Quality rating**	**variable**	**intervention**	**duration**	**change from baseline/ Δ**	**% analysed**
	Low Allocation concealment was unclear: risk of allocation bias Groups were unbalanced at baseline	Body weight (kg)	Cognitive/behaviour treatment	12 months & 6 months follow-up	Baseline: 90.9 ±16.6 endpoint: 87.4 ±14.8	46/61=75% Test:23/31 Control:23/30
			Usual care		Baseline: 84.3 ± 17 endpoint: 86 ±17.4	
		BMI score (kg/m2)	Cognitive/behaviour treatment		Baseline: 32.4 ± 5 endpoint: 30.8 ±5.3	
			Usual care		Baseline: 28.7 ± 4.3 endpoint: 29.3 ±4.6	
Study ID	**Behaviour treatment (lifestyle modification)**					
McKibbin et al, 2006/10.(135)	**Quality rating**	**Variable**	**Intervention**	**Duration**	**Change from baseline/ Δ**	**% analysed**
	Low Concealment unclear: risk of allocation bias Randomisation & double-blind were used, yet no information	Body weight (kg)	lifestyle modification	24 weeks	Baseline: 222.3 ± 49.6 endpoint: **217.2 ± 46.8†**	57/64=89%
			Usual care		Baseline: 212.1 ± 36.8 endpoint: **218.9 ± 37.3†**	
		BMI score (kg/m2)	lifestyle modification		Baseline: 33.6 ± 6.8 endpoint: **32.9 ± 6.6†**	
			Usual care		Baseline: 32.9 ± 6.2 endpoint: **33.9 ± 6.6†**	
		WC (cm)	lifestyle modification		Baseline: 46.0 ± 7.4 endpoint: **45.1 ± 6.9†**	
			Usual care		Baseline: 45.4 ± 4.4 endpoint: **46.0 ± 4.3†**	
		FBG (mmol/L)	lifestyle modification		Baseline: 163.9 ± 94.8 endpoint: 125.7 ± 58.8	
			Usual care		Baseline: 147.2 ± 72.9 endpoint: 143.4 ± 79.0	

		HbA1C(%)	lifestyle modification		Baseline: 7.4 ± 2.9 endpoint: 6.9 ± 2.1	
			Usual care		Baseline: 6.7 ± 2.1 endpoint: 6.8 ± 1.7	
		Cholesterol (mmol/L)	lifestyle modification		Baseline: 169.7 ± 47.1 endpoint: 160.1 ± 36.4	
			Usual care		Baseline: 186.8 ± 54.4 endpoint: 186.2 ± 42.2	
		HDL(mmol/L)	lifestyle modification		Baseline: 34.8 ± 8.3 endpoint: 34.9 ± 9.5	
			Usual care		Baseline: 38.1 ± 10.5 endpoint: 38.8 ± 11.0	
		LDL(mmol/L)	lifestyle modification		Baseline: 99.4 ± 32.7 endpoint: 91.7 ± 31.6	
			Usual care		Baseline: 116.8 ± 47.8 endpoint: 108.4 ± 36.7	
		TGs(mmol/L)	lifestyle modification		Baseline: 224.4 ± 195.5 endpoint: **188.5 ± 133.6†**	
			Usual care		Baseline: 188.2 ± 97.8 endpoint: **215.3 ± 112.0†**	
Study ID	**Cognitive/ behaviour treatment (CB)**					
Weber, et al 2006. (134)	**Quality rating**	**variable**	**intervention**	**duration**	**change from baseline/ Δ**	**% analysed**
	Fair Open-label design Concealment unclear: risk of allocation bias	% of body weight loss (Ib)	Cognitive/ behaviour treatment (CB)	16 weeks	2.9%	15/17=88%
			Treatment as usual (TAU)		0.6%	
		% change in mean BMI	Cognitive/ behaviour treatment (CB)		2.9%	
			Treatment as usual (TAU)		0.8%	
		WC (cm)	Cognitive/ behaviour treatment (CB)		**Δ** : –3.32 ± 4.2	

			Treatment as usual (TAU)		**Δ**: +1.02 ± 4.3	
		Hip circumference (cm)	Cognitive/ behaviour treatment (CB)		**Δ** : –3.3 ± 4.5	
			Treatment as usual (TAU)		**Δ** : +0.3 ± 2.7	
		Body weight (kg)	Cognitive/ behaviour treatment (CB)		**Δ** : –5.4±6.5	
			Treatment as usual (TAU)		**Δ** : –1.3±7.3	
Study ID	**Behavioural treatment (BT)**					
Brar et al, 2005. (136)	**Quality rating**	**variable**	**intervention**	**duration**	**change from baseline/Δ**	**% analysed**
	Fair Randomisation technique & concealment unclear: risk of allocation bias Sample size not adequately powered	Body weight (kg)	Behavioural treatment (BT)	14 weeks	**Δ** : –2.0±3.79	Test:22/28=75% Control:28/37=75 % (intention to treat)
			Usual care		**Δ** : –1.1±3.11	
		The proportion of patients with ≥5% weight loss at the endpoint	Behavioural treatment (BT)		**9 (26.5%)**	
			Usual care		**4 (10.8%)$**	

Table keynotes: †differences in changes from baseline between the intervention and control at endpoints, values in bold represent significant results, * results reported in mean difference estimate (95% CI), Δ: the mean difference between the baseline and the endpoint, $: proportion of patients (N; %). Abbreviations: BMI: body mass index, WC: waist circumference, FBG: fasting blood glucose, HbA1c: glycosylated haemoglobin, HDL: high-density lipoprotein, LDL: low-density lipoprotein, VLDL: very low-density lipoprotein, TGs: triglycerides, TC: total cholesterol

Few studies measured metabolic outcomes mainly blood glucose and lipid.(132,133,135) According to their findings, the overall effect of behavioural modification on metabolic dysregulations was generally non-significant, with two studies (133,135) only reporting improvements in lipid profile. One of the identified trials (133) reported a significant reduction in LDL level (-8.77mmol/L, p=0.04) in the intervention group compared to usual care at the study endpoint (Table 3-14).

By looking at the methodological quality of the included studies, most studies lacked information regarding allocation concealments. Studies with inadequate allocation concealment can yield large treatment effect estimates when compared to studies applying masked recruitment.(132,138) Also, the variations in sample sizes and study designs can contribute to the differences in the treatment effects observed across the studies.

3.5.3. Combined pharmacological and non-pharmacological approaches (N=2)

Two studies (120,139), investigated the effectiveness of some pharmacological plus non-pharmacological approaches such as lifestyle modification and behavioural change on body weight among antipsychotic users. Nonetheless, the findings from the two studies were indecisive.

3.5.3.1. Antipsychotic switching with behavioural intervention

A study done by Meyer (139) investigated the efficacy of switching from olanzapine to risperidone in obese patients with schizophrenia. Although the primary objective was to evaluate the effects of switching between antipsychotic drugs (olanzapine to risperidone) on the prevalence of MS, the results from the subgroup analysis comparing the effect of adding behavioural therapy to the treatment group showed an initial reduction in BMI from

baseline. Nevertheless, no further improvements were obtained in body weight after initiating the non-pharmacological treatment.

3.5.3.2. Metformin with lifestyle intervention

Wu and colleagues (120) conducted a randomised control trial in a sample of 128 subjects treated with clozapine, comparing the concomitant use of metformin and placebo in the presence or absence of lifestyle intervention. Both groups reported significant improvements in outcome measures including body weight and metabolic variables. However, the effect size that was observed with the group-included combination therapy (metformin and lifestyle modifications) was higher than the effects detected in the metformin group; combined therapy (BMI: −1.8 kg/m^2) vs metformin only (BMI: -1.2 kg/m^2). Also, body weight loss from combined therapy was higher (−4.7kg; $p<0.05$) compared to treatment with metformin only (−3.2kg; $p<0.05$). The combined therapy also showed a significant reduction in fasting blood glucose (−7.2mg/dl; $p<0.05$) from baseline.

3.6. Discussion

This review evaluated the evidence regarding the prevalence of cardiometabolic side effects associated with antipsychotic use. This review also assessed and synthesised evidence about the available interventions that were meant to minimise the cardiometabolic side effects of antipsychotics. When reaching the first aim, this review reported a high prevalence of MS in patients on maintenance antipsychotic therapy. Similar findings were reported by a meta-analysis investigating the prevalence of MS and its possible causes in schizophrenia. The authors concluded that MS was predominant in chronic patients using antipsychotic drugs for the long term.(140) Reported prevalence of MS varied largely across the studies ranging from 11% to 87%. Despite the limited evidence, this prevalence of MS was reported to be high among chronically ill patients on maintenance antipsychotic therapy.

Also, the review findings showed various but relatively high prevalence of individual components of metabolic syndrome. Elements represented obesity were mostly addressed across the studies. Besides, the prevalence of weight gain (i.e., central obesity & BMI>30 kg/m^2) was higher compared to the other components of MS, as the reported prevalence reached up to 62%. and a high rate of dyslipidaemias among subjects treated with antipsychotic drugs.

It is noteworthy that in this review, the prevalence of pre-metabolic syndrome (pre-MS), which was defined as the presence of two diagnostic components of MS(79,81), was only reported in one study.(95) Looking at individual elements of MS, one of the identified studies (81) reported a high proportion of antipsychotic-medicated subjects who were presented with at least two defining elements of MS regardless of not being diagnosed with MS. A fact that reveals a rather unsatisfactory health profile in people taking antipsychotic drugs, in those even without an established diagnosis of MS. In other words, there is a risk that the prevalence of patients experiencing individual components of MS can be underestimated.

Furthermore, the narrative synthesis demonstrated various degrees of cardiometabolic risks across different antipsychotic drugs. For example, clozapine and olanzapine have been associated with the highest risks for cardiometabolic dysregulations. Similarly, the available evidence (140) showed that specific antipsychotics, primarily clozapine, olanzapine and quetiapine, were associated with the high prevalence of weight gain, dyslipidaemia and hyperglycaemia.

This review found a low rate of cardiometabolic dysregulations in patients treated with aripiprazole and ziprasidone. Consequently, a low prevalence of metabolic syndrome was observed. Supportive results were reported by a meta-analysis investigating weight changes

among antipsychotic users. As it concluded, all antipsychotics were associated with a certain level of weight changes with different degrees of severity except for ziprasidone and aripiprazole.(141)

Although the information was limited, one study identified in this review indicated a higher prevalence of cardiometabolic abnormalities among the antipsychotic polypharmacy group compared to the users of single-treatment regimens. However, due to the methodological variations across the included studies along with the limited data and the relatively short duration, it was difficult to conclude the most effective approach to mitigate cardiometabolic side effects among antipsychotic users.

This review also, identified several interventions to alleviate cardiometabolic side effects among antipsychotic users. Among the identified strategies, this review highlighted the potential benefits of using add-on therapy of some non-psychotropic drugs for managing the cardiometabolic side effects of antipsychotics. Metformin demonstrated consistent improvements in body components (body weight and BMI). Similar results from the meta-analysis that was done by Mizuno (142) supported the use of metformin as adjunctive therapy in managing olanzapine-induced hyperglycaemia when switching antipsychotics is not feasible due to psychotic relapse concerns.

Upon non-pharmacologic approaches, exercise-based interventions have the best evidence to induce or maintain weight loss in patients prescribed clozapine or olanzapine weight loss. Consistent with our findings, Donnelly (143) demonstrated weight loss with exercise alone in a group of 141 overweight or obese (BMI 31 kg/m2) men and women in the Midwest Exercise Trial 2. At the endpoint, observed weight losses range from 3.9 ± 4.9kg to 5.2 ± 5.6kg.

In this review, behavioural interventions did not induce significant weight reduction in the short term; however, a significant weight reduction was observed in some studies that were conducted for the long term (12-18months).(126,133) This was consistent with the findings of other reviews of educational interventions for weight loss among persons with diabetes (144,145) where comprehensive, intensive, group dietary and behavioural changing programs produced a mean loss of 8-10 kg at six months with a sustained 30% to 35% weight loss for the next one year. This indicates that weight reduction is achievable with behavioural change approaches, but sustained, long-term, and intensive follow-up may be essential.

3.7. Critical appraisal of the studies included in the present review

This systematic review identified a range of studies examining the prevalence of cardiometabolic side effects associated with antipsychotics. The reported wide range of prevalence of cardiometabolic side effects could be a result of methodological heterogeneity across the studies.

The patients identified by the review differed in the extent to which they were representative of the patients who experienced cardiometabolic side effects during treatment with antipsychotic therapy. For example, a number of studies limited their samples to patients treated with clozapine, which is mostly used in refractory cases of psychosis. Similarly, a study investigated the prevalence of metabolic abnormalities among schizophrenic patients prescribed clozapine and long-acting injection (LAIs) antipsychotics. The latter are known to be used in patients with treatment adherence issues.(146)

Furthermore, the generalisation of the findings to the wider population was limited given the small sample size across the selected studies. Most of the included studies did not provide information on whether the sample size was adequately powered to estimate the

minimum number needed to detect the differences in outcomes. Where sub-group analysis was used, the samples were stratified further into smaller sub-groups. The small sizes can reduce the precision of the estimated prevalence and result in false estimates. Thus, the results of the findings must be interpreted with caution.

Additionally, prevalence data may be influenced by operationalised definitions for the studied outcomes. For example, certain metabolic outcomes reported by most studies such as dyslipidemia and hyperglycemia were defined either through a prescription for a lipid-lowering medication or the presence of the abnormal lipid value. Also, the use of general definitions (e.g., defining criteria for MS) may result in an overall high prevalence data leading to overestimation. Whereas, applying more specific defining criteria can result in some level of restrictions leading to underestimation of the reported prevalence. For example, a study conducted in South Korea applied the ATP-III diagnostic criteria for MS, which may be considered general for a population with unique characteristics. Unlike other defining criteria such as the IDF and the ATP-III, criteria such as the Japanese committee applied restriction definition for central obesity.

The present review also identified various interventions that targeted cardiometabolic side effects in antipsychotic users. The methodological differences made the comparison between those studies difficult particularly due to the nature of the trials. This is particularly true for studies with specific characteristics that may not allow the fulfilment of quality features. For example, randomisation and blinding were not always feasible for studies using open-label and non-randomised designs. Yet, it would be feasible to blind the data collector and the assessor. However, related information was not adequately described. Also, random allocation can be problematic in studies assessing non-pharmacological interventions such as education due to some ethical concerns. In addition to the absence of randomisation, other

methodological deficiencies such as the common absence of control groups and blind assessors contribute to biased results.

Additionally, studies using a randomised controlled design in this review were not free from bias such as lack of blinding, particularly when an open design was applied. This is important for outcome measures that are subjected to measurement bias such as body weight, where the data collector can change the measures if no blinding is performed. Yet, we believe that outcome measures related to laboratory assessments such as blood glucose and lipid panel are objective and unlikely to be affected by the lack of blinding.

Regarding the studies reporting non-pharmacological approaches, most of the studies compared the effect of the target intervention against a control group, which was often defined as usual care provided by the site. However, in studies assessing non-pharmacological approaches, details about the control intervention were poorly reported in several studies, which may subject these studies to outcome measures bias.

The generalisability of the included studies may be negatively affected by the sample size applied by the studies. Precisely, the sample size applied in several studies was relatively small and the majority of studies did not provide adequate information regarding the adequacy of the used sample such as the power analysis. Furthermore, it is highly important to verify whether the observed non-significant results in the studies were due to a lack of relationship between the groups or due to inadequate statistical power. Also, in most studies addressing the interventions, the recruited subjects received clozapine and olanzapine, which limit the generalisability of the findings. Moreover, many non-pharmacological interventions were designed to involve a single institution. This may limit their ability to achieve statistical power and generalisability.

Finally, a key quality feature that was predominant across the studies included in this review was the considerably low reporting quality that was detected across the studies. It is worth noting that the reporting quality does not accurately reflect the study quality. Differences in the quality of reporting may obscure important differences in methodologic quality. Therefore, due to inadequate reporting, the overall quality rating for individual studies was negatively affected.

3.8. Limitations of the present review

The major limitation of this review was the significant lack of reporting across the selected studies. The quality of evidence in individual studies, as rated by reviewers using the JBI scale, was low; however, the quality instruments (JBI) used in the study mainly assessed the validity of the studies but not the quality of the reporting. Consequently, the overall quality rating for the included studies in this review was severely affected by the poor quality of reporting across the studies. For example, the lack of studies on specific details related to the randomisation process led us to downgrade the overall quality of the evidence.

Most of the included studies consistently used primary data (data were collected directly from the patients), where clinical and laboratory data were used to report information on antipsychotic use and cardiometabolic dysfunctions. Such data sources may not allow for sufficient sample sizes and cannot efficiently be used to study population-level trends. Thus, the included studies were not sufficiently powered to detect cardiometabolic abnormalities in antipsychotic users and did not allow the assessment of sub-populations by medication type when available. For example, in some subgroups (e.g., the acutely ill population), there was a lack of conclusive data on the most significant endpoints (e.g., particularly antipsychotic drugs' association with cardiometabolic events).

Also, this review was limited to the record that was published in the English language.

Another potential limitation of this review was its main narrative approach with no focus on comparing the magnitude of cardiometabolic changes among antipsychotic users.

Regarding the studies addressing pharmacological interventions, most of the included studies were conducted over a relatively short period (8-12 weeks). Therefore, long-term effects and adverse effects were not evaluated. Notably, most studies assessed the effectiveness of the intervention in this review according to the presence of effect differences in the study outcomes between the compared groups, not based on the magnitude of change induced by the interventions from baseline between the groups. The p-value informs the reader that an effect does exist; however, it does not provide information about the size of the impact produced by the intervention.(147,148) Thus, based on the reported results, it was difficult to conclude the rank order of identified interventions regarding their effectiveness to alleviate cardiometabolic side effects among antipsychotic users in this review.

3.9. Conclusions

Although treatment with antipsychotic medications has been linked to several cardiometabolic abnormalities including weight gain and abnormalities in lipid and glucose metabolism, little evidence is available to show the individual cardiometabolic profile for different antipsychotics.

Various pharmacological and non-pharmacological interventions have been evaluated to prevent or alleviate the cardiometabolic risks of antipsychotics. The limited data provided some evidence suggesting that the augmentation of the antipsychotic regimen with other medications and antipsychotic switching possess some benefits in alleviating the cardiometabolic dysregulations associated with antipsychotic drugs, particularly weight gain.

Broad recommendations for the use of adjunctive pharmacological therapy for antipsychotics-included cardiometabolic complications or any other intervention approaches may be early. Further research is needed to establish the long-term efficacy and safety of the proposed approaches. Also, our findings may not be broadly generalisable. This is difficult due to the methodological heterogeneity along with the low methodological quality of the identified studies, which was affected further by the poor study reporting of key quality features. Hence there is a need for high-quality studies in the future that can demonstrate the nature of the cardiometabolic profile of different antipsychotics and the effectiveness of different interventions to mitigate the side effects.

Chapter 4 Barriers to Monitoring, Counselling and Management of Cardiovascular and Metabolic Health of Patients Prescribed Antipsychotic Drugs: Qualitative Systematic Review

Summary of the chapter

The results of the qualitative review (Second review), which aims to explore barriers to managing and monitoring cardiometabolic side effects among antipsychotic users, are presented in this chapter.

Manuscript number (2)

Note for plagiarism check: This chapter in its entirety is being submitted for publication. It is likely to be published and be available online by the time of the plagiarism check.

Printed tile of the Manuscript: Barriers to monitoring, counselling and management of cardiovascular and metabolic health of patients prescribed antipsychotic drugs: a systematic review.

Status: published

Location in the thesis: page 120

Authors' contribution: This review is part of R.AA's PhD work. VP and ZJ supervised this PhD. All authors contributed to the study design. The literature search was performed by R.AA and verified by VP. Literature retrieving, screening, summarising, data extraction, quality assessment and data analysis were conducted by R.AA. The manuscript drafting and writing were done by R.AA. All authors reviewed and approved the manuscript for final submission.

Title page

Barriers to Monitoring and Management of Cardiovascular and Metabolic Health of Patients Prescribed Antipsychotic drugs: A Systematic Review

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Barriers to Monitoring and Management of Cardiovascular and Metabolic Health of Patients Prescribed Antipsychotic drugs: A Systematic Review

Abstract

Background: The use of atypical antipsychotics which currently form the primary choice pharmacotherapy for several mental health conditions have been linked to cardiovascular and metabolic side effects. This systematic review aimed to investigate the barriers to monitoring and management of cardiovascular comorbidities in patients prescribed antipsychotic medicines.

Methods: A protocol-led (CRD-42018106002) systematic literature review was conducted by searching Medline, Embase, and PsycINFO databases 2003 until October 2019. Cochrane, Centre for Review and Dissemination (CRD) and PRISMA guidelines were followed. Studies investigating barriers to monitoring and management of cardiovascular comorbidities in patients prescribed antipsychotic medicines were included.

Results: A total of 23 records were included. Key barriers included a) healthcare system-related factors such as lack of knowledge and expertise amongst care providers, available resources, confusion around remit and roles, fragmentation of care such as across general practitioners and psychiatrists, and time constraints and b) patient-related factors such as disability resulting from mental health conditions, knowledge and skills of the patients.

Conclusion: Barriers to monitoring and management of cardiovascular and metabolic health of patients taking antipsychotic medicines are multidimensional. Apart from educational interventions directed to both patients and healthcare professionals, the results suggest a need for the improvement of wider system-related factors to improve physical health of patients prescribed antipsychotic medicines.

Clearer guidelines, clarity of remit and roles amongst service providers are necessary in addition to educational interventions directed at patients and healthcare professionals in improving physical health monitoring, counselling and management of patients prescribed antipsychotic medicines.

Registration: A protocol was developed and registered with PROSPERO as per PRISMA-P guidelines (CRD 42018106002).

Key words: Antipsychotics, Comorbidity, Drug Interactions and Side Effects, Patient Counselling Research, Primary Care

Barriers to Monitoring and Management of Cardiovascular and Metabolic Health of Patients Prescribed Antipsychotic drugs: A Systematic Review

4.1. Background

Patients with severe mental illnesses face inequality in health and access to healthcare and face early deaths. For example, a recent meta-analysis suggested that schizophrenia is associated with a weighted average of 14.5 years of potential life lost, with females being particularly disadvantaged over males. (76) Cardiovascular disorders including coronary heart disease and cerebrovascular disorders disease are the leading cause of deaths in persons with severe mental illnesses. (76,149)

The use of atypical antipsychotics which currently form the primary choice pharmacotherapy for the management of psychotic episodes in schizophrenia, bipolar disorders and other several mental illnesses, have been linked to cardiovascular and metabolic side effects.(76) Patients with severe mental illnesses such as schizophrenia are at dual disadvantage of being inherently predisposed to metabolic abnormalities and often this is worsened by the subsequent use of antipsychotics.(76) Results from a meta-analysis assessing the prevalence of metabolic abnormalities between antipsychotic naïve patients and chronically treated found that the rate of individual metabolic abnormalities was significantly higher in the chronically treated group.

In 2003, the Food and Drug Administration (FDA) launched a black box warning regarding the diabetogenic effect of antipsychotics. (40) In response to these warnings, a panel of regulatory bodies and professional associations including the American Diabetes Association (ADA)/American Psychiatric Association (APA) published a consensus statement that

recommends early and regular monitoring of metabolic side effects among antipsychotics users.(40)

Recently the National Institute for Health and Care Excellence (NICE) guidelines for managing schizophrenia have introduced updates to include management of cardiovascular and metabolic abnormalities in patients with schizophrenia. (22) The updates included: measuring bodyweight (plotted on a chart); waist circumference, pulse and blood pressure, fasting blood glucose, glycosylated haemoglobin (HbA1c), blood lipid profile and prolactin levels. Additional measures including electrocardiogram (ECG) should be conducted for patients with specific cardiovascular risk such as diagnosis of high blood pressure, medical history of cardiovascular disease and during hospital admission.

Despite current guidelines, rate of screening and management of metabolic and cardiovascular health has been reported to be sparse. A study exploring the prevalence of undiagnosed metabolic abnormalities in patients with severe mental illnesses in England, reported a very low proportion of patients had undergone annual screening and monitoring for cardiovascular risks factors such as blood pressure (2%), weight (0%), waist circumference (0%), any glucose (7%) and lipid profile (4%).(150)

Despite the positive outcomes which have been associated with the introduction of atypical antipsychotics on the quality of life of people with severe mental illness, (151) the associated cardiovascular and metabolic risks of these drugs may limit their use. Given that cardiovascular disorders are leading cause of deaths in patients with severe mental illness and quantitative data suggesting suboptimal follow up and monitoring practices, it is important to understand the factors associated with sub-optimal monitoring, counselling and management of cardiovascular and metabolic side effects that may be contributing to excess morbidity and mortality in this population.

This study aimed to systematically review the barriers and facilitators to the monitoring, counselling and management of cardiovascular and metabolic side effects in patients taking antipsychotic medicines.

4.2. Methods

4.2.1. Search strategy and eligibility criteria

A protocol was developed and registered (CRD 42018106002). An electronic search was performed for literature from 2003 until October 2019 using Medline, Embase, and PsycINFO databases. The search was limited to the English language due to constraints in time and funding to undertake the translation. This time frame was selected as it corresponds to the FDA warnings for risks of metabolic dysregulations associated with antipsychotic medicines. A search strategy was developed based on keywords and medical subject headings. The applied search strategy is available in Appendix IV-A of the thesis. Cochrane, Centre for Review and Dissemination (CRD) and PRISMA guidelines (Appendix IV-B) were followed in conducting and reporting the review.

The inclusion criteria were formulated using the PIC/o mnemonic for qualitative evidence which stands for participants, the phenomenon of interest and context.(152) Key inclusion criteria were: (i) patients aged ≥ 18 years old using one or more antipsychotics for severe mental illnesses; (ii) healthcare professionals who are involved in the care of the patients which reported barriers to screening, monitoring and management of cardiovascular and metabolic side effects in patients prescribed antipsychotic medicines. In studies which did not specify patient antipsychotic use as inclusion criteria but reported participant perspectives around barriers to the monitoring of cardiovascular or metabolic health based on their mental health diagnosis, such studies were also included in the review.

4.2.2. Study identification and data extraction

Title and abstracts were screened for eligibility. After duplicate removal, records with irrelevant titles or abstracts were excluded from the search. Two reviewers undertook the screening and reviewing process independently. Conflicts regarding the results were resolved by consensus or after a discussion with a third reviewer.

The extracted data included: participants' characteristics, the data collection method, the phenomenon under the study and the study main findings. Each finding was assigned a level of credibility: Unequivocal [U], Credible [C], or Unsupported [US], according to the criteria from the Joanna Briggs Institute.(153) Findings were rated as unequivocal if they were directly supported by illustrations. Findings were labelled as credible if they were indirectly cited in the original study (derived from the meaning). If the findings were drawn from the authors' conclusion, the reviewer would label them as unsupported. An inductive thematic synthesis approach was applied. Quality assessment was done using Joanna Briggs Institute Assessment and Review Instrument (JBI-QARI) for qualitative studies.

4.3. Results

4.3.1 Included studies

A total of 22 records were included in the final synthesis which related to 21 studies. (152–172)

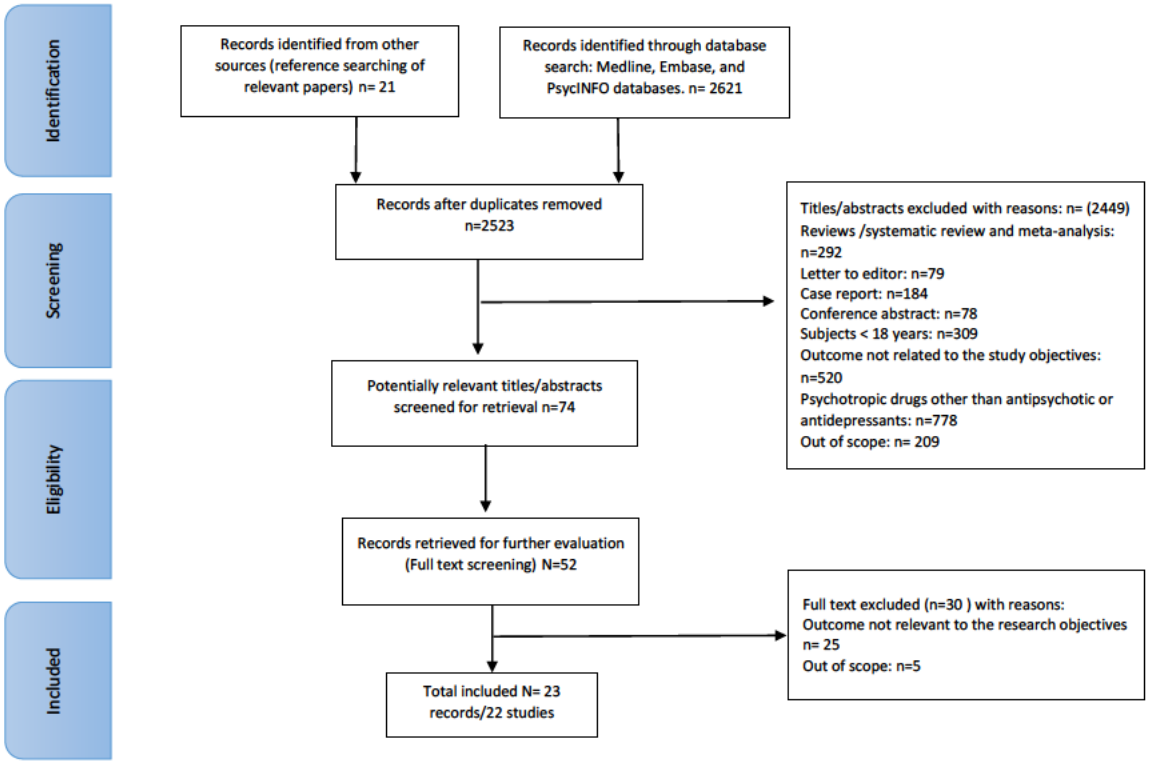


Figure 4-1. PRISMA-flow chart of literature searching

4.3.2. Study characteristics

The majority of the studies were conducted in Europe (155,158,172,174,159–161,166–168,170,171) and America. (154–156,162,163,169,173) Five studies recruited participants from community mental health settings(156,157,159,162,165), whereas 10 studies recruited participants from secondary care settings (154,155,157,160,162,163,165,169-171) and two recruited participants from tertiary centres (169,170) Four studies did not specify the setting type.(160, 163, 166,167,174) A total of 10 studies investigated patients' views (154,155,157-160,162-164,169,171) and 10 studies focused on providers' prospective (160,164-167,169,170,172-174). Only two studies (157,171) examined the perspective of both mental healthcare professionals and patients.

Among the studies that included patients, only three studies exclusively targeted regular antipsychotic drug users.(158,160,171) The majority of the studies recruited patients based

on clinical diagnoses with mental health conditions but included patient perspectives in relation to cardiovascular and metabolic health monitoring and hence were included.(155, 157,159,160,162-164,169,174) Five of these studies focused on participants diagnosed with psychosis (157,158,160,164,171), while the majority included wide range of mental health conditions.(154,155,169,174)

Various range of healthcare professionals were included in the studies that looked at healthcare professionals' perspectives (154,156,157,160,164-167,169,170,173,174) including mental health nurses (166,172,173), community mental health staffs (164,166,169), and primary care providers.(170) Full study characteristics are reported in Tables 4-1 and 4-2.

Table 4-1.Charateristics of studies including patients

Study ID & Country	Conserns regarding the methodological limitations	Aim	Design	Data collection method	Setting	Sample size	Participants	Mental health diagnosis	Proportion of patients prescribed antipsychotic drugs	Information on the use of antipsychotic by patients
Blixen, 2016;USA.(154)	Low concerns	To assess perceived barriers to self-management among patients with both SMI and DM in order to inform healthcare delivery practices	Exploratory, observational and phenomenological approach	Interview: semi-structured	Urban safety net clinic	20 subjects with severe mental conditions	Patients with severe mental illness	schizophrenia, schizoactive disorder, bipolar disorder or major depression	Not reported	No specific information regarding the type of antipsychotic drug use however participants described barriers to monitoring and management of cardiovascular and metabolic side effects
Graham, 2014; Canada. (155)	Low concerns	To potentially enhance health initiatives by exploring facilitators that help mental health service users engage in better health behaviours and the types of health programs mental health service users want to develop	Qualitative study	Focus group interviews (5 groups)	Psychosocial rehabilitation centre	37 mental health service users	Patients with mental health conditions	Broad range of mental conditions (Schizophrenia, bipolar related disorders, depressive disorders, anxiety disorders, obsessive-compulsive disorders)	Not reported	No specific information regarding the type of antipsychotic drug use however participants described barriers to monitoring and management of cardiovascular and metabolic side effects

Study ID & Country	Conserns regarding the methodological limitations	Aim	Design	Data collection method	Setting	Sample size	Participants	Mental health diagnosis	Proportion of patients prescribed antipsychotic drugs	Information on the use of antipsychotic by patients
Johnstone, 2009; UK. (156)	Low concerns	To investigate the barriers to uptake of and adherence to physical activity in community dwelling patients with a diagnosis of schizophrenia	Qualitative study	Semi-structured interviews	Community mental health services	27 community dwelling patients with a diagnosis of schizophrenia	Patients with mental illness	Patients with diagnosis of schizophrenia for a minimum of one year	100%	Second-generation antipsychotic 52%: Clozapine 44%. First-generation antipsychotic 4%
Kristiansen ,2015; Denmark .(157)	Low concerns	To explore physical health problems and their causes in patients with severe mental illness, as well as possibilities for prevention and treatment from the patients' and staff's perspectives	Qualitative study	Focus group interviews (6 groups)	Three outpatients clinics	33 participants: staff: n=19 and patients: n=14.	Mental healthcare staff and patients with mental health conditions	Patients with schizophrenia or substance abuse	Not reported	No specific information regarding the type of antipsychotic drug use however participants described barriers to monitoring and management of cardiovascular and metabolic side effects
McDevit, 2006;USA.(158)	Low concerns	To explore perceived barriers and benefits to physical activity in people with serious and	Qualitative exploratory study	Focus group interviews (4 groups)	2 community based psychiatric rehabilitation centres	34 participants	Patients with mental health conditions undergoing community based	No specific information regarding the diagnosis of mental conditions	Not reported	No specific information regarding the type of antipsychotic drug use however participants described barriers

Study ID & Country	Conserns regarding the methodological limitations	Aim	Design	Data collection method	Setting	Sample size	Participants	Mental health diagnosis	Proportion of patients prescribed antipsychotic drugs	Information on the use of antipsychotic by patients
		persistent mental illness (SPMI) who were enrolled in community-based psychiatric rehabilitation.					psychiatric rehabilitation			to monitoring and management of cardiovascular and metabolic side effects
Pearsal, 2014; UK.(159)	Low concerns	To examine the attitudes, views, and experiences of patients who had declined to participate in a healthy living programme	A qualitative study using grounded theory	Interview	Community mental health services	30 patients with a diagnosis of schizophrenia, schizoaffective or bipolar affective disorder	Patients with mental health conditions declined to take part in a healthy living programme based in a community mental health team	Patients with schizophrenia, schizoaffective or bipolar affective disorder	Not reported	No specific information regarding the type of antipsychotic drug use however participants described barriers to monitoring and management of cardiovascular and metabolic side effects
Pitman, 2011; UK.(160)	Low concerns	To assess current practice and attitudes related to screening and reduction in risk factors for cardiovascular disease, preferences for	Cross sectional study	Survey	Community psychiatric services	227 service users, 143 primary care staff, and 166 community mental health team (CMHT) Staff.	Mental healthcare staff and patients with mental health conditions	Patients with wide range of mental conditions (Schizophrenia, bipolar disorder, depression and anxiety)	Not reported	No specific information regarding the type of antipsychotic drug use however participants described barriers to monitoring and management of cardiovascular and

Study ID & Country	Conserns regarding the methodological limitations	Aim	Design	Data collection method	Setting	Sample size	Participants	Mental health diagnosis	Proportion of patients prescribed antipsychotic drugs	Information on the use of antipsychotic by patients
		service provision, and perceived barriers to service uptake.								metabolic side effects
Rastad, 2014; Sweden. (161)	Low concerns	To study the perception and experience of barriers to and incentives for physical activity in daily living in patients with schizophrenia, as reported by the patients themselves.	Qualitative exploratory study	Semi-structured interviews	Multicentre (3 psychiatric outpatient clinics)	20 patients with schizophrenia or schizoactive disorder	Patients with mental health conditions	Patients with schizophrenia or schizoactive disorder	100%	No data available on the type of antipsychotics
Yarborough,2011;USA. (162)	Low concerns	To adapt a successful lifestyle/weight loss intervention for this population, deliver it in mental health clinics, and concurrently measure implementation factors	Mixed-methods: Qualitative interviews with intervention observation sessions	Interview	Two public mental health clinics	Control group (N=32) Intervention group (N=16)	Patients with mental health conditions	No specific information regarding the diagnosis of mental conditions	Not reported	Patients should be stable on antipsychotic therapy ≥30 days, but no specific information regarding type of antipsychotics; Participants described barriers to monitoring and management of cardiovascular and

Study ID & Country	Conserns regarding the methodological limitations	Aim	Design	Data collection method	Setting	Sample size	Participants	Mental health diagnosis	Proportion of patients prescribed antipsychotic drugs	Information on the use of antipsychotic by patients
										metabolic side effects
Yarborough, 2016; Portland. (163)	Low concerns	To identify modifiable factors associated with making and maintaining healthy lifestyle changes in order to inform clinicians and improve the development of future interventions for individuals with serious mental illnesses	Mixed-methods: Qualitative interviews with intervention observation sessions	Interview	Multicentre (unclear)	84 participants	Patients with mental health conditions	No specific information regarding the diagnosis of mental conditions	Not reported	All patients should be stable on antipsychotic therapy ≥30 days, but no specific information regarding type of antipsychotics; participants described barriers to monitoring and management of cardiovascular and metabolic side effects
Vandyk, 2012; Canada (164)	Low concerns	To explore the subjective experience of weight and lifestyle from the perspective of people with schizophrenia	Qualitative study within constructivism paradigm	Interview	Outpatient clinic at psychotic hospital	19 patients diagnosed with schizophrenia or schizoactive disorder	Patients with mental health conditions	Schizophrenia or schizoactive disorders	100%	Atypical antipsychotics100 %, conventional antipsychotics 39%
Wärdig, 2015;	Low concerns	To describe how persons with psychosis	Qualitative, phenome	Interview: semi-	Psychiatric outpatient care	40 participants with psychosis	Patients with severe	Patients diagnosed with psychosis	Not reported	The participants were on outpatient care with

Study ID & Country	Conserns regarding the methodological limitations	Aim	Design	Data collection method	Setting	Sample size	Participants	Mental health diagnosis	Proportion of patients prescribed antipsychotic drugs	Information on the use of antipsychotic by patients
Sweden. (165)		perceive participation in a lifestyle intervention, and use these perceptions to present factors to for consideration in future interventions	nological approach	structured			mental illness			diagnosed psychosis and medicines use

Table 4-2. Characteristics of studies not involving patients as participants

Study ID & Country	Conserns regarding the methodological limitations	Aim	Design	Data collection method	Setting	Sample size	Participants	Information on the use of antipsychotic by patients
Bergqvist, 2013; Sweden.(166)	Low concerns	To explore mental health professionals' experiences of assisting people with a psychotic disorder to implement lifestyle changes in an effort to prevent metabolic syndrome.	Phenomenology	Interview	Psychiatric outpatient care.	12 healthcare staff members (9 specialised nurses, 2 Outpatients' therapists, 1 nursing assistant.	Mental healthcare staffs	Participants described barriers to monitoring and management of cardiovascular and metabolic side effects
Happell, 2013; Australia. (167)	Low concerns	The current study seeks to explore nurse views on screening/monitoring of the physical health of consumers with SMI, in mental healthcare.	Qualitative exploratory study	Focus group interviewers (6 groups)	Regional mental healthcare service	38 nurses	Community mental health nurses	Nurses described barriers to monitoring and management of cardiovascular and metabolic side effects amongst their patients
Hultsjö, 2012; Sweden. (168)	Low concerns	To describe mental health staff experiences of giving support to prevent type 2 diabetes mellitus (DM) among people with psychosis in community psychiatry.	Qualitative exploratory study	Semi-structured interviews	Community mental health services	12 community healthcare staff	Community mental healthcare staff	Interviews were conducted in the context of antipsychotics increasing risks of cardiovascular and metabolic comorbidities
Hultsjö, 2013; Sweden. (168)	Low concerns	To explore and analyse mental healthcare staff's (MHCS) knowledge and experiences of	Qualitative exploratory study	Semi-structured interviews	Unclear	12 mental healthcare staff	Mental healthcare staff	Participants described barriers to monitoring and management of cardiovascular and

Study ID & Country	Conserns regarding the methodological limitations	Aim	Design	Data collection method	Setting	Sample size	Participants	Information on the use of antipsychotic by patients
		diabetes care for persons with psychosis						metabolic side effects
Hyland, 2003; Australia. (169)	Moderate concerns	To examine the attitudes and practices of case managers working in Area Mental Health Services (AMHS) towards the physical health of people with chronic mental illness.	Mixed-method ; cross sectional study and interview	Focus group interviews (4 groups)	Multicentre (4 mental health clinics)	111 case managers working in community mental health	Community mental health case managers	Participants described barriers to monitoring and management of cardiovascular and metabolic side effects
Mangurian, 2013; USA. (170)	Low concerns	To examined primary care providers' beliefs about the roles that primary care providers and psychiatrists should play in metabolic monitoring and treatment of metabolic abnormalities among people with severe mental illness.	Cross sectional study	survey	Urban safety net clinic	214 primary healthcare providers from 23 public community health Clinics.	Primary healthcare providers	Participants described barriers to monitoring and management of cardiovascular and metabolic side effects amongst their patients
McDonell, 2011; USA. (171)	Moderate concerns	To assess the relative importance of patient, provider, and systemic barriers to metabolic syndrome management for	Cross sectional study	Survey	Not specific	68 medical, mental health, and other stakeholders who care for patients	Wide range of healthcare professionals.	All healthcare providers who participated were involved in delivery of care for adults

Study ID & Country	Conserns regarding the methodological limitations	Aim	Design	Data collection method	Setting	Sample size	Participants	Information on the use of antipsychotic by patients
		persons with severe mental illness				with severe mental illness.		prescribed antipsychotics
Mwebe, 2017;UK. (172)	Low concerns	To explore nurses' views of their role in the screening and monitoring of the physical care needs of people with serious mental illness in a mental health service provider	Qualitative exploratory study	Semi-structured interviews	Mental health inpatient centre	10 mental health nurses	Mental health nurses	Nurses described barriers to monitoring and management of cardiovascular and metabolic side effects amongst their patients
Robson, 2013; UK. (173)	Low concerns	To examine mental health nurses' attitudes to physical healthcare and explore associations with their practice and training.	Cross sectional study	Survey	National Health Service (NHS) Mental Health Trust	Sample of 585 qualified mental health nurses	Mental healthcare staff (mental health nurses)	Participants described barriers to monitoring and management of cardiovascular and metabolic side effects amongst their patients
Wheeler, 2010;New Zeeland. (174)	Low concerns	To invest health practitioners' views on their role in assessing and managing their clients' cardiovascular risk profile. We also sought to explore the practitioners' perceptions of barriers and solutions for the	Qualitative study	Semi-structured interview	Unclear	Sample of 9 participants	Healthcare professionals (psychiatrists/psychiatric trainees, general practitioners, nurse specialists, mental health pharmacists, and consumer advisors.	Healthcare professionals described barriers to monitoring and management of cardiovascular and metabolic side effects

Study ID & Country	Conserns regarding the methodological limitations	Aim	Design	Data collection method	Setting	Sample size	Participants	Information on the use of antipsychotic by patients
		management of cardiovascular risk in people with mental illness.						

4.3.3. Quality of the included studies

The assessment was based on the four critical appraisal categories of qualitative evidence: i) credibility, ii) transferability, iii) dependability, and iv) confirmability. Of the ten elements that are presented by the assessment tool (JBI), most studies fulfilled at least 6 criteria. Most studies met quality indicators related to the congruity of the selected method to answer the research question, rigour sampling and data collection method, and representation of participants' voice. Confirmability across the studies was generally weak as none of the included studies failed to provide information regarding the potential influence of the researcher on the study results (Appendix IV-C). This review included studies that met the inclusion criteria despite the methodological quality. The quality assessment of the studies was used to guide the judgment of the relative contribution of each study to the review findings. For this review, the CERQual approach was adopted to define confidence in the review findings.(175) The trustworthiness (confidence) of each finding was ranked as either high, moderate or low based on the adequacy of the data and the methodological quality of the studies contributing to that finding. The emerging finding was considered to be of high confidence if adequate supportive data were provided and the contributing studies were of low methodological concerns.

4.3.4. The emerged themes

A total of 40 themes were extracted, then inductively categorised into nine categories and further into two synthesised findings extrinsic and intrinsic factors. A detailed description of the identified themes and corresponding sub-themes is reported in Table 4-3. Key categories and themes are described below.

Table 4-3. Themes, Categories, and synthesised findings in relation to barriers to monitoring and management of cardiovascular and metabolic health of patients prescribed antipsychotic medicines.

Themes	Category	Synthesised findings
Social context and support (155,157,158,162,165)	Family and community factor	Extrinsic factors
Lack of support from family/friends (154,163,167,171)		
Poor communication/ coordination between different healthcare providers /sectors (154,159,164,167,169,170,172,174)	Provider and healthcare system factors	
Insufficient physician time (157-160,166,170,173)		
Fragmentation of care (157,160,162,166)		
Patient- healthcare professional relationship and communication (157,164)		
Issue of lack of clarity for responsibility for conducting physical healthcare (164,166)		
Lack of resources to manage healthy life-style (157,160,162,171,172,174)	Lack of resources	
Lack of equipment or suitable space (159,162,174)		
Staff turnover (159,162)		
Lack of qualified staff to manage physical health issues (160)		
Primary care providers are not paid enough (160)		
Lack of insurance (167)		
Cost of running interventions or groups (159)		
Lack of access to qualified psychiatric follow-up (152,160,170)	The Intervention site and the intervention characteristics	
Intensity of the applied intervention (164,165)		
Leadership is not making managing physical health issues among patients with SMI a priority (159,160,164)		
Difficulty traveling to specialised service (159)		
Transportation problems (154)		
Poor patient attendance (159)		

Themes	Category	Synthesised findings
Mental health condition related disabilities (158,160,163,165,169,172,174)	Mental health condition as a barrier	Intrinsic Factors
Severity of psychotic symptoms (158,160,169-171)		
Consequences associated with the side effects of the antipsychotic medications (160,165,167,169)		
Stigma/Isolation/estrangement (154,156,157,161,166)		
Motivation level among participants regarding general health issues (155, 159,160,162,164,167,171,173)	Psychological factors	
Participants views and behaviour toward specific intervention (158,159,162,164,173)		
Participants' views and behaviour regarding screening, monitoring of general health issues (154,159,169)		
Stress (154,159,174)		
Participants' knowledge about healthy lifestyle (167,169-171-174)	knowledge and skills	
Participants' knowledge about the medicines side effects (162,173)		
Lack of knowledge and training among healthcare providers to manage physical health issues (156,157,160,165,166,174)		
Functional limitation (154,174)	multiple-physical comorbidities	
Negative effects of certain conditions e.g. pain (160)		
Non-concordance with drug therapy (174)	Compliance issues	
Social context and support (155,157,158,162,164)	Family and community factor	
Lack of support from family/friends (154,162,167,171)		

4.3.4.1. Extrinsic factors

This theme includes factors related to the patients' community and their surroundings. (152-158,163-172)

a. Provider and healthcare system factors

Care coordination and teamwork between different sectors and healthcare professionals were deemed essential for timely screening and monitoring.(164,167,169-171) This finding was considered as moderate confidence because five studies of low methodological concerns contributed with data to the findings of this review. All of those studies were assessed as having minor methodological concerns related to reflexivity as it was not clear whether the individuals collecting the data were also providing healthcare to the patients. According to one study (169), the low rate of physical health examination in patients with psychosis was attributed to the lack of care delivery integration between general practitioners and psychiatrists. Similarly, primary care providers complained about the lack of collaboration between healthcare professionals from different sectors which resulted in difficulties to refer patients to specialised care.(170)

Managing general health conditions in patients with mental health conditions such as diabetes were not considered as a priority in some primary care settings.(160,164,174) Effective communication between healthcare providers was cited as vital.(154,156,174) For instance, general practitioners pointed out that communication difficulties often occurred during the transfer of care across sectors (e.g. primary to secondary care), and as a result, essential information including test results was often missed.(158)

Time constraints was a main restriction for effective interaction between health professionals and their patients.(156,157,160,166,170,173,174) Patients complained about their inability to discuss their conditions with their healthcare professionals due to short

consultation time.(170) Similarly, mental health nurses were concerned regarding their inability to check patients' physical health due to their heavy work schedule.(166)

The positive relationship between patients and their healthcare providers were reported to be helpful for better health outcomes.(164,172) The patient-provider relationship was reported to be indirectly influenced by the behaviour of healthcare providers at the time of consultation. Patients reported that the disinterest they observed from the healthcare professionals resulted in a lack of trust between the two parties. Consequently, patients may hesitate to share their physical issues with their providers.(154,174)

b. Lack of Resources

Health professionals considered resource limitations and restrictions imposed by funding bodies such as national health systems and insurance companies as barriers that hinder their ability to manage the physical health of patients.(160,162,166,169-172) This theme emerged from seven studies that all had some methodological limitations. The overall confidence in this finding was considered moderate as five studies had low methodological concerns (reflexivity was not properly addressed) and most of the studies contributed to adequate data.

The lack of financial support from organisational bodies appeared to affect the quality of care delivered to manage physical health issues in patients with mental health conditions.(156,160,163,166,170,172,174) This factor contributed to several issues mainly lack facilities and equipment to screen physical health issues; lack of professional training necessary to manage general health conditions (e.g.,diabetes).(162,166,174) Participants, particularly healthcare providers in mental health clinics, reported difficulties to collect patients' blood sample due to the unavailability of laboratory services at the clinic. Consequently, patients had to be referred to another centre to carry out the analysis.(174)

Similarly, mental health nurses pointed out that lack of economic support was a major factor that hindered embedding physical health screening and monitoring into their clinic.(166,172,174)

Notably, insufficient financial support appeared to impair the performance of staff working in mental health services.(156,158,159) The increased concerns regarding the notable increase in resignation rate among healthcare providers, as they were not satisfied with the increased workload and decreased payment.(160,162,174) Patients shared similar views regarding the costs of the available services to manage their physical health.(156,160,162,171,172) Patients participated in lifestyle/weight loss interventions programs complained about their inability to afford the money to buy healthy food.(162) Similarly, healthcare professionals highlighted the poor financial status of the patients as a barrier for their compliance with cardiovascular screening.(171)

Further concerns raised regarding the availably of competent staff to manage physical health issues in patients with mental health conditions.(174) Both healthcare professionals and patients agreed on the importance of professional training as it was seen as a facilitator that enables the providers to manage comorbid general health conditions.(157,158,160,165,166,174) As a result, healthcare professionals in mental healthcare services had to limit their efforts and focus on managing mental health conditions only despite co-existing morbidities such as diabetes.(160,162) The limited appointments within general practices were also cited as a barrier.(160,174)

c. The intervention site and the intervention characteristics

The subcategories related to this theme reflected factors related to the intervention setting and the characteristics of the applied intervention (e.g. physical health management programmes). Lack of access to specialist healthcare professionals or services to check

physical health issues among patients was indirectly cited as a barrier by both patients and healthcare professionals.(154,155,160,164,170,174)

Both healthcare professionals and patients agreed that scarce facilities for monitoring physical health (e.g., general practices), could result in travelling difficulties among patients and hence irregular cardiovascular follow-up.(154,174) The intensity of the exercise sessions was highlighted as a barrier that prevents patients from regularly participating in exercise-based interventions.(164) However, despite the low methodological concerns, the confidence in this sub-theme was low due to the inadequacy of the data.

d. Patients' family and community factors

This theme comprises factors that are related to patients-family/community relationship. The confidence of this finding was considered moderate. As there were minor concerns about the adequacy of the data; nine studies that collectively offered plethora of data to this finding, were characterised by minor methodological limitations. Social support was vital for successful management of co-morbidities in patients with psychosis.(163,165,167,172,174) Many patients agreed that group-based interventions had a positive impact on their relationship as it contributed to new friendships.(155,167,172) Furthermore, involving family members in lifestyle modifying interventions deemed to have positive and long-term impacts for patients and their families.(164,167)

However, the same experience was not always associated with positive results for others.(158,164) Anxiety resulting from being surrounded by "strangers" represented additional burden for some patients and hence hindered their participation in group-based interventions.(158) A similar effect was reported by another study (164), which highlighted that participants (patients) in group-based exercise tended to compare their achievement with their peers which consequently resulted in their withdrawal from the sessions.

4.3.4.2. Intrinsic factors (patients related factors)

Mental health condition, psychological factors, participants' knowledge and skills and existing comorbidities were the key barriers to undergoing screening, monitoring and managing cardiovascular and metabolic issues in patients with mental health problems (Table 4-3).

a. Mental health condition as a factor

This theme and its related sub-themes: disabilities associated with the psychotic disorder, consequences of the antipsychotic medications regarding participation in physical health activities, the severity of psychiatric illness and stigma/isolation/estrangement were recognised by both patients and care providers that negatively affect screening, monitoring and management of cardiovascular co-morbidities.(154,157,158,160,161, 163,165,167,169,171,172) In general, this finding was scored of moderate confidence as this theme and its related sub-themes had minor methodological concerns and high adequacy of the data.

The severity of psychotic symptoms; adverse effects of psychotropic medicines were recognised by both patients and care providers that negatively affect screening, monitoring and management of cardiovascular co-morbidities.(158,160,161,162,165,169,172) A major difficulty, from healthcare professionals' perspective, was the aggressive behaviour and depression resulting from the psychotic symptoms.(160,170) Mental health nurses spoke of the need to prescribe tranquilisers that would manage aggressive behaviour among patients with mental health conditions which would enable better screening and monitoring.(165) Additionally, patients reported that some psychotic symptoms, mainly depression prevented them from actively participating in physical activities.(160,163)

The severity of psychotic symptoms represented another barrier for screening and management of cardiovascular comorbidities for both patients and healthcare providers.(160,161,165,167,169-171) According to one study (170), around 35% of participants (community healthcare professionals) agreed that the more severe mental health conditions, the more difficult to conduct screening of co-morbidities. Similarly, there was a notable lack of cooperation among patients toward simple procedures, including giving blood samples.(165)

Both healthcare professionals and patients expressed their concerns regarding some side effects of psychotic medicines which interfere with patients' engagement in physical activities.(158,165,167,169) Health professionals stated that the sedative side effects of some psychotropic medications could make it difficult for patients to participate in exercise-based programmes.(158,165) Findings of a study exploring diabetic care experience and knowledge among mental healthcare staffs showed that low rate of patients' attendance to diabetes appointments was associated with the hangover symptoms of psychotic medicines mainly drowsiness.(167)

"Mental health stigma" or having mental health conditions was highlighted in several studies as a patient-related barrier to effective screening and management of cardiovascular co-morbidities.(154,157,160,171) The effect of stigma was reflected as difficulties raised from the distorted image of being mentally ill, which can affect a patient's interaction with others (e.g. family). For example, patients believed that having mental health conditions compromised their relationship with their families by assuming that they are incapable of dealing with their daily life challenges. Consequently, patients felt isolated and estranged among their own families and hence hesitated to ask for help when needed.(154)

b. Psychological factors

Intrinsic psychological factors such as participants' views, feelings, behaviour and attitude were the most commonly cited factors. Patients with mental health conditions seemed to hold various views and attitudes toward their conditions which could affect their motivation to receive treatment of any kind. Patients highlighted negative attitudes and views such as hopelessness, low self-esteem/motivation as major barriers for receiving cardiovascular or metabolic care.(154,155,158,159,162,164,167,169,172,173)

Motivation was perceived as a driving force for adopting healthy lifestyle among patients with mental health conditions.(155,159,162,170,171,173) Patients' optimism of a good healthy life was strongly associated with the intentions to participate in physical activity programs.(171) On the contrary, lack of motivation among patients with mental health conditions was a major obstacle that prevented adopting healthy life behaviour.(164,170,171,173) Particularly, low expectation associated with mental health conditions acted as a barrier for some patients to initiate physical activities.

Participants including healthcare providers and patients, agreed that patients' negative views towards specific interventions that are intended to manage cardiovascular side effects (e.g. exercise-based interventions) could affect their adherence or participation in the program, mainly due to general dislike or disinterest.(169,173,174) Previous unsuccessful experiences shaped participants' views towards particular intervention such as exercise.(158,164) For instance, patients, who underwent a failed experience, felt distressed when their expectations were not met, and hence, they would withdraw from the program.(164)

Generally, patients expressed unfavourable attitude toward physical health screening and monitoring. In several studies, patients tended to ignore their physical health due to several

reasons including lack of concerns over their general health (159,169,174) additional to lack sense of worth.(169) Some studied showed that patients' excessive concerns regarding their general health represented an additional burden that would hinder their abilities to manage their physical health issues.(154,159,174) Several studies (12/21) contributed to this finding (154,155,158-160,162,164,167,169,171,173,174), which were ranked to have minor methodological concerns mainly lacking the author's reflexivity on the findings. Consequently, the themes related to this finding were considered to have moderate confidence owing to the adequacy of the data contributing to this theme and associating sub-themes.

c. Knowledge and skills

Healthcare providers tend to agree on the importance of having solid knowledge about cardiovascular and metabolic risks associated with antipsychotic drugs and the necessary skills to manage them.(156,165,167) Healthcare professionals expressed their concerns about the difficulty to identify patients in need for cardio-metabolic monitoring and hence their inability to manage those patients (160,167,169,174) properly. For example, one study aimed to explore mental healthcare staff's knowledge and experiences to manage diabetes in patients with psychosis identified that key factors affecting diabetic care delivered by mental healthcare staff was having knowledge about diabetes as it increased their confidence to deal with susceptible diabetic cases among patients.

Besides, participants' knowledge about positive lifestyle habits such as a healthy diet was cited as a facilitator for patient's participation in weight management programs.(164,167, 169,170,174) Patients' felt that having solid knowledge about the nutritional facts was important as it helped them adopt healthy lifestyle.(159,163) Patients' knowledge about the metabolic side effects of antipsychotic medicines increased their awareness of their general

health and hence motivated those to take actions (participate in physical health activity programs).(163) However, knowledge did not necessarily associate with positive health outcomes.(163,173) Robson (173) found that around 21.7% of the respondents (n=125/577) agreed that patients' knowledge about the side effects of their psychotic medicines was associated with low adherence.

d. Physical comorbidities in patients with mental health conditions

For some patients, managing multiple-comorbidities was stressful and difficult.(161,171,172) For instance, a complex treatment regimen for both mental health and chronic conditions (e.g. diabetes) caused difficulties among patients due to the concurrent demands of competing co-morbidities.(172) Also, physical complications such as chronic pain and fatigue resulted in difficulties for patients during exercise-based interventions.(172) The finding was graded as low confidence since only three studies contributed with data to this theme, all were rated to be of low concern due to the lack of researcher reflexivity and one study offered thin data.

4.4. Discussion

To the best of our knowledge, this is the first systematic review of contributory factors for effective monitoring and management of cardiovascular and metabolic comorbidities in patients taking antipsychotic medicines. This review identified a number of potential key factors which affect the screening and management of physical health issues, namely cardiovascular and metabolic side effects of antipsychotic drugs.

Themes concerning mental health conditions as identified in this study can be related to the stigma model proposed by Knaak (176) and Ahmedani (177) Personal stigma refers to the self-perception of stigma. Interpersonal stigma refers to the stigmatised attitudes/

beliefs towards individuals with mental health conditions. Structural stigma refers to the discrimination in healthcare services that patients may encounter. Patients may lack confidence and hesitate to share issues related to their physical health. Evidence on studies associated with mental health- stigma in healthcare (177) showed that even well-trained professionals working in mental health disciplines are subjected to interpersonal mental health stigma. This can result in a lack of mutual trust between patients and healthcare professionals and hence affect information sharing between the involved parties. Anti-stigma intervention for HCPs, such as the 'targeting the roots of healthcare provider stigma', (178) can be useful. This model requires improving: the ability of healthcare professionals to manage and cope with their emotions when working with patients in challenging situations; improving competence and confidence of staff; and addressing the lack of awareness of one's prejudices.

This systematic review shows that symptoms associated with severe mental health conditions often make healthcare professionals and patients engage in physical health monitoring. Particularly, the aggression and depressive symptoms associated with these conditions alongside the sedative effects of some antipsychotic medicines presents as a barrier to effective monitoring and management. Appropriate choice of drug therapy is imperative in managing symptoms of severe mental health that can enable better communication between patient and healthcare professionals.(179) Family and carer involvement is imperative in the process. Peer-led support groups have also been shown to be effective in improving hope, recovery and empowerment (180) There is a scope for such interventions to be tested in improving physical health monitoring programmes.

The organisational and system-related barriers to the monitoring of physical health amongst patients taking antipsychotic medicines require urgent attention. Fragmentation of

care was identified to be a key barrier. Fragmented responsibilities of specialist mental health services, primary care including community psychiatric clinics were shown to have led to confusion amongst healthcare professionals with regards to the roles and responsibilities in monitoring physical health and the referral process. While NICE guideline in England provides clear remit for primary care in monitoring physical health, the practice seems to be suboptimal. In addition, there is a need to improve on the knowledge of mental health service providers on physical health and monitoring. Furthermore, the studies demonstrated lack of resources and funding that constrained their responsibilities. In the UK, the one appointment one problem culture often contributed to the problem. The resource was also a patient-related barrier as studies described a lack of means for the patients to afford healthy eating and exercise.

This review suggests that having solid and trusting relationship was vital for patients with mental health conditions as it promotes better health outcomes. The review highlighted a pattern of hesitation to seek help among patients. Patients with mental health conditions often feel isolated from the community. Subsequently, they tend to be more independent and become their own counsellors, (181) which causes more isolation. Therefore, considering the psych-social aspects of mental health conditions by involving family and friends in the management process is vital.

4.4.1. Critical appraisal of the included studies

The methodological limitations of the body of data supporting the review findings were assessed to identify whether any methodological weaknesses within the individual studies has impacted the confidence level in the study findings. When assessing the four quality features of qualitative research, the assessment indicated that the elements reflecting the reflexivity of the researcher were significantly lacking such as information highlighting the

researchers' position and their influence in the studied context and how these perspectives were articulated and considered during the design of the study. For example, according to the context of this review, it was not clear whether the researcher was a GP providing care for patients taking antipsychotics, or an outsider researcher (undergraduate researcher). Also, the level of knowledge and experience of the researcher in relation to the topic under investigation was unclear.

Reflexivity is a key indicator of trustworthiness in qualitative research since collecting and understanding the data may be framed by researcher presuppositions. However, addressing details about the interaction of the participating researcher can be difficult because such information may not be usually provided within the research manuscript. All of the included studies were published as papers in health research journals, leading to word limitations not particularly well suited for reporting qualitative research. Also, there is no clear guidance to show how reflexivity can be employed as a strategy in qualitative research and to monitor the researcher's subjectivity in generating credible findings.(182) In this review, the overall confidence level of the findings can be substantially impacted by the lack of reflexivity across the studies, despite the compensation provided by the other quality features that existed in the studies.

Most of the included studies (n=18) used individual or group interviews. A small proportion of the studies (3/21) used surveys to gather data about the management of cardiometabolic complications in patients with mental illness. The data collection technique used among the individual studies can affect the nature of the data and can affect the confidence level in the results particularly if the method was not appropriate for the study design. For example, the confidence level in findings obtained from a study where

participants response were collected by a questionnaire may be low due to the lack of depth and richness of the collected data.

4.4.2. Strengths and limitations

The current review has several limitations. Somes of the included studies in this review did not recruit patient participants based on their use of antipsychotic drugs. However, during full-text screening, it was decided to include the studies where participant accounts of barriers to follow-up and monitoring of cardiovascular side effects of antipsychotic drugs were presented in the results. Moreover, the included studies originated mainly from the Western countries, which limit the generalisability of our findings.

Despite the limitations, this review provides an insight into potential factors influencing screening and management of cardiovascular and metabolic side effects of antipsychotics. The review employed an inductive thematic synthesis of qualitative studies of participants' perceptions from various backgrounds. Using such an approach provides reflexivity as it involves exploring the available evidence from participants' perspectives. Besides, our flexibility in the study inclusion criteria needs to be considered when generalising the study findings. Furthermore, the methodological quality of included studies was assessed using Joanna Briggs (BJI) assessment tools, which provides uniform and structured evaluation of the studies.

4.4.3. Implications for practice

Despite the evidence and guidelines that support the importance management of cardiovascular and metabolic side effects of antipsychotics, regular assessment of the implementation of such guideline is imperative. Participants of the studies included in the systematic review prefer integrated models of monitoring and management of both physical and mental health, and there is a need to minimise fragmentation of care. This can be

facilitated by addressing the contributory factors to monitoring and management of the side effects as identified in this systematic review.

Individualised interventions to tailor the needs of the patients shown to minimise barriers to participation in exercise-based interventions. Patients with severe mental health conditions often face barriers to managing their physical health due to negative symptoms and cognitive impairment. Therefore, knowledge-based interventions alone are not adequate. Persistent and sustainable involvement is necessary. Peer-led support network is known to be important in promoting engagement in physical exercise. These are particularly important where patients lack family and friends support. Funding bodies and stakeholders must understand the needs of their employers. This can be fulfilled by promoting professional development within the organisation.

Previously, suggestions have been made around clinical, particularly nursing staff being trained to manage both physical and mental health issues in order to provide person-centred care. Previous literature has shown that nurses are generally in favour of physical healthcare as part of their role. (183) However, those without the background of generalist nurse training were less comfortable about their expertise. Appropriate reimbursements should be provided to uptake additional roles in community mental health and specialist psychiatric units.

4.4.4. Future directions

Currently, this review suggests that numerous patients prescribed antipsychotics are not properly monitored, counselled or managed for cardiovascular and metabolic side effects. The limited number of the available studies addressed factors barriers/facilitators for screening and management of antipsychotics associated cardiovascular and metabolic issues. This suggests poor empirical evidence which underpins current information practice

in contributory factors for the management of cardiovascular and metabolic side effects of antipsychotic medicines. Further research is required to address contributory factors for sub-optimal management of cardiovascular and metabolic side effects of antipsychotics from the perspectives of patients, healthcare professionals, family and carers of patients with severe mental health problems.

While this review focused on barriers for screening and management of cardiovascular comorbidities in patients with mental health conditions, future research should be directed to elicit facilitators to neutralise those barriers. Furthermore, future research should target stigma facilitators at different levels. Further studies on healthcare professionals' stigma are essential to address all dimensions of stigma across different levels. Obtaining the views of wider stakeholders would provide further insight into the barriers and facilitators to resource allocations between mental and general health sectors. Multi-morbidity including poor mental, physical health and substance misuse and poor access to services can lead to homelessness and social disparities. (184–186) There is a need to develop innovative services delivery models, such as outreach programmes to support patients with severe mental health (187–189) and evaluate their impact on health and quality-of-life outcomes.

4.5. Conclusions

This study demonstrates that barriers to monitoring, counselling and management of cardiovascular and metabolic health of patients taking antipsychotic medicines are multidimensional. Knowledge-based interventions alone will be insufficient in improving the practice. There is a need to address the fragmentation of care, lack of resources to address co-morbidity in clinical consultations and stigma in the healthcare setting. There is a scope to

develop, implement and evaluate peer and family support-based interventions in improving the practice.

List of abbreviations

ADA: American Diabetes Association

APA: American Psychiatric Association

C: Credible

CRD: Centre for Review and Dissemination

ECG: Electrocardiogram

FDA: Food and Drug Administration

JBI-QARI: Joanna Briggs Institute Assessment and Review Instrument

NICE: National Institute for Health and Care Excellence

PRISMA: Preferred reporting items for systematic review and meta-analysis

PRISMA-P: Preferred reporting items for systematic review and meta-analysis- Protocol version

U: Unequivocal

US: Unsupported

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by the University of Birmingham, United Kingdom. RAA is supported for her PhD by the Royal Embassy of Saudi Arabia, London, United Kingdom. The funding bodies had no roles in the design, conduct, analysis of data and preparation of this manuscript.

Authors' contributions

This work related to RAA's PhD study. VP and ZJ were the supervisors to the study. All authors designed and conducted the study. RAA led the write up to which all authors contributed through editing and recommendations. All authors agreed to the final version of the manuscript.

Acknowledgements

We would like to thank the University of Birmingham Library services for helping to source the literature.

Data availability

All data associated with the manuscript has been reported in the manuscript and supplemental materials.

Conflicts of Interests

No authors have any conflicts of interests to disclose.

Chapter 5 Evaluating the Extent of Cardiometabolic Screening and Monitoring in Patients Prescribed Antipsychotic Drugs: Longitudinal Analysis of Data from The Health Improvement Network (THIN) Database

Summary of the chapter

This chapter presents the work associated with an observational study evaluating the level of cardiometabolic monitoring among patients prescribed antipsychotics using the THIN database. It presents the method used, including the study cohort's development and the analysis plan. It also discusses the findings and their relation to the body of evidence.

5.1. Introduction

Although the aetiology of cardiovascular diseases (CVDs) in people with mental health conditions is multidimensional, research evidence suggests that antipsychotics have the potential to cause cardiovascular risk or accelerate pre-existing conditions.(8) In 2003, the U.S. Food and Drug Administration (FDA) launched a black box warning regarding the diabetogenic effect of antipsychotics.(190,191) In response to these warnings, a panel of regulatory bodies and professional associations, including the American Diabetes Association (ADA)/American Psychiatric Association (APA), published a consensus statement that recommends early and regular monitoring of metabolic side effects among antipsychotic users.(40) Consequently, cardiometabolic dysregulations management in patients with mental illness has received considerable attention and focused on clinical guidance and healthcare policy.(192) In July 2014, the National Institute for Health and Care Excellence (NICE) guidelines for managing schizophrenia in adults were updated to include monitoring and managing cardiometabolic abnormalities.(22) Effective monitoring and management of cardiometabolic abnormalities in patients taking antipsychotics aim to: (I) identify high-risk populations, for example, diabetic patients prescribed clozapine; (ii) track cardiometabolic disturbances among antipsychotic users and assess their association with antipsychotic therapy.(193)

Despite the NICE recommendations, routine cardiometabolic monitoring has remained suboptimal. As a result, undiagnosed and untreated cardiovascular and metabolic diseases among patients prescribed antipsychotics remain high due to suboptimal screening, leading to missed opportunities for using primary preventive measures, (194) exacerbating co-existing comorbidities and decreased life span. In addition, evidence reveals that people with mental illness face some disparities in cardiometabolic screenings and monitoring compared to the general population.(36,195) To alleviate the risks of cardiometabolic side effects of antipsychotics, there is a need for a detailed understanding of how healthcare professionals currently respond to those side effects in people prescribed antipsychotics.

5.1.1. Aim and objectives

This study sought to investigate the level of adherence to cardiometabolic monitoring guidelines in primary care. This was achieved by assessing the prevalence of cardiometabolic monitoring outcomes recorded for patients prescribed antipsychotic drugs. Also, the study aimed to identify and compare the monitoring patterns in patients treated with different antipsychotic agents.

5.2. Material and method

5.2.1. Research proposal

A protocol for this study was developed by the research student (RAA) and reviewed by the supervisory team and an external expert panel. The proposal for this study is found in the appendices of this thesis (Appendix II-E).

5.2.2. Ethical approval

Studies using the THIN database gain ethical approval from the UK National Health Service Southeast Multicentre Research Ethics Committee. The Scientific Review Committee (SRC)

approved the study protocol (no. SRC 19THIN070). The decision letter is provided in Appendix II-C.

5.2.3. Study design

This was a retrospective longitudinal open cohort study using patients' clinical data from the THIN database. The study was reported as per the STrengthening the Reporting of Observational studies in Epidemiology (STROBE) statement for observational studies.(196)

5.2.4. Data source

The THIN database is an extensive electronic database containing routine patient records collected from approximately 562 general healthcare practices (GPs) around the UK. The THIN database is considered a representative data source of the UK population as approximately 11 million (≈ 6.2%) of the UK population. Clinical data related to medical diagnoses, disease symptoms and examinations are coded using the Read coding system. This standard clinical terminology system is used by general practices in the UK, allowing the data to be structured to facilitate data entry and extraction. Such information includes but is not limited to patients' demographics, the diagnosed condition, longitudinal records of symptoms, routine clinical care measures, laboratory investigations, written prescriptions by GPs, other treatments and therapies and referrals to specialised care.(197)

Also, the THIN database has a hierarchical prescription coding system that mainly classifies drug information using the British National Formulary (BNF) codes. The first coding level refers to the BNF chapter. For example, drugs in BNF Chapter 4 (Central Nervous System) always begin with '04'. The subsequent level gives information related to sub-sections within the particular chapter (e.g.,'0403' refers to Antipsychotic Drugs in Chapter 4 Section 3 of the BNF). The remaining characters of the BNF code add additional information related to the drug (e.g., generic or branded, drug strength and dosage form, etc.). The

coding system records information related to the prescribed drugs, including the date of issue, the generic name, strength and the drug formulation. To reduce underreporting of events and improve the validity of the dataset, all actively recorded patients taking antipsychotic medication should be participating in the practice for at least one year. This enabled sufficient time for patients' data transfer between different practices. Also, the same period allowed the practice to achieve Acceptable Mortality Recording (AMR), which is the year at which the level of recording of all-cause mortality by each practice is deemed acceptable; based on a comparison with the predicted numbers of deaths derived from National statistics given the individual practice's demographics.(198)

5.2.5. Participants and cohort identification

This study included patients prescribed long-term antipsychotics for mental health conditions, primarily schizophrenia-related disorders, affective mood disorders, and depression.

Inclusion criteria

1) Adult patients (aged ≥18 years) registered with primary care services in which the service was contributing to the THIN database, and prescribed antipsychotics for at least 12 months.
2) Patients with an established diagnosis of mental illness, primarily schizophrenia-related disorders, affective mood disorders, and depression (defined as a clinical READ code for diagnosing schizophrenia and other mental illness).
3) The participants were considered eligible if they were prescribed any of the antipsychotics mainly for diagnosed mental health conditions (defined as having a prescription drug code for antipsychotics for at least one year).

Patients who dropped out before completing one year of follow-up were excluded. Data for the last 15 years, from 1st January 2003 to 31st December 2018, were extracted. To identify our cohort, the THIN database was searched for antipsychotic drugs using a drug code list for antipsychotics in conjunction with READ codes related to mental illness, mainly schizophrenia and psychosis, bipolar, and major depression. The two code lists (Drug & READ codes) were created based on the literature and this work's objectives and eligibility criteria. Both code lists were reviewed by the abstractors before executing the final data extraction (JC and AS). This allowed systematic and valid data extraction. Additionally, the research team and the data providers further verified and piloted the code lists. Key quality elements in the data were fulfilled, including enhancing the data integrity using an inter-rater approach and working with field specialists who are experts in health information (the data providers).(199) Details related to the code lists are provided in the supplementary appendices of this thesis (Appendices VI A&B).

The code lists can be found in the appendices of this thesis (Appendices V-C and V-A). The cohort began on Jan 1, 2003; this date was selected as the warnings regarding the increased metabolic risks of second-generation antipsychotics were first introduced by the FDA.(191) Patients were considered on stable antipsychotic treatment if they had at least four consecutive antipsychotic prescriptions within one year. Patients had to be ≥ 18 years old by the date of their fourth prescription to be eligible for the study. The process of cohort identification is detailed in Figure 5-1.

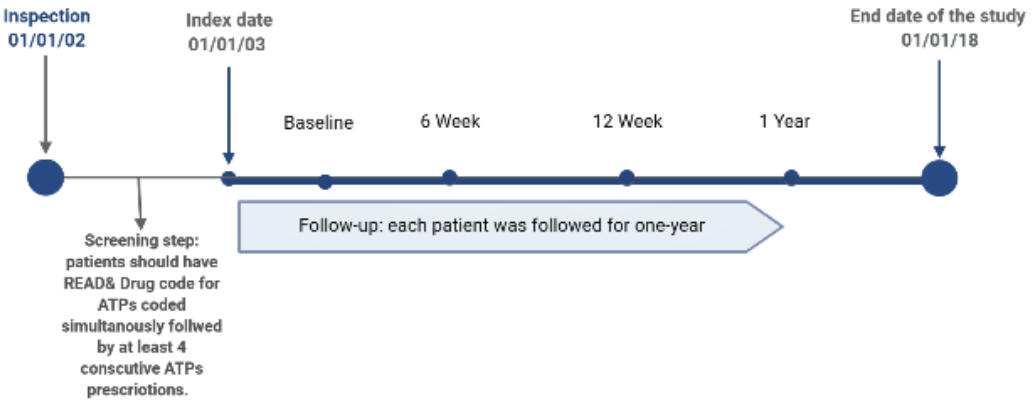


Figure 5-1. Flow diagram of the data extraction process and selection. ATPs: antipsychotics. Data were extracted for 15 years, but each patient was followed for only one year. Created by BioRender.com. (16)

To ensure patients' eligibility for treatment chronicity, a testing window was set up where records were screened one year earlier than the study start date to ensure patients had at least four repeated antipsychotic prescriptions (trial period) (Figure 5-1). Then the index date was adjusted to be the date of the first antipsychotic prescription that was directly issued after the patient was diagnosed with mental illness. Participants were followed until the earliest of the following dates: outcome event, death, patient leaving practice, the practice stopped contributing to the database, and study end date (Dec 31, 2018); thus, the cohort follow-up is variable as patients leave the study at different times.

The data were tailored to focus on monitoring patterns within the first year after the first antipsychotic prescription. Then records of outcome measurement were extracted for one year at any time in the database. This allows investigation of cardiometabolic monitoring patterns for the first year of initiating the antipsychotic treatment.

5.2.6. Definitions of study outcome

The outcomes of interest were the prevalence (proportion in %) of patients with at least one monitoring record for any cardiometabolic components according to the local/national guidelines.(22) For each patient, information related to cardiometabolic outcomes, including records for body composition, blood pressure, blood glucose and lipid panel, were extracted. Also, baseline values were collected for each outcome. In addition, other information related to the patient clinical characteristics, including diagnosed mental illness and the prescribed antipsychotic were extracted.

5.2.7. Outcome measurements

The term 'cardiometabolic profile' refers to the analysis of body compositions and biochemical parameters, including:

I. Parameters for body weight: body mass index (BMI) & waist circumference (WC)
II. Blood pressure (BP)
III. Parameters for blood glucose: random blood glucose (RBG), fasting blood glucose (FBG) and glycosylated haemoglobin (HbA1c).
IV. Lipid profile: high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides (TGs).

The NICE/RCP guidelines recommended measurement of body composition, BP, fasting plasma glucose, and lipid profile to be taken at baseline, then at 6 weeks, 12 weeks, and then annually. The patients were defined to be monitored if they had records of the outcomes of interest at any time point (Table 5-1).

Table 5-1. Summary of monitoring and associated time-points recommended by the NICE guidelines

Standard monitoring	**Time points**				
	Baseline	Week-6	Week-12	Annually	Clinically indicated
Body mass index	✔	✔	✔	✔	✔
Waist circumference	✔		✔	✔	✔
Blood pressure	✔		✔	✔	✔
Blood glucose	✔		✔	✔	✔
Lipid profile	✔		✔	✔	✔

Reproduced from (22)

5.2.8. Baseline monitoring

The outcome measures for baseline monitoring were defined as the earliest event recorded up to 180 days before the start of the study (index date) and up to 7 days after the index date. The baseline value was the latest record closest to the index date.

5.2.9. One year follow-up monitoring

We only included measurements for one year. For each time point, follow-up monitoring for a specific time point was determined if monitoring records for a specific outcome existed around that time point. A time window of ±20 days for each time-point monitoring outcome was set up for each time point. Such practice allows flexibility to capture the outcome at each time point and helps minimise unintentional skipping. For instance, for patients to be monitored at week-6, relevant records should be available between 8-42 days from the prior time-point check (baseline) until the next time-point (week-6). The same concept was applied to the remaining time points. A period of 43-84 days from the previous corresponding time-point (week-6) was selected for the 3-month checkpoint. Similarly, 85-365 days from the previous corresponding time-point was applied for the one year checkpoint. Since Primary care usually invites patients once a year, patients who were

screened just over the 1-year time window, because of a delay in their response, were overlooked, leading to underestimated monitoring rate.

5.2.10. Monitoring consistency

Regular monitoring was defined as the proportion of patients who underwent complete monitoring of one particular cardiometabolic outcome at all recommended time points, regardless of the presence of any abnormalities within one year. On the contrary, incomplete, or irregular monitoring was defined as the proportion of patients with no outcome records at any time point within one year of antipsychotic initiation, i.e., 0 events of BMI monitoring records at baseline.

5.2.11. Analysis strategies and statistical plan

The monitoring prevalence was calculated for each cardiometabolic parameter within the 1st year of starting the antipsychotic therapy. The prevalence was reported as proportions (%) and corresponding 95% confidence intervals (CI). Also, the effect of baseline antipsychotics on the monitoring pattern at different time points was assessed. Therefore, to predict the odds of a patient having monitoring at each time point (baseline, 6 weeks, 12 weeks, and one year), a binary logistic model was conducted for patients who have been followed for at least one year. Due to the dynamic nature of this cohort, time was restrained by including a time-varying covariate in the model. So, the exposure status of the antipsychotics could be equal for all patients.

Descriptive statistics (proportions: %) were reported using frequency tables to describe the baseline characteristics of the included participants. Baseline demographics and clinical characteristics were reported using descriptive statistics as numbers and proportions. The baseline values for different outcome parameters were reported as mean ± standard

deviation (SD) or median (interquartile range: IQR). The statistical analysis was done using Statistical Package for STATA Version 17.1.

5.2.12. Data cleaning and management

As we handled secondary data, such type of data set was presented with flaws, therefore, the data set had to be tied up to convert them into a form that is software friendly (STATA) and to facilitate the analysis process, such process is known as data cleaning. Data cleaning is a process by which irrelevant, incorrect and missing data parts are detected, removed, modified, or replaced from the dataset. The dataset was prepared as follows:-

First, the data were extracted as multiple excel spreadsheet files: two main datasets containing baseline data (Rubaantipscyhoticbasecohortschizov2_fullDB20200203063057; Rubaextractv3needsmultipleoutcomes_fullDB20200812083243) and nine corresponding datasets containing follow up data for the following outcomes: blood glucose, fasting blood glucose, glucose tolerance test, HbA1c, blood pressure, HDL,LDL,VLDL,TGs and waist circumference. At this stage, the two datasets were merged based on a key column (Patient-practice ID), which was used as a linker to link the data from the different files. Datasets of the same format (wide format) were merged using the power query function in excel.

The next step involved data editing and screening to detect any errors in the data during data entry. Since the THIN data were originally collected for clinical management, not research, it contains unwanted data that may not be used. The deletion of redundant data were undertaken. Also, record matching and grouping: records of similar outcomes, such as records of BMI, were conducted.

Concerning variable rename, some variables were renamed to facilitate the analysis since some entry characters included capitalisation, which cannot be recognised by some statistical software e.g. STATA.

To facilitate the data analysis, the involved variables may need to have further requirements. In the presence of nominal or string variables (variables that include letter characters such as names), encoding and recoding were performed by giving numeric values to the string variables to be recognisable and readable by the statistical software (STATA). Similarly, data decoding was applied for certain variables that were transformed from the THIN database as codes. For instance, psychotic conditions and antipsychotic drug names were extracted from the THIN as codes, therefore they were translated into names to facilitate the analysis. Additionally, for the sake of the analysis, essential variables were generated from other variables as dummy variables so they can be used for further analysis. For example, the patient's age at the study index was calculated from existing variables such as date of birth and exit date as that variable was not available in the original dataset.

Also, inconsistent data entry was checked by displaying the data as frequency tables then it was corrected by unifying all characters. For example, string variables that were entered in different ways (e.g. fem, FemalE and Femle), were identified and unified. All string variables in the dataset were transformed into lower cases so data can be translated by STATA. Likewise, syntax errors like white spaces (extra white spaces at the beginning or the end of a string) were necessarily removed as the used statistical software (STATA) was syntax sensitive.

Data diagnosing was performed to check for duplicates and outliers. With respect to duplicated entries, all datasets (files) were checked for duplicated data entries to identify

duplicated records of the same case. This was done in excel by using the duplicate removal function which checked cases with duplicated entries.

The data were also checked for extreme values (outliers). This was performed via tabulation and visualised with histograms to check the distribution of the data. Extreme values in our data set existed as laboratory values with extreme values or outliers such as awkward BMI values (e.g. 5000). In our dataset, the outliers were retained and managed using the Winsorization technique.(200) Before the outliers values were winsorised, the extreme values were checked whether they existed in practice. For example, the minimum fasting blood glucose that equals 3 was considered an outlier since it was below the detectable limit in practice. Values of the extreme thresholds (top 99% and bottom 1%) were checked and compared with the smallest values of each percentile. If the largest value of the top percentile was extremely large and unreasonable (e.g., the top 99% of BMI was 200) then it was rounded to the next closest percentile value (95%).

5.3. Results

5.3.1. Cohort characteristics

Between 2003 and 2018, 11,435 adult patients diagnosed with mental illness and treated with antipsychotics were eligible for the study. The demographic characteristics and comorbidities of the selected cohorts are described in Table 5-2.

Table 5-2. Baseline demographic and clinical characteristics of the study cohort

Characteristics	Proportion of patients n (%)	mean (S.D) or median (IQR)
Total number of the cohort	11,435	
Deceased cases	1,302 (11.0)	
Gender		
Overall	11,435	
Male	5,175 (45.3)	
Female	6,260 (54.7)	
Age band (years) at index		46 (IQR 33- 62)
17-30	2,072 (18.1)	
31-40	2,159 (18.9)	
41-50	2,409 (21.1)	
51-60	1,652 (14.5)	
61-70	1,038 (9.1)	
71-80	1,105 (9.7)	
≥81	1,000 (8.8)	
Diagnosed mental illness		
Schizophrenia, schizotypal and delusion	1,447 (12.6)	
Mood [affective] disorders	9,988 (87.3)	
Treatment duration with antipsychotic (years)		3.3 (IQR1.3- 6.2)
Prescribed antipsychotic		
First-generation	Total: 1,728 (15.1)	
Amisulpride	232 (2.0)	
Benperidol	4 (0.03)	
Chlorpromazine	531 (4.6)	
Flupentixol	286 (2.5)	
Fluphenazine	9 (0.08)	
Haloperidol	314 (2.8)	
Levomepromazine	55 (0.5)	
Pericyazine	76 (0.7)	
Pimozide	1 (0.01)	
Sulpiride	66 (0.6)	
Thioridazine	2 (0.02)	
Trifluoperazine	142 (1.2)	
Zuclopenthixol	14 (0.1)	
Second-generation	Total: 9,707 (84.9)	
Aripiprazole	618 (5.4)	
Clozapine	3 (0.03)	
Lurasidone	3 (0.03)	
Olanzapine	3,090 (27.0)	
Paliperidone	5 (0.04)	
Quetiapine	4,230 (37.0)	
Risperidone	1,754 (15.3)	
Baseline clinical profile		

Characteristics	Proportion of patients n (%)	mean (S.D) or median (IQR)
Blood pressure (mmHg)	Total: 4,959 (43.3)	SBP 128.9(18) DBP 77.2(10.6)
Low BP (Systolic :60-90 or Diastolic: <60)	22 (0.4)	
Normal BP (Systolic: 90-120 or Diastolic: 60-80)	1,113 (22.4)	
Pre-HTN (Systolic: 120-140 or Diastolic: 80-90)	2,287 (46.1)	
HTN (Systolic >140 or Diastolic >100)	1,537 (31.0)	
Unrecorded†	6,476 (57.0)	
Body compositions		
Body mass index (BMI); (kg/m2)	Total: 2,915 (26)	27.4(7.7)
Underweight (<18.5)	154 (5.28)	
Normal (18.5 – 24.9)	1,089 (37.4)	
Overweight (25.0 – 29.9)	800 (27.4)	
Obese 1 (30.0 – 34.9)	397 (13.6)	
Obese 2 (35.0 – 39.9 and above)	475 (16.3)	
Unrecorded	8,476 (74.1)	
Waist circumference (cm)	Total: 73 (0.6)	96.59(15.8)
Low risk for CVD Male (< 102 cm or 40 inch) or Female (< 88 cm or 35 inch)	33 (45.2)	
High risk for CVD Male (>102 cm or 40 inch) or Female (>88 cm or 35 inch)	40 (54.7)	
Unrecorded	11,362 (99.3)	
Glycaemic profile		
Fasting blood glucose (mmol/L)	Total: 540 (4.7)	5.5(1.7)
Normal (< 5.6 mmol/L) or (<100 mg/dl)	364 (67.3)	
Pre-diabetic (5.6 to 7.0 mmol/L) or (100 to 125 mg/dl)	107 (19.7)	
Diabetic (≥7.0 mmol/L) or (≥125 mg/dl)	70 (12.9)	
Unrecorded	10,895 (95.2)	
HbA1c (mmol/mol)	1,029 (9)	42.5(19.7)
(Normal <47 mmol/mol or <5.7%)	761 (74)	
(Pre-diabetic >5.7% but ≤ 48 mmol/L or < 6.4%)	12 (1.1)	
(Diabetic > 48 mmol/mol or >6.5%)	256 (24.8)	
Unrecorded	10,406 (91)	
Lipid profile		
LDL (mmol/L)	Total: 1,499 (13.1)	2.9 (1.1)
(Normal lipid profile ≤3 mmol/L)	1,086 (72.2)	
(Dyslipidaemia >3 mmol/L)	416 (27.7)	
Unrecorded	9,936 (86.8)	
HDL (mmol/L)	Total: 1,831(16)	1.4 (0.54)
(Normal lipid profile ≥1 mmol/L)	1,831	

Characteristics	Proportion of patients n (%)	mean (S.D) or median (IQR)
Unrecorded	9,604 (83.9)	
TGs (mmol/L)	Total: 1,650 (14.4)	1.7(1.1)
(Normal lipid profile ≤2.3 mmol/L)	1,394 (84.4)	
(Dyslipidaemia > 2.3 mmol/L)	256 (15.5)	
Unrecorded	9,785 (85.5)	

Table keynotes: †this corresponds to the non-recorded patients; CVDs: cardiovascular diseases; BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; HbA1c: glycosylated haemoglobin, HDL: high-density lipoprotein, LDL: low-density lipoprotein, TGs: triglycerides; IQR: interquartile range; SD: standard deviation; n: the absolute number of patients.

The median age of the cohort at the study entry was 46 years (IQR 33-62), with the majority being middle-aged (41-50 years) and the cohort comprised more female participants (54.7%) compared to males (45.3%). Most patients were prescribed second-generation antipsychotics (SGAs) at baseline (n=9707, 84.8%), and 1728 (15.1%) were prescribed first-generation antipsychotics (FGAs). The median follow-up for the people prescribed antipsychotics was 3.3 years (IQR 1.3-6.2). Antipsychotic medications with known high cardiometabolic risk (e.g., quetiapine, olanzapine and risperidone) were the most frequently prescribed 37%, 27% and 15.3%, respectively.

Regarding cardiometabolic profiles, a total of 6,599 patients (52%) had evidence of any cardiometabolic baseline testing. Among these groups, only 3% of the patients were free of any biochemical abnormalities, while the majority had at least one abnormal lab value at baseline (n=4,627, 96.7%). Over half of the patients were overweight or obese (57%), while a small fraction (n=73, 0.6%) was presented with central obesity. Around 28% of the patients (n=445) with baseline glycaemic measures had diabetes at baseline. Data for established modifiable cardiovascular risk factors were extracted except for data related to smoking history and alcohol drinking habits as they were not available for extraction (Table 5-3).

Table 5-3. Proportions of patients with existing cardiovascular risk factors (n=9,148)

Risk factors	**Proportion patients n (%)**
Age ≥50 years	4,795 (52.4)
Male gender	5,175 (56.5)
BMI≥25 kg/m^2	1,654 (18.0)
Waist circumference (at risk)	40 (0.4)
(Male≥ 94cm or 37 inches) (Female ≥80cm or 31.5 inches)	14* 26*
Diabetes	
Fasting blood glucose (≥7.0 mmol/L or ≥126 mg/dl) HbA1c (> 48 mmol/mol or >6.5%)	177 (0.9) 268 (2.9)
Dyslipidaemia	
(LDL >3 mmol/mol) (TGs >2.3 mmol/mol)	416 (4.5) 256 (2.7)
High blood pressure	
Pre-HTN (Systolic 120-140 or Diastolic 80-90)	2,287 (25.0)
HTN (Systolic >140 or Diastolic >100)	1,537 (16.8)

Table keynotes: *% > 0.1. Abbreviations: BMI: body mass index, HbA1c: glycosylated haemoglobin, LDL, low-density lipoprotein, TGs: triglycerides, HTN: hypertension. n: the absolute number of patients.

Most of the cohort (80 %) had at least one cardiometabolic risk factor at baseline. Over half of the patients (52.4%) were aged >50 years old and were males (56.5%). A small proportion of patients presented other CV risk factors (Table 5-3).

5.3.2. Changes in cardiometabolic monitoring frequencies (2003–2018)

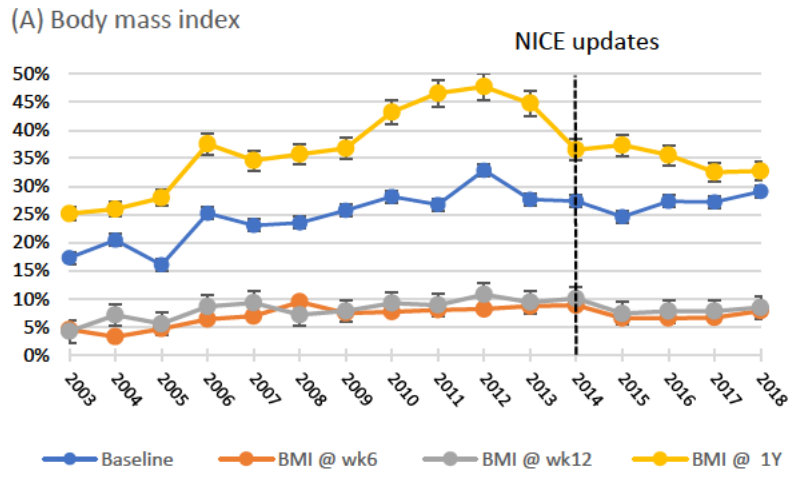
Generally, the majority of the cohort failed to receive complete monitoring for any outcome. Furthermore, parameters related to central obesity and TGs were never measured among the minority who received regular monitoring. Table 5-4 provides details of patients' proportions who received complete cardiometabolic monitoring over the study period.

Table 5-4. Summary of patients who underwent regular vs irregular cardiometabolic monitoring over the study period (2003-2018)

Outcome parameter	Proportion of patients who had †regular monitoring n (%)	Proportion of patients who had irregular monitoring n (%)
BMI	96 (1.0)	11,339 (99.0)
Waist circumference	None	11,435
Blood pressure	190 (2.0)	11,245 (98.0)
HbA1c	9 (0.1)	11,426 (99.9)
FBG	12 (0.1)	11,423 (99.9)
HDL	6 (0.1)	11,429 (99.9)
LDL	4 (0.03)	11,431 (99.9)
TGs	None	11,435

Table keynotes: †regular monitoring was defined as a patient having monitoring records (e.g., blood pressure) at all recommended time points (baseline, week-6, week12 and one year), n: the absolute number of patients.

Figures 5-2 to 5-4 show the yearly baseline and subsequent follow-up monitoring frequencies for different cardiometabolic outcomes (2003 and 2018). The present study detected inconsistent monitoring patterns for different cardiometabolic outcomes before and after the NICE guidelines' updates.



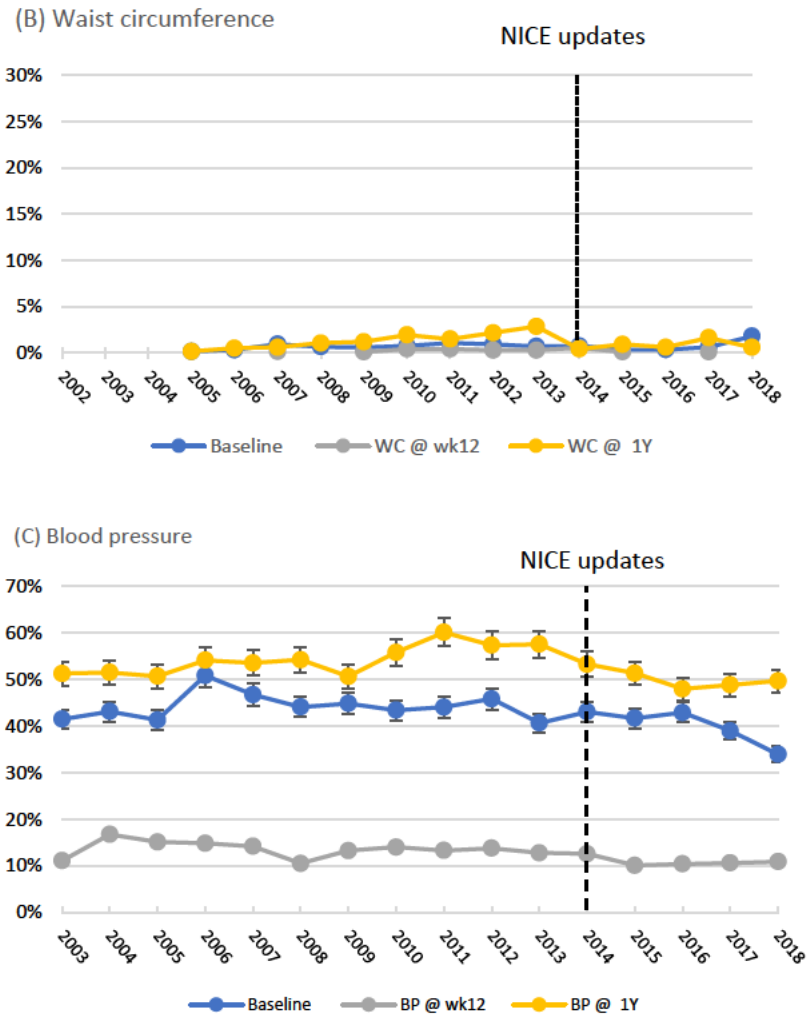
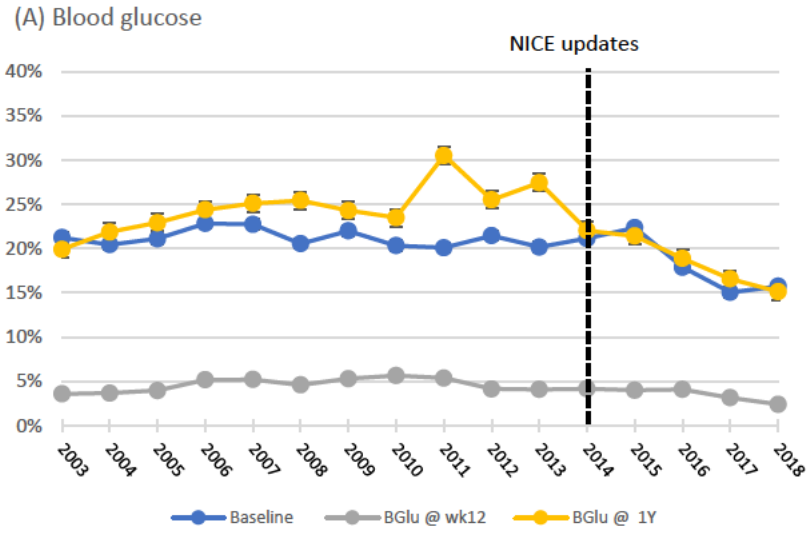
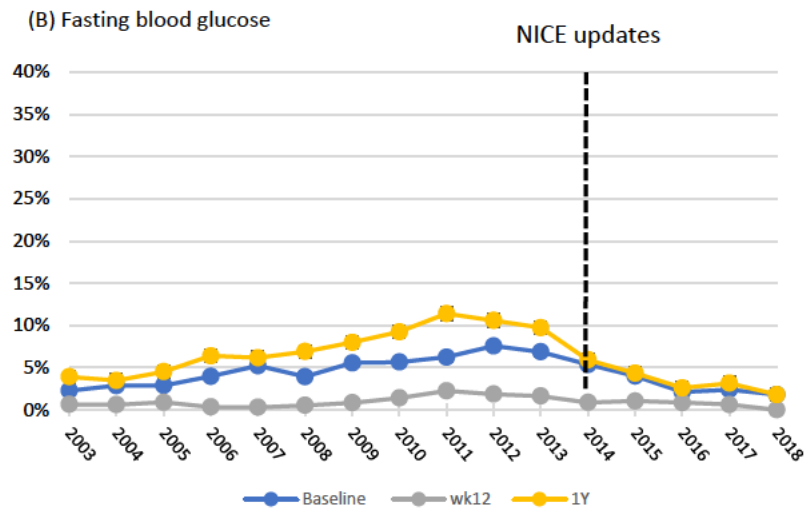


Figure 5-2. Differences in metabolic monitoring at baseline, 12 weeks, and one year by body compositions: BMI (A) & waist circumference (B) and blood pressure (C) from 2003 – 2018.





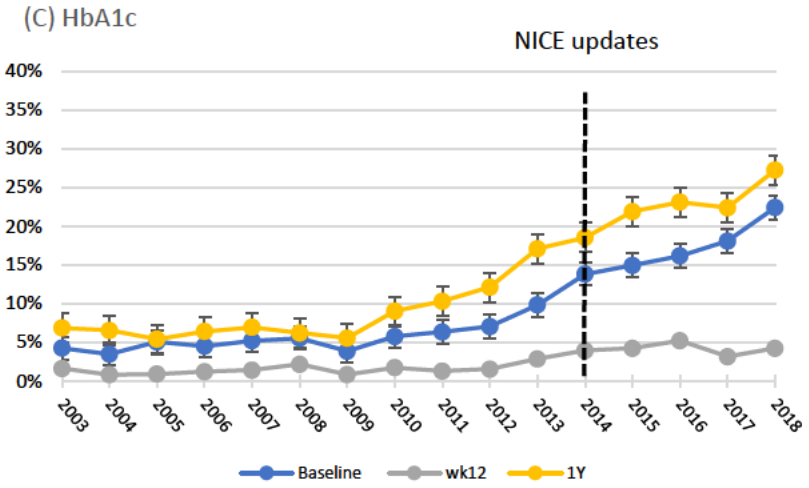
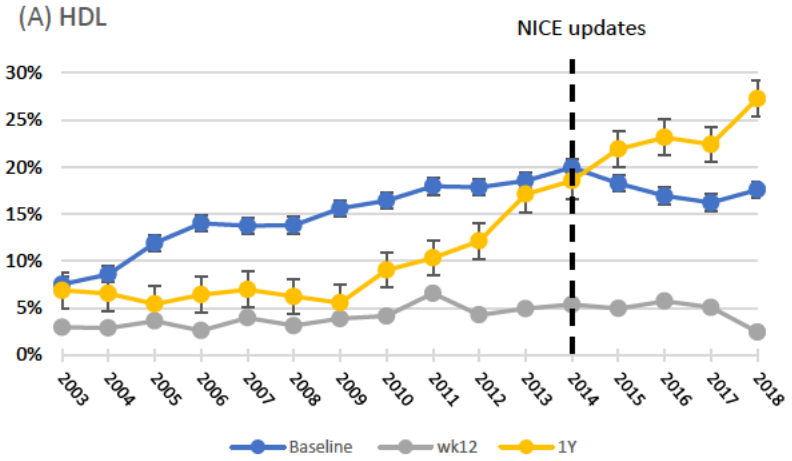


Figure 5-3. Differences in metabolic monitoring at baseline, 12 weeks, and one year by blood glucose (A), fasting blood glucose (B) & glycosylated haemoglobin (C) from 2003 – 2018.



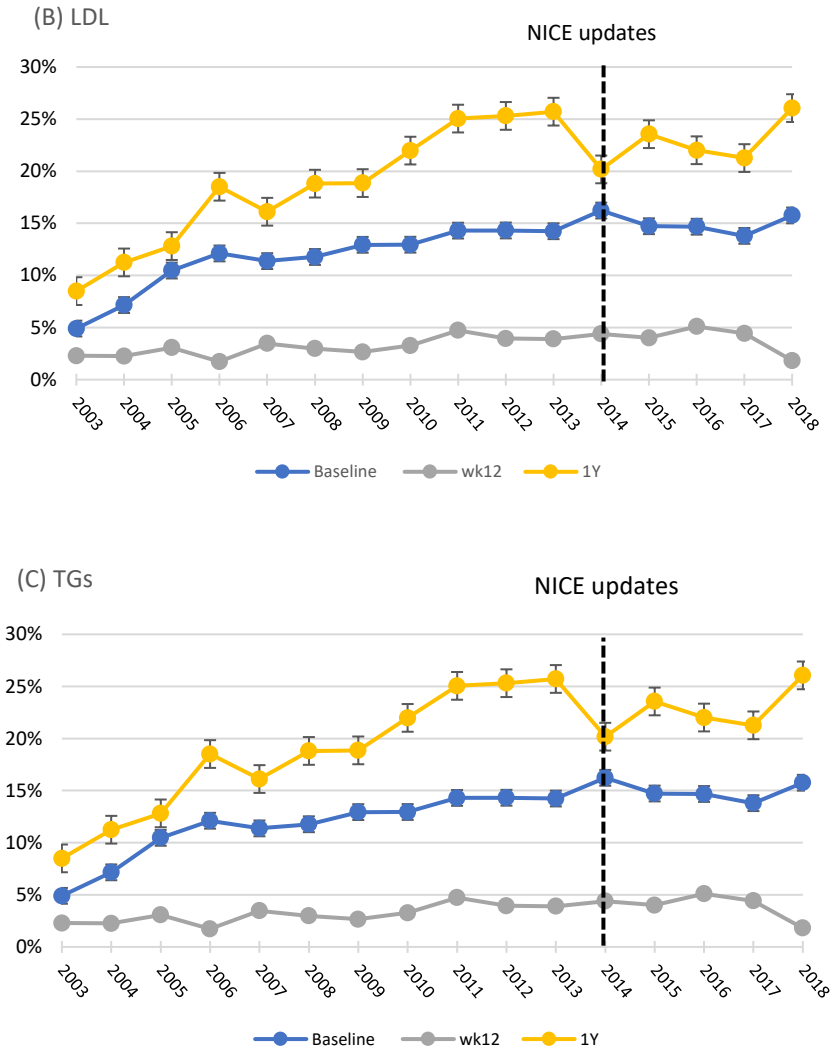


Figure 5-4. Differences in metabolic monitoring at baseline, 12 weeks, and one year by HDL (A), LDL (B) & TGs (C) from 2003 – 2018.

5.3.2. Baseline monitoring

Over the study period, 6,599 patients (52%) had evidence of any baseline cardiometabolic testing in any year. Generally, the annual baseline monitoring demonstrated variable patterns among different outcomes. BMI was the most documented parameter at baseline (Figure 5-2, A) among the outcomes reflecting body compositions. The yearly proportions of patients receiving baseline body weight (BMI) monitoring increased from 17 % to reach its peak of 33% in 2012, then gradually reduced to 29% at the end of the study period (the year 2018). Baseline measures for central obesity (WC) showed a fluctuating pattern that

increased sharply until 2013 to drop in 2014, yet the measures did not exceed 3% in any year.

The yearly proportions of patients receiving baseline blood pressure monitoring remained steady with no clear change over time. There was no consistent increase or decrease in the frequency of blood pressure monitoring at baseline or follow-up. Regarding biochemical monitoring, the proportion of patients receiving baseline HbA1c monitoring in each calendar increased over the study period for patients prescribed antipsychotics from 4 % in 2003 to 22% in 2018 (Figure 5-3, C). Despite this increase, the yearly baseline frequency for HbA1c monitoring did not exceed 30%. However, the annual baseline lipid monitoring pattern has improved for all the lipid parameters over the study period and continued to rise after the guidelines update in 2014 (Figure 5-4).

5.3.3. One year follow-up monitoring

The subsequent annual follow-up monitoring for most outcomes gradually increased from 2003 until 2014, when the NICE clinical guidelines for managing psychosis and schizophrenia in adults (201) were updated to include physical health monitoring (Figure 5-2 to 5-4). Besides, except for plasma lipids, the frequency of the subsequent annual cardiometabolic monitoring did not improve beyond the year of the update of the NICE guidelines in 2014. However, subsequent follow-up data on the time-points assessment (weeks-6 & week-12) for all outcomes within one year remained relatively stable over the study period.

Some outcomes, particularly WC, showed fluctuating monitoring patterns over the years. For example, a small number of patients had records for WC (n=138, 1%); with an overall yearly monitoring pattern that fluctuated over the years showing a rapid increase to reach the maximum level by 2013 to sharply drop again to 1% in 2018 (Figure 5-2, C). Similarly, the

annual follow-up prevalence for random blood glucose steadily decreased during the study period, while the proportion of patients with fasting blood glucose monitoring rose gradually (2003 to 2014); however, both measurements declined rapidly the years later.

Conversely, the monitoring patterns for other parameters related to blood sugar seemed to improve steadily. For example, the haemoglobin monitoring profile showed a relatively steady improvement in the yearly follow-up monitoring patterns that continued slightly after the NICE guidelines' implementations until the end of the study period. Likewise, the annual follow-up lipid monitoring prevalence was generally improving.

5.3.4. Cardiometabolic monitoring patterns across different antipsychotic drugs

Infrequent cardiometabolic monitoring was also observed across individual antipsychotic drugs. Table 5-5 to Table 5-7 showed the monitoring prevalence at different time points for each cardiometabolic outcome for the top 10 prescribed antipsychotic drugs.

Table 5-5. Descriptive data of the differences in body weight and blood pressure monitoring at baseline, 6, 12 weeks and one year by different index antipsychotic drugs (only the top ten prescribed antipsychotics were included in the table)

Prescribed antipsychotic	**Presence of a test within these time points n (%); [95% CI]**									
	BMI				**WC**			**BP**		
Total FGAs (1,505)	**Baseline**	**6 weeks**	**3 months**	**12 months**	**Baseline**	**3 months**	**12 months**	**Baseline**	**3 months**	**12 months**
Amisulpride (232)	74(31%); [25%-38%]	16(6%); [3%-10%]	19 (8%); [5%-12%]	96 (41%); [34%-48%]	4(1%); [0%-4%]*	1(0%)*; [0%-2%]	4(0%)*; [0%-4%]*	130(55%); [49%-62%]	46(19%); [14%-25%]	146 (62%); [56%-69%]
Chlorpromazine (531)	139(26%); [22%-30%]	37(6%); [4%-9%]	48(9%); [6%-11%]	189(35%); [31%-39%]	1(0%)*; [0%-1%]*	NR	2(0%)*; [0%-1%]*	197(37%); [32%-41%]	64(12%); [9%-15%]	250(47%); [42%-51%]
Flupentixol (286)	73(25%); [20%-30%]	26(9%); [6%-13%]	19(6%); [4%-10%]	97(33%); [28%-39%]	NR	1(0%)*; [0%-1%]*	2 0%)*; [0%-2%]*	139(48%); [42%-54%]	42(14%); [10%-19%]	152(53%); [47%-59%]
Haloperidol (314)	88(28%); [23%-33%]	24(8%); [4%-11%]	29(9%); [6%-12%]	107(34%); [28%-39%]	2(0%)*; [0%-2%]*	NR	2(0%)*; [0%-2%]*	182(57%); [52%-63%]	55(17%); [13%-22%]	203(64%); [59%-69%]
Trifluoperazine (142)	38 (26%); [19%-34%]	7(4%); [2%-9%]	9(6%); [2%-11%]	46 (32%); [24%-40%]	3(2%); [0%-6%]*	NR	NR	72(50%); [42%-59%]	19 (13%); [8%-20%]	75(52%); [44%-61%]
Total SGAs (9,692)	**Baseline**	**6 weeks**	**3 months**	**12 months**	**Baseline**	**3 months**	**12 months**	**Baseline**	**3 months**	**12 months**
Aripiprazole (618)	195 (31%); [27%-35%]	56(9%); [6%-11%]	64(10%); [8%-13%]	278 (45%); [41%-49%]	8(1%); [0%-2%]*	NR	14(2%); [1%-3%]	280 (45%); [41%-49%]	87(14%); [11%-17%]	358 (57%); [53%-61%]
Olanzapine (3,090)	746 (24%); [22%-25%]	240 (7%); [6%-8%]	284 (9%); [8%-10%]	1,179(38%); [36%-39%]	18(0%)*; [0%]*	3(0%)*; [0%]*	35(1%); [0%-1%]*	1,256 (40%); [38%-42%]	385(12%); [11%-13%]	1,625 (52%); [50%-54%]
Quetiapine (4,230)	1,082(25%); [24%-26%]	266(6%); [5%-7%]	327(7%); [6%-8%]	1,585(37%); [36%-38%]	26(0%)*; [0%]*	13(0%)*; [0%]*	52(1%); [0%-1%]*	1,808(42%); [41%-44%]	506(12%); [10%-12%]	2,209 (52%); [50%-53%]
Risperidone (1,754)	453(25%); [23%-27%]	150(8%); [7%-9%]	150(8%); [7%-9%]	683(39%); [36%-41%]	11(0%)*; [0%-1%]*	3(0%)*; [0%]*	25(1%); [0%-2%]*	781(44%); [42%-46%]	224(13%); [11%-14%]	970(55%); [52%-57%]

Table keynotes: *value < 0.00. Abbreviations: SGAs: second-generation antipsychotics, FGAs: first-generation antipsychotics, BMI: body mass index, WC: waist circumference, CI: confidence interval, NR: observation not recorded, n: the absolute number of patients.

Table 5-6 Descriptive data of the differences in glucose, monitoring at baseline, 12 weeks and one year by different index antipsychotic drugs (only the top ten prescribed antipsychotics were included in the table)

Prescribed antipsychotic	**Presence of a test within these time points n (%); [95% CI]**								
	BG			**FBG**			**HbA1c**		
Total FGAs (1,505)	**Baseline**	**3 months**	**12 months**	**Baseline**	**3 months**	**12 months**	**Baseline**	**3 months**	**12 months**
Amisulpride (232)	60(25%); [20%-31%]	19(8%); [5%-12%]	52(22%); [17%-28%]	20(8%); [5%-12%]	4(2%); [0%-4%]*	23(9%); [6%-14%]	30(12%); [8%-17%]	7(3%); [1%-6%]	27(11%); [7%-16%]
Chlorpromazine (531)	100(18%); [15%-22%]	29(5%); [3%-7%]	135(25%); [21%-29%]	9(1%); [0%-3%]*	3(0%)*; [0%-1%]*	19(3%); [2%-5%]	28(5%); [3%-7%]	12(2%); [1%-3%]	38(7%); [5%-9%]
Flupentixol (286)	60 (20%); [16%-26%]	11(3%); [1%-6%]	59(21%); [16%-25%]	13(4%); [2%-7%]	2 (0%)*; [0%-2%]*	12 (4%); [2%-7%]	23(8%); [5%-11%]	4(1%); [0%-3%]*	22(8%); [4%-11%]
Haloperidol (314)	88(28%); [23%-33%]	21(7%); [4%-10%]	89(28%); [23%-33%]	14(4%); [2%-7%]	1 (0%)*; [0%-1%]*	18(6%); [3%-8%]	40(12%); [9%-16%]	9(3%); [1%-5%]	40(13%); [9%-16%]
Trifluoperazine (142)	26(18%); [12%-25%]	4(3%); [0%-7%]*	38(27%); [19%-34%]	5(2%); [1%-8%]	NR	8(5%); [2%-10%]	7(5%); [2%-9%]	3(2%); [0%-6%]*	16(11%); [6%-17%]
Total SGAs (9,692)	**Baseline**	**3 months**	**12 months**	**Baseline**	**3 months**	**12 months**	**Baseline**	**3 months**	**12 months**
Aripiprazole (618)	115(18%); [15%-21%]	18(3%); [1%-4%]	157(25%); [22%-29%]	29(5%); [3%-6%]	9(1%); [0%-2%]*	32(5%); [3%-7%]	91(16%); [12%-17%]	28(4%); [3%-6%]	133(22%); [18%-24%]
Olanzapine (3,090)	597(19%); [17%-20%]	145(4%); [3%-5%]	724(23%); [21%-24%]	149(5%); [4%-5%]	32(1%); [0%-1%]*	239(8%); [6%-8%]	215(7%); [6%-7%]	57(2%); [1%-3%]	336(11%); [9%-12%]
Quetiapine (4,230)	883 (21%); [19%-22%]	163(3%); [3%-4%]	960(23%); [21%-23%]	208(5%); [4%-5%]	52(1%); [0%-1%]*	294(7%); [6%-8%]	403(10%); [8%-10%]	103(2%); [1%-2%]	575(14%); [12%-14%]
Risperidone (1,754)	361(20%); [18%-22%]	87(4%); [3%-6%]	420(24%); [21%-26%]	88(5%); [4%-6%]	17 (0%)*; [0%-1%]*	118(7%); [5%-8%]	175(10%); [8%-11%]	39(2%); [1%-3%]	269(15%); [13%-17%]

Table keynotes: *value < 0.00. Abbreviations: SGAs: second-generation antipsychotics, FGAs: first-generation antipsychotics, BG: blood glucose, FBG: fasting blood glucose, HbA1c: glycosylated haemoglobin, CI: confidence interval, NR: observation not recorded, n: the absolute number of patients.

Table 5-7 Descriptive data of the differences in lipid profile monitoring at baseline, 12 weeks and one year by different index antipsychotic drugs (only the top ten prescribed antipsychotics were included in the table)

Prescribed antipsychotic	**Presence of a test within these time points n (%); [95% CI]**								
	HDL			**LDL**			**TG**		
Total FGAs (1,505)	**Baseline**	**3 months**	**12 months**	**Baseline**	**3 months**	**12 months**	**Baseline**	**3 months**	**12 months**
Amisulpride (232)	51(22%); [16%-27%]	21(10%); [5%-13%]	27(12%); [7%-16%]	41(18%); [12%-23%]	17(7%); [4%-11%]	54(23%); [17%-29%]	53(10%); [17%-28%]	22(9%); [6%-14%]	64(28%); [21%-33%]
Chlorpromazine (531)	52(10%); [7%-12%]	18(3%); [2%-5%]	38(7%); [5%-9%]	50(10%); [7%-15%]	16(3%); [1%-4%]	90(17%); [13%-20%]	53(10%); [7%-12%]	22(4%); [2%-6%]	98(18%); [15%-22%]
Flupentixol (286)	42(15%); [10%-19%]	12(4%); [2%-7%]	22(8%); [4%-11%]	33(12%); [8%-15%]	9(3%); [1%-5%]	38(13%); [9%-17%]	36(13%); [8%-16%]	10(3%); [1%-6%]	44(15%); [11%-20%]
Haloperidol (314)	65 (21%); [16%-25%]	9(3%); [1%-5%]	40(13%); [9%-16%]	47(15%); [11%-19%]	5(2%); [0%-3%]*	62(20%); [15%-24%]	55(18%); [13%-22%]	5(2%); [0%-3%]*	71(23%); [18%-27%]
Trifluoperazine (142)	18(13%); [7%-19%]	6(4%); [1%-8%]	16(11%); [6%-17%]	15(11%); [6%-16%]	5(4%); [1%-8%]	19(13%); [8%-20%]	16(11%); [6%-17%]	5(4%); [1%-8%]	23(16%); [10%-23%]
Total SGAs (9,692)	**Baseline**	**3 months**	**12 months**	**Baseline**	**3 months**	**12 months**	**Baseline**	**3 months**	**12 months**
Aripiprazole (618)	121(20%); [16%-22%]	30(5%); [3%-6%]	133(22%); [18%-24%]	102(17%); [13%-19%]	26(4%); [2%-6%]	172(28%); [24%-31%]	107(17%); [14%-20%]	30(5%); [3%-6%]	179(29%); [25%-32%]
Olanzapine (3,090)	434(14%); [12%-15%]	138(4%); [3%-5%]	336(11%); [9%-12%]	50(2%); [1%-2%]	105(3%); [2%-4%]	659(21%); [19%-22%]	408(13%); [11%-14%]	115(4%); [3%-4%]	723(23%); [21%-24%]
Quetiapine (4,230)	725(17%); [16%-18%]	191(5%); [3%-5%]	575(14%); [12%-14%]	33(1%); [0%-1%]*	163(4%); [3%-4%]	849(20%); [18%-21%]	645(15%); [14%-16%]	171(4%); [3%-4%]	919(22%); [20%-22%]
Risperidone (1,754)	292(17%); [14%-18%]	75(4%); [3%-5%]	269(15%); [13%-17%]	47(3%); [1%-3%]	61(3%); [2%-4%]	378(22%); [19%-23%]	257(15%); [13%-16%]	65(3%); [2%-4%]	416(24%); [21%-25%]

Table keynotes: *value < 0.00. Abbreviations: SGAs: second-generation antipsychotics, FGAs: first-generation antipsychotics, HDL: high-density lipoprotein, LDL: low-density lipoprotein, TGs: triglycerides, CI: confidence interval, n: absolute number of patients.

Generally, no clear pattern emerged when comparing prevalence of monitoring between different antipsychotic drug classes. The Baseline and the one-year follow-up monitoring were recorded more frequently in both drug classes. Among different antipsychotics, the monitoring pattern for most outcomes (BMI, BP, and blood glucose) was nearly similar. However, specific antipsychotic drugs were monitored more frequently for certain parameters. For example, patients receiving aripiprazole tend to receive the yearly HbA1c monitoring more frequently at 22% than patients taking olanzapine, quetiapine and risperidone, at 11%, 14 % and 15%, respectively. Additionally, the subsequent yearly follow-up for biochemical measures (HDL) was slightly higher among olanzapine, quetiapine and risperidone users than among other antipsychotics.

Conversely, for antipsychotics with metabolic liability (olanzapine, quetiapine and risperidone), the baseline data for LDL monitoring were not recorded for over 90% of the cases. Similarly, the prevalence of baseline triglycerides monitoring was less frequently recorded (<20%) than the proportions of subjects receiving annual monitoring.

5.3.5. Antipsychotic treatment profile as baseline predictors for cardiovascular monitoring

A multivariate binary logistic regression model was applied to predict monitoring patterns for cardiometabolic outcomes based on the type of antipsychotic prescribed at baseline. Only the three most common antipsychotics of each class were included in the analysis. The most frequently prescribed second-generation antipsychotics were quetiapine (n=4,230) risperidone (n=3,090) and olanzapine (n=1,754), while chlorpromazine (n=531), haloperidol (n=314) and Flupentixol (n=286) were the most commonly prescribed first-generation antipsychotics. The number of patients taking clozapine was very small to comprise a group. Details for the association between exposure to antipsychotics and the odds of having cardiometabolic monitoring are provided in Tables 5-8 and 5-9

Table 5-8. Results of multivariate binary logistic regression of cardiometabolic monitoring probability at different time points for the three most prescribed first-generation antipsychotics.

Predictor	**likelihood of having BMI recorded at different endpoints**			
Antipsychotic type prescribed at index	**Baseline OR (95%CI)**	**6 weeks OR (95%CI)**	**12 weeks OR (95%CI)**	**One year OR (95%CI)**
Amisulpride†	1	1	1	1
Chlorpromazine	0.75(0.52 - 1.1)	0.79(0.42 - 1.4)	1.24(0.7 - 2.3)	0.72(0.52 - 1.02)
Haloperidol	0.85(0.6 - 1.3)	1.14(0.5 - 2.2)	1.2(0.61 - 2.4)	0.81(0.5 - 1.2)
Flupentixol	0.7(0.4 - 1)	1.13(0.6 - 2.2)	0.8(0.43 - 1.8)	0.7(0.5 - 1)
Predictor	**likelihood of having WC recorded at different endpoints**			
Antipsychotic type prescribed at index	**Baseline OR (95%CI)**		**12 weeks OR (95%CI)**	**One year OR (95%CI)**
Amisulpride	1		1	1
Chlorpromazine	0.23(0.03 - 1.7)		0.4(0.01 - 20)	0.3(0.1 - 1.4)
Haloperidol	0.8(0.14 - 4.9)		0.8(0.02 - 43)	0.6(0.12 - 3.1)
Flupentixol	0.14(0.01 - 3.1)		2.2(0.1 - 54)	0.5(0.1 - 2.6)
Predictor	**likelihood of having BP recorded at different endpoints**			
Antipsychotic type prescribed at index	**Baseline OR (95%CI)**		**12 weeks OR (95%CI)**	**One year OR (95%CI)**
Amisulpride	1		1	1
Chlorpromazine	0.41(0.3 - 0.6)		0.64(0.41 - 1.0)	0.6(0.4 - 0.8)
Haloperidol	1(0.7 - 1.4)		0.9(0.6 - 1.5)	1.1(0.7 - 1.5)
Flupentixol	0.64(0.4 - 0.93		0.8(0.5 - 1.2)	0.73(0.5 - 1.1)
Predictor	**likelihood of having BG recorded at different endpoints**			
Antipsychotic type prescribed at index	**Baseline OR (95%CI)**		**12 weeks OR (95%CI)**	**One year OR (95%CI)**
Amisulpride	1		1	1
Chlorpromazine	0.64(0.43 - 0.95)		0.9(0.4 - 1.6)	1.1(0.8 - 1.6)
Haloperidol	1.13(0.73 - 1.7)		1.2(0.6 - 2.4)	1.4(0.9 - 2.2)
Flupentixol	0.74(0.48 - 1.1)		0.6(0.3 - 1.3)	0.8(0.6 - 1.3)
Predictor	**likelihood of having FBG recorded at different endpoints**			
Antipsychotic type prescribed at index	**Baseline OR (95%CI)**		**12 weeks OR (95%CI)**	**One year OR (95%CI)**
Amisulpride	1		1	1
Chlorpromazine	0.2(0.1 - 0.4)		0.3(0.1 - 1.2)	0.26(0.13 - 0.5)
Haloperidol	0.5(0.21 - 1.0)		0.1(0.004 - 1.7)	0.6(0.3 - 1.2)
Flupentixol	0.4(0.2 - 0.8)		0.4(0.1 - 2.0)	0.3(0.2 - 0.7)
Predictor	**likelihood of having HbA1c recorded at different endpoints**			
Antipsychotic type prescribed at index	**Baseline OR (95%CI)**		**12 weeks OR (95%CI)**	**One year OR (95%CI)**
Amisulpride	1		1	1
Chlorpromazine	0.4(0.2 - 0.7)		1.1(0.4 - 3.2)	0.6(0.3 - 1.0)
Haloperidol	1(0.6 - 2.0)		1(0.3 - 3.6)	1.1(0.7 - 2.1)

Flupentixol	0.6(0.3 - 1.2)	0.7(0.2 - 2.7)	0.7(0.4 - 1.3)
Predictor	**likelihood of having HDL recorded at different endpoints**		
Antipsychotic type prescribed at index	**Baseline OR (95%CI)**	**12 weeks OR (95%CI)**	**One year OR (95%CI)**
Amisulpride	1	1	1
Chlorpromazine	0.4(0.2 - 0.5)	0.4(0.2 - 0.8)	0.6(0.32 - 1.0)
Haloperidol	0.8(0.5 - 1.2)	0.4(0.2 - 1.0)	1.1(0.61 - 2.1)
Flupentixol	0.52(0.3 - 0.9)	0.5(0.23 - 1.1)	0.7(0.4 - 1.2)
Predictor	**likelihood of having LDL recorded at different endpoints**		
Antipsychotic type prescribed at index	**Baseline OR (95%CI)**	**12 weeks OR (95%CI)**	**One year OR (95%CI)**
Amisulpride	1	1	1
Chlorpromazine	0.42(0.3 - 0.7)	0.43(0.21 - 0.9)	0.6(0.4 - 0.9)
Haloperidol	0.62(0.4 - 1.1)	0.3(0.1 - 0.8)	0.7(0.42 - 1.1)
Flupentixol	0.5(0.3 - 0.8)	0.5(0.2 - 1.1)	0.5(0.3 - 0.73)
Predictor	**likelihood of having TGs recorded at different endpoints**		
Antipsychotic type prescribed at index	**Baseline OR (95%CI)**	**12 weeks OR (95%CI)**	**One year OR (95%CI)**
Amisulpride	1	1	1
Chlorpromazine	0.4(0.2 to 0.61)	0.5(0.3 - 1.0)	0.5(0.34 - 0.75)
Haloperidol	0.7(0.4 - 1.1)	0.3(0.1 - 0.71)	0.7(0.43 - 1.1)
Flupentixol	0.5(0.3 - 0.8)	0.4(0.2 - 1.0)	0.45(0.3 - 0.71)

Table keynotes: † reference category is amisulpride (OR=1) as the analysis was run against exposure antipsychotic (categorical variable) and only categories represented the three APs frequently prescribed were listed. Abbreviations: OR: Odds Ratio; BMI: body mass index; BP: blood pressure; BG: blood glucose; FBG: fasting blood glucose; HbA1c: glycosylated haemoglobin; HDL: high-density lipoproteins; LDL: low-density lipoprotein; TGs: triglycerides.

Table 5-9. Results of multivariate binary logistic regression of cardiometabolic monitoring probability at different time points for the three most prescribed second-generation antipsychotics.

Predictor	**likelihood of having BMI recorded at different endpoints**			
Antipsychotic type prescribed at index	**Baseline OR (95%CI)**	**6 weeks OR (95%CI)**	**12 weeks OR (95%CI)**	**One year OR (95%CI)**
Amisulpride†	1	1	1	1
Quetiapine	0.72(0.53 - 0.9)	0.72(0.42 - 1.2)	1.02(0.6 - 1.7)	0.81(0.61 - 1.1)
Olanzapine	0.6(0.5 - 0.9)	0.95(0.6 - 1.6)	1.2(0.7 - 2.1)	0.81(0.6 - 1.1)
Risperidone	0.71(0.51 - 0.9)	1.1(0.61 - 1.8)	1.15(0.7 - 2)	0.82(0.6 - 1.1)
Predictor	**likelihood of having WC recorded at different endpoints**			
Antipsychotic type prescribed at index	**Baseline OR (95%CI)**		**12 weeks OR (95%CI)**	**One year OR (95%CI)**
Amisulpride	1		1	1
Quetiapine	0.4(0.1 - 1.4)		1.3(0.1 - 22)	0.64(0.2 - 1.9)
Olanzapine	0.41(0.11 - 1.6)		0.51(0.02 - 9.9)	0.61(0.2 - 1.8)
Risperidone	0.44(0.1 - 1.8)		0.92(0.05 - 17)	0.8(0.2 - 2.4)
Predictor	**likelihood of having BP recorded at different endpoints**			
Antipsychotic type prescribed at index	**Baseline OR (95%CI)**		**12 weeks OR (95%CI)**	**One year OR (95%CI)**
Amisulpride	1		1	1
Quetiapine	0.53(0.4 - 0.72)		0.6(0.4 - 0.8)	0.7(0.5 - 0.9)
Olanzapine	0.5(0.4 - 0.64)		0.61(0.42 - 0.9)	0.7(0.5 - 0.9)
Risperidone	0.56(0.4 - 0.8)		0.63(0.43 - 0.94)	0.7(0.5 - 0.9)
Predictor	**likelihood of having BG recorded at different endpoints**			
Antipsychotic type prescribed at index	**Baseline OR (95%CI)**		**12 weeks OR (95%CI)**	**One year OR (95%CI)**
Amisulpride	1		1	1
Quetiapine	0.76(0.55 - 1.1)		0.53(0.3 - 0.9)	0.9(0.7 - 1.3)
Olanzapine	0.7(0.6 - 0.97)		0.7(0.4 - 1.2)	0.9(0.7 - 1.4)
Risperidone	0.74(0.52 - 1.1)		0.7(0.4 - 1.2)	1(0.7 - 1.4)
Predictor	**likelihood of having FBG recorded at different endpoints**			
Antipsychotic type prescribed at index	**Baseline OR (95%CI)**		**12 weeks OR (95%CI)**	**One year OR (95%CI)**
Amisulpride	1		1	1
Quetiapine	0.5(0.3 - 0.8)		0.51(0.2 - 1.3)	0.6(0.4 - 0.9)
Olanzapine	0.5(0.3 - 0.8)		0.4(0.2 - 0.9)	0.6(0.4 - 1.1)
Risperidone	0.5(0.3 - 0.8)		0.4(0.13 - 1.1)	0.6(0.4 - 0.9)
Predictor	**likelihood of having HbA1c recorded at different endpoints**			
Antipsychotic type prescribed at index	**Baseline OR (95%CI)**		**12 weeks OR (95%CI)**	**One year OR (95%CI)**
Amisulpride	1		1	1
Quetiapine	0.71(0.5 - 1.1)		1(0.4 - 2.5)	1.2(0.7 - 1.8)

Olanzapine	0.5(0.3 - 0.8)	0.7(0.24 - 1.7)	0.9(0.6 - 1.4)
Risperidone	0.7(0.4 - 1.2)	0.8(0.3 - 2.2)	1.3(0.8 - 2.1)
Predictor	**likelihood of having HDL recorded at different endpoints**		
Antipsychotic type prescribed at index	**Baseline OR (95%CI)**	**12 weeks OR (95%CI)**	**One year OR (95%CI)**
Amisulpride	1	1	1
Quetiapine	0.6(0.5 - 0.93)	0.5(0.3 - 0.8)	1.2(0.7 - 1.8)
Olanzapine	0.52(0.4 - 0.74)	0.41(0.24 - 0.7)	0.9(0.7 - 1.4)
Risperidone	0.61(0.4 - 0.8)	0.4(0.23 - 0.7)	1.2(0.8 - 2.1)
Predictor	**likelihood of having LDL recorded at different endpoints**		
Antipsychotic type prescribed at index	**Baseline OR (95%CI)**	**12 weeks OR (95%CI)**	**One year OR (95%CI)**
Amisulpride	1	1	1
Quetiapine	0.6(0.4 - 0.9)	0.5(0.3 - 0.84)	0.7(0.5 - 0.9)
Olanzapine	0.51(0.3 - 0.73)	0.4(0.21 - 0.7)	0.73(0.5 - 1.0)
Risperidone	0.6(0.4 - 0.84)	0.41(0.2 - 0.8)	0.8(0.5 - 1.1)
Predictor	**likelihood of having TGs recorded at different endpoints**		
Antipsychotic type prescribed at index	**Baseline OR (95%CI)**	**12 weeks OR (95%CI)**	**One year OR (95%CI)**
Amisulpride	1	1	1
Quetiapine	0.6(0.43 - 0.9)	0.4(0.3 - 0.74)	0.7(0.5 - 0.9)
Olanzapine	0.51(0.4 - 0.73)	0.4(0.21 - 0.63)	0.71(0.5 - 1.0)
Risperidone	0.54(0.4 - 0.8)	0.4(0.2 - 0.67)	0.71(0.51 - 1.0)

Table keynotes: † reference category is amisulpride (OR=1) as the analysis was run against exposure antipsychotic (categorical variable) only categories represented the three APs frequently prescribed were listed. Abbreviations: OR: Odds Ratio; 95%CI: confidence interval; BMI: body mass index; BP: blood pressure; BG: blood glucose; FBG: fasting blood glucose; HbA1c: glycosylated haemoglobin; HDL: high-density lipoproteins; LDL: low-density lipoprotein; TGs: triglycerides.

Generally, the odds of having any baseline monitoring were low for both antipsychotic classes. Among first-generation antipsychotic users, subjects receiving chlorpromazine had significantly low odds of baseline monitoring (BP, FBG and lipids) as described in Table 5-8. Within one year of follow-up, antipsychotics with documented cardiometabolic side effects, mainly olanzapine, quetiapine and risperidone, were not associated with improving the monitoring patterns for body weight, blood pressure, or blood glucose (random and fasting blood glucose) among users. However, second-generation antipsychotics were associated with an increased likelihood of HbA1c and HDL monitoring, although it did not reach a significant level.

5.4. Discussion

5.4.1. Main findings

The NICE guidelines for psychosis and schizophrenia recommend appropriate physical health checks, including yearly checks for the cardiometabolic variables. To the best to our knowledge, this is the first work attempting to provide a comprehensive evaluation of the yearly cardiometabolic monitoring among antipsychotic users against the NICE standards since the FDA warnings in 2003 until the NICE schizophrenia guidelines' updates in 2014 in the UK population. However, considering the NICE guidelines, none of the targeted outcomes was regularly monitored per the definition adopted in this study.

The findings of this work revealed a considerable variation in the overall cardiometabolic monitoring prevalence for different outcomes. Outcomes related to BP and BMI were more likely to be recorded than the biochemical outcomes (blood glucose and lipid) at all endpoints, while waist circumference was barely recorded. These findings were comparable to other nations, where various and suboptimal cardiometabolic monitoring rates in mental health were observed. For example, in a US study(202) investigating cardiometabolic screening in a state community mental health system, the findings showed that the one year assessment of patients using antipsychotics varied across different outcomes (54.3 % for weight, 40.4 % for glucose, 29.1 % for triglycerides, 33.6 % for BP, 29.6 % for cholesterol, and 5.7 % for WC). Although the study (202) was not directly comparable to our work, it was conducted in a community healthcare setting, a system that emulates the current work environment.

A key finding in this study was the extremely low prevalence of waist circumference measurement. Similar findings were observed in a large study that reported that waist circumference was not recorded in the reviewed files, despite the efforts (quality

improvement audit) to improve the overall screening performance for metabolic syndrome components in chronically antipsychotic users. (203) These findings, combined with ours, suggest that central obesity (waist circumference) measurements were less likely to be recorded as they might be viewed as 'special procedures' that are not routinely performed. (204)

The current study also detected a noticeably low prevalence of glucose monitoring compared to other biochemical parameters (e.g., plasma lipids). These findings contradict similar studies reporting a considerably high prevalence of glucose testing in patients prescribed antipsychotics. For example, two US studies investigated the impact of educational audits on cardiometabolic screening state in a community mental health system (202,205) and the metabolic testing for adults newly prescribed antipsychotics in a state Medicaid program. Compared to our findings, both studies showed high proportions of patients (≈40% to 70%) receiving yearly blood glucose testing, while lipid testing reached 40%.(202,205) It is important to note that the relatively high prevalence of blood glucose and lipid check observed in these works was likely to be a responsive action to the interventions applied. Nonetheless, maintaining long-term performance is crucial.

5.4.2. Monitoring patterns at different time points (baseline, week-6, week-12, and one year)

By looking at the frequencies of monitoring at different endpoints, our findings showed that the frequency of baseline monitoring for any outcome barely reached 50 % in any year. Although disappointing, these observations were similar to prior work that showed low tendencies to conduct baseline cardiometabolic monitoring among new antipsychotic users. This was demonstrated by an audit conducted between 2006 and 2012 as a part of a quality improvement program in the UK.(203) The audit findings demonstrated that the proportions

of participants on antipsychotics receiving routine measurements for BMI and BP in the previous year (before the audit) barely reached 20%.

Similar results were reported by further studies assessing the metabolic monitoring practices in antipsychotic users, as the baseline monitoring of body weight was reported in less than 50 % of the patients.(206,207) In conjunction with ours, these findings support the importance of baseline monitoring for cardiometabolic abnormalities in antipsychotic users. There is a clinical significance to this since previous evidence pointed out that the rapid onset of disturbance in metabolic parameters can be alerting signs for long-term metabolic complications (207), emphasising early detection.

5.4.3. Monitoring patterns before and after the update of the NICE guidelines

In a population of adult patients initiating prescribed antipsychotic therapy, the present study detected inconsistent monitoring patterns for different cardiometabolic outcomes within one year of antipsychotic treatment before and after the NICE guidelines' updates. When comparing our work with the available evidence, previous research also documented inconsistent rates of cardiometabolic screening and monitoring in people with mental illness regardless of the local guidelines. A meta-analysis assessing the cardiometabolic monitoring practices in antipsychotic users used data pooled from various nations before and after guidelines implementation.(36) Except for body weight and BP, the analysis reported inadequate monitoring levels for most testing procedures to post the implementation of the guideline. In addition, similar to our findings, the same systematic review reported a small, but statistically significant increase in glucose testing (15.4%, p=0.005), where the monitoring level improved from inadequate to suboptimal after the guideline's implementation.

Further study provided supportive evidence for improved cardiometabolic monitoring rate following the implementation of local or national guidelines for cardiometabolic monitoring, primarily for blood glucose and lipids. The study findings showed more than a 50% increase in glucose testing and a 40% increase in lipid testing from baseline.(208) Although these observations may contradict ours, the present study detected a slight but promising rise in the frequency of annual follow-up monitoring for some biochemical variables, mainly lipids and glycosylated haemoglobin, after the NICE updates in 2014. Although the findings differ between this study and the previous work, it is essential to note that the previous work (208) was done in a psychiatric setting. This supports the claim that psychiatrists may be more aware of the FDA warnings than primary care physicians.

5.4.4. Antipsychotic and cardiometabolic monitoring

Due to their low risk of neurological side effects, namely motor symptoms, SGAs have been widely used to treat both psychotic and nonpsychotic psychiatric disorders in the past two decades.(27) However, SGA use was linked to significant weight gain and other metabolic complications, leading to significant cardiovascular and metabolic health concerns among SGAs users.(13,27) Considering the effect of antipsychotics prescribed at index on the monitoring profile, the baseline and short-term monitoring frequency were below 50% in the current study. Nevertheless, it was even lower among patients prescribed second-generation antipsychotic medications than those who used first-generation antipsychotics. We used a univariate logistic regression model to determine the effect of the antipsychotic type prescribed at the index on the monitoring patterns at different time points. According to our model, the findings indicate that the overall effect of atypical antipsychotic use had a converse relationship with the cardiometabolic monitoring pattern. These results suggest

that the use of antipsychotic drugs may not considered a driving force for conducting cardiometabolic monitoring in primary care. Such association between type of prescribed antipsychotic and the probabilities of cardiometabolic monitoring seem to be understudied.

5.5. Limitations of the study

The THIN database is subjected to the limitations inherent in all routinely collected data, which may include inconsistencies, variation between GPs, incompleteness and lack of data richness. There may be selection bias due to general practices participating in THIN voluntarily, and there may be under-recording of cardiometabolic monitoring among potentially eligible patients. Similarly, the inclusion criteria of the studied cohort were restricted to patients receiving monitoring for the first year of antipsychotic therapy, which may have led to an under-representation of eligible patients who had been prescribed antipsychotics for more than one year. Additionally, selection bias can be manifested in a different form in the present study. Particularly, drugs with a greater propensity for inducing weight gain may be used less often in patients who are already overweight. However, It was not possible to assess this form of bias due to the lack of relevant information from the data set.

Also, the present study was subjected to misclassification bias since the estimation of patients with cardiovascular risk factors who received cardiometabolic monitoring in the cohort was based on the presence of the recorded laboratory results and not based on the clinical READ code for the condition. For example, some patients may have recorded high blood pressure just at the time of visit (white coat hypertension), however; based on the recorded blood pressure value, the patient would be likely to be classified to have a risk factor.

There was a general lack of richness in the data used in this study, which was accompanied by several weaknesses. The impact of antipsychotic switching on the monitoring patterns was not assessed in this study. This study relied on records of antipsychotic prescriptions that were issued after the established diagnosis of the mental illness, however; patients at the beginning of antipsychotic therapy often undergo a trial period. Information on concurrently prescribed antipsychotics was not available in the extracted dataset, thus we could not assess the effect of altering antipsychotics on the monitoring pattern.

The patients in the study cohort would likely have been prescribed other psychotropic medications. Supportive evidence that demonstrated high rates of psychotropic polypharmacy have been estimated in the UK, but the recruited patients in those studies have been prescribed at least one antipsychotic at the date of data collection.(209) The common psychotropic medications prescribed to patients are likely to be including antidepressants and mood stabilizers (210), which can also contribute to metabolic side effects and the monitoring pattern.(9) However, such assumptions need further investigation since the information regarding the co-psychotropic prescriptions was not available in the extracted data.

Furthermore, it was challenging to determine the exact context in which monitoring occurred and therefore there is no certainty that the laboratory tests were undertaken specifically because the patient was being treated with an antipsychotic drug. In other words, the information that was extracted from the database did not explain the actual reasons for the monitoring.

Finally, our study did not address the influence of cardiometabolic profiles on the monitoring patterns. This was mainly due to the unavailability of the relevant data since the baseline clinical data were only available at the extraction. Such findings are of clinical significance since 80% of the cohort consisted of participants prescribed antipsychotics of high cardiometabolic risks at the study index. Furthermore, in the current study, the baseline and short-term monitoring frequency were generally below 50%, yet, it was even lower among patients prescribed atypical antipsychotic medications compared to people using conventional drugs. Thus, further investigations are recommended to establish the effects of the metabolic profile of individual antipsychotics on cardiometabolic monitoring behaviour.

5.6. Conclusions

In light of the increased use of second-generation antipsychotics and the consolidating evidence of their cardiometabolic side effects, it is concerning that metabolic screening rates over the last 15 years remained nearly as low as they were when the NICE guidelines were updated in 2014. Combined with previous findings, our study revealed a low prevalence of visceral fat and glucose monitoring in patients with mental illnesses taking antipsychotic drugs compared to other outcomes. Also, the current study found that a large proportion of patients receiving SGAs did not receive any baseline and follow-up cardiometabolic monitoring, which is parallel with the rapid increase in antipsychotic prescribing practices in the last few years. However, these phenomena do not imply a causal relationship but call for observation.

Although the NICE recommendations focused on adults taking second-generation antipsychotics, there is a great possibility that primary care providers may have overlooked the recommendations. This indicates a substantial need for improvement in providing routine screening and appropriate follow-up care for cardiometabolic risk factors among this

population. An overall discussion and conclusions for the entire thesis are presented in the next chapter.

Chapter 6 Final Discussion and Conclusions

Summary of the chapter

This chapter aims to triangulate findings from different phases of the study. The first part discusses the key study findings and their implication for the practice. The second part of this chapter provides reflective commentary on the methodology adopted for this PhD student covering strengths, limitations, and generalisability of the findings. Finally, this chapter presents future research opportunities that need to be addressed.

Part I: Discussion of the key findings

6.1. Key finding's part (A): Joint discussion of the systematic review results

The systematic review presented three main outcomes: i) prevalence of cardiometabolic side effects of antipsychotic drugs, ii) available interventions to minimise cardiometabolic side effects of antipsychotics **(Chapter3)**, iii) barriers and facilitators for proper management of the targeted side effects **(Chapter 4)**.

6.1.1. Prevalence of cardiometabolic side effects among different antipsychotics

A key finding of this review was the high prevalence of cardiometabolic dysregulations among effective antipsychotic drugs such as olanzapine and clozapine despite the limited data. The different effects of clozapine-related antipsychotics on body weight, glucose regulation and lipid profile presented in this review are in line with the published findings from the consensus development conference on antipsychotic drugs, obesity and diabetes.

However, limited data were available for the other antipsychotic agents. The evidence for the effects of risperidone, quetiapine, aripiprazole and ziprasidone treatment on weight gain and metabolic diseases was less extensive than for clozapine and olanzapine in this review. Although the information was very limited, the data related to quetiapine and risperidone demonstrated a high prevalence of metabolic syndrome and its components.

Notably, the data available for quetiapine, risperidone, and amisulpride were insufficient to draw clear conclusions. These published data do, though, suggest that treatment with risperidone or quetiapine may be associated with an increase in cardiometabolic risks. Similarly, initial indications from the available data suggest that antipsychotics such as ziprasidone and aripiprazole did not adversely affect blood glucose regulation in treated patients, despite the limited data.

The literature reported that new antipsychotics mainly aripiprazole, lurasidone, and ziprasidone were reported to be associated with the best metabolic outcomes (211), which makes these drugs the preferred options in patients at increased risk of developing metabolic complications. The limited data related to these antipsychotics in this review makes it difficult to develop rational conclusions about the risk of cardiometabolic abnormalities with the new antipsychotics. Therefore, we could not obtain meaningful results regarding the prevalence of different cardiometabolic side effects in newer antipsychotics.

Besides, newly released antipsychotics such as zotepine, brexpiprazole, cariprazine or paliperidone were not highlighted in the studies included in this review. These findings highlight the existing gap regarding the nature of the cardiometabolic profiles for the newer antipsychotics. These findings are essential especially with the notable change in prescribing trends of antipsychotics, along with the recognition of olanzapine and clozapine being associated with cardiometabolic abnormalities. Therefore, the effect of these drugs on cardiometabolic profiles is less clear and requires further study.

Although the information is very limited, our review identified one study highlighting the cardiometabolic safety of antipsychotic polypharmacy. The study findings indicated that

polypharmacy may represent an independent factor for the high prevalence of metabolic side effects among antipsychotic users, yet no confirmatory evidence can be drawn from it. Besides, these findings should be interpreted with caution, as most of the identified studies were not designed to detect the association between therapeutic regimens and the pattern of metabolic side effects of antipsychotic drugs. Also, the study identified by the review did not ascertain the nature of the combined drugs to determine whether some combinations of antipsychotics were less harmful than others. However, it is important to highlight the relevance of this potential complication associated with the use of antipsychotic polypharmacy owing to the fact that the available evidence indicates a noticeable increase in the use of combination therapy of antipsychotic drugs.(212)

6.1.2. Adjunctive pharmacological interventions for cardiometabolic side effects and polypharmacy

The findings of the quantitative review **(Chapter 3)** provided supportive evidence that antipsychotics with neutral cardiometabolic profiles namely aripiprazole and ziprasidone, were the most investigated antipsychotic agents used as alternatives when switching antipsychotics to minimise cardiometabolic side effects. The main reason to switch antipsychotic medications was lack of tolerability and clinical response.(213) In this review **(Chapter 3)**, the switching was aimed at minimising the cardiometabolic side effects by using an antipsychotic drug with a favourable cardiometabolic profile.

A major concern associated with antipsychotic switching is the risk of psychotic deterioration.(214) Although the findings of the quantitative review **(Chapter 3, data related to the interventions)** support the switching of antipsychotic drugs based on their high to low metabolic risks, the practice of changing antipsychotic drugs in the treatment of stable

psychotic patients remains controversial.(215) Notably, the evidence favouring the switching of antipsychotic drugs was mostly found among patients with a history of treatment resistance, for whom clozapine was mostly prescribed.(215) The prescribers must consider the long-term efficacy of the new antipsychotic regimen before switching an antipsychotic to one with a more favourable cardiometabolic profile.

Furthermore, the quantitative review (**Chapter 3, data related to the interventions)** showed a growing interest in the use of anti-obesity and some antipsychotic drugs as adjunctive therapy to minimise the cardiometabolic side effects of antipsychotics. Most data support the use of metformin, while efficacy data were limited for the other pharmacological agents. Regardless of the promising effects of adjunctive treatment, the issues associated with polypharmacy make the tolerability of such a regimen questionable.(214) The qualitative review **(Chapter 4)** supports this finding by highlighting that managing the medications used for other conditions (e.g., lipid-lowering agents) represent an additional burden for patients taking antipsychotics due to the complexity of the treatment regimen. This agrees with previous qualitative work on the demerits of polypharmacy in which participants with mental illness stated that handling multiple medications for different conditions can be overwhelming.(216,217)

According to the quantitative review (**Chapter 3; data related to the interventions**), exercise-based interventions showed conflicting yet significant effects in reducing antipsychotic-induced weight gain. Some qualitative evidence **(Chapter 4)** partially supported the unsatisfactory outcome of non-pharmacological interventions. Previous work has highlighted that poor adherence is a major barrier to the success of exercise-based interventions in the general population.(218) Although, in the quantitative review,

adherence to interventions was not often assessed in the studies targeting non-pharmacologic interventions (**Chapter 3; data related to the interventions**), non-adherence to non-pharmacological interventions (e.g., exercise) was reflected in some qualitative studies **(Qualitative review)**.

6.1.3. Barriers to the management and monitoring of cardiometabolic side effects in antipsychotic users

This review identified several potential key factors which affect the management and monitoring of cardiometabolic side effects of antipsychotic drugs. Among the identified key factors, having mental illness seems to act as a barrier to managing physical health in two ways. First, the psycho-pathological characteristics of mental illness seem to be a barrier on their own. As our findings revealed, the difficult behaviour observed in patients with mental illness such as their objection to giving blood samples was a hindrance to the screening of cardiometabolic side effects of antipsychotics and hence their management. Such behaviour was supported by previous evidence on difficult patients in mental health care that defined people with MI as difficult patients.(219) The adjunctive difficulty is reflected by the poor cooperation between patients with mental disease and their healthcare professionals.(219)

Difficult patients can be defined based on four domains that distinguish them: i) the chronicity of the MI, ii) lack of reflective capabilities, iii) their dependency on others, and vi) the pathological characteristics of the condition.(219) All these domains individually or collectively make dealing with patients with MI a difficult task. Additionally, mental disease self-stigma acts as an additional barrier to managing physical issues among patients with mental health conditions.(177) Generally, people with MIs often experience different types of emotional discrimination that result from underestimating, dismissing, and dehumanising

by their surroundings. Thus, patients may lack the confidence to share issues related to their physical health as evident in mental health stigma indicated patients who often hesitate to ask questions about their physical health.(177)

A step beyond labelling patients with mental illnesses is excluding them from the health care system. The poor quality of care observed among patients with mental illness can be associated with the complex system structure. Patients with mental illness face many issues that prevent them from getting optimal care for their physical health issues.

An important result of the study concerning fragmentation in mental health care is the lack of clarity or ambiguity regarding the roles around screening and monitoring the physical health of patients with mental illness among healthcare providers working with patients with mental illness. A clear job description is essential to clarify roles and duties among healthcare providers in different health sectors is crucial.

6.2. Key findings part (B): Discussion of key findings from the observational study

The present work attempted to explore adherence to cardiometabolic monitoring for patients prescribed antipsychotic medications according to NICE monitoring guidelines.(22) This was done by exploring the monitoring prevalence and patterns for different cardiometabolic outcomes in primary care (**THIN database study).**

6.2.1. Summary of the main findings and implications for practice

6.2.2.1. Overall monitoring remains insufficient

The observational study (**THIN database study**) demonstrated clear variations in the monitoring patterns for cardiometabolic side effects among patients prescribed antipsychotics in primary care for different outcomes (BMI, WC, BP, glucose, and plasma lipids). Blood pressure and BMI were more likely to be recorded among the measured

outcomes. These findings suggest that patients were more likely to have their blood pressure and BMI checked since these measures were built into the typical medical visit and electronic medical record procedures.

6.2.2.2. Monitoring level of waist circumference

A key finding of this study **(THIN database study)** was the negligible level of WC monitoring among the screened data. These findings were in line with the results in the quantitative review **(Chapter 3),** in which measurements for central obesity were not frequently measured. Internationally, BMI and WC have been recognised as the standard weight-related health-risk measures.(220) However, BMI may not accurately reflect the health risks among patients with apparent normal BMI but unmeasured excess visceral fat. Conversely, measurements such as WC have been accepted as indicators of visceral adipose tissue and other metabolic conditions, such as insulin resistance, type 2 diabetes, and metabolic syndrome.(220)

The under-recorded central obesity in the current study and previous works can be attributed to several reasons, including that this assessment may not be routinely carried out in general practice. In some studies (204,221), the measurements of central obesity were not included in the assessment of metabolic monitoring as the service did not assess WC measurements. Moreover, the lack of knowledge among physicians and patients regarding the importance of measuring central obesity in those at risk as well as the inconsistency in the quality of practice guidelines on screening for metabolic risk could explain the suboptimal WC monitoring rates.(222,223) Furthermore, dynamic and busy primary care environments can represent challenges for clinicians in performing such simple assessment procedures. Some clinicians have even argued that measuring WC in routine

practice represents an additional burden.(224) Thus, some have proposed patients' self-measurement of WC; however, this solution is challenged by associated reliability issues. For example, qualitative evidence addressing healthcare providers' views regarding WC monitoring in UK primary care settings revealed that measuring WC was not an acceptable procedure for some patients for number of reasons including self-preservations.(204) Our findings suggest that the evidence targeting the improvement of WC assessment in primary care is currently lacking. More research is therefore needed in this area.

6.2.2.3. Monitoring level of plasma glucose and lipid

Another important finding of the current study was the very low level of monitoring related to blood glucose **(THIN database study).** The detected monitoring level for plasma glucose (HbA1c) in this study was extremely low compared to other studies (202) regardless of the fact that the initial regulatory risk communication on metabolic risks and second-generation antipsychotics (SGAs) focused on diabetes.(40) According to a recent, large retrospective study (n = 9,316), the annual monitoring rates reached 79.6% for glycaemia and 41.2% for lipids within 180 days before and after the antipsychotic prescription.(205) The considerable variation in glucose monitoring levels in this study and similar work can be linked to the observation periods used. For example, some studies applied broad baseline testing (180 days before or after drug initiation), while others used a conservative window baseline (30 days before or after drug initiation).(205) Thus, caution is advised when comparing our results to those of previous works, as the screening rates are highly sensitive to the time window used to operationalise the measure.

On the contrary, this work **(THIN database study)** detected a relatively high-frequency rate of lipids monitoring for SGA-associated adverse effects compared to other biochemical

outcomes (e.g., glucose). Apart from SGA-related considerations, other concurrent trends may partially explain these results. For example, the screening practices for diabetes and lipid-related screening in general primary care populations have changed over the last decade. In particular, the NICE guidelines for cardiovascular disease risk assessment were updated in 2016. (201,225) Accordingly, the diagnostic requirements for dyslipidaemia were changed to consider non-high-density lipoprotein (non-HDL) cholesterol as a better indicator of CVD risk than low-density lipoprotein (LDL) cholesterol since it is more accurate, practical, and cost-effective and does not require a fasting blood sample. Nevertheless, the practices of GPs, pharmacies, and laboratories with regard to the lipid profiles of patients prescribed antipsychotic drugs may need to be updated.(225)

6.2.2.4. Baseline vs. follow-up monitoring

When comparing the baseline frequencies against the one-year follow-up monitoring among different cardiometabolic outcomes, our findings revealed that patients tend to receive follow-up measurements one year after starting treatment with antipsychotics more often than the baseline and short-term measurements (three months). Such findings are of clinical significance since half of our cohort comprised patients aged > 50 years at baseline, and around 20% were nearly 50 years. Consequently, the CVD risk for these groups would have increased at the end of the study as the patients were older. While considering the adherence to the guidelines at different endpoints (baseline vs. one-year follow-up), our results are more alarming, thus calling for the targeting of adherence to baseline monitoring.

6.2.2.5. Effect of antipsychotic metabolic profile on monitoring level

Although the included cohorts in this study comprised vast numbers of patients prescribed SGAs with high metabolic liabilities, the findings of this work demonstrate apparent

deficiencies in cardiometabolic monitoring in such patients despite the FDA warnings (191) and NICE recommendations.(22) Indeed, it could be speculated that clinicians should automatically monitor metabolic abnormalities in those SGAs.

The regression model applied in this study revealed a significant negative association between the monitoring level and the use of SGAs. Accordingly, the researcher concluded that prescribing antipsychotics is not a driving force for conducting cardiometabolic monitoring in primary care. Furthermore, the model revealed that the antipsychotics with known high metabolic risks were not strong determinants for cardiometabolic testing.

It is hard to justify the negative association between antipsychotic drugs and the monitoring frequencies detected in this study (**Chapter 5**) since antipsychotic prescribing as a moderator for cardiometabolic monitoring has been scarcely studied. Few studies explored the use of antipsychotics as an indicator for cardiometabolic monitoring (226,227); however, the reported findings were inconclusive. Further reports from reaudit data in 2008 (208) showed that patients prescribed clozapine were more likely to be monitored for metabolic syndrome if they had dyslipidaemia or diabetes. Combined with our findings, these results strongly suggest that reasons other than initiating SGAs, such as co-existing morbidities, are more important determinants of cardiometabolic monitoring among antipsychotic users. Thus, further qualitative research targeting prospective healthcare providers in primary care regarding the importance of cardiometabolic monitoring among antipsychotic users is crucial.

6.2.2.6. Potential reasons for the inconsistent monitoring

The researcher argues that fluctuated monitoring patterns observed in this study can be partially attributed to the factors highlighted earlier in this thesis **(Qualitative review,**

Chapter 4). The review **(Chapter 4)** identified some intrinsic factors reflecting a lack of knowledge and awareness among healthcare providers in terms of identifying patients in need of cardiometabolic monitoring. This was supported by further evidence, which found that less than 30% of psychiatrists correctly identified all five diagnostic criteria of metabolic syndrome listed by the National Cholesterol Education Program (NCEP).(36) Further evidence has highlighted the barriers to compliance with monitoring guidelines, such as the lack of familiarity with the monitoring guidelines among healthcare providers in primary care.(170,228) For example, evidence regarding the improvement of screening for metabolic syndrome components among patients with mental illness indicated that workers in mental health settings were the most likely to comply with the screening process compared to those working in primary care.(203) Additionally, it could be argued that the inconsistency in quality-of-practice guidelines regarding metabolic risk screening, which at least partly causes an insufficient understanding of these guidelines among healthcare providers, may account for the low monitoring rate. A recent review of the guidelines for the screening and monitoring of cardiometabolic risk has concluded that not all guidelines are of sufficient quality to guide clinicians in screening and monitoring practices.(229)

Notably, the observed improvements in lipid monitoring in this study can be linked to the changes in medical practice induced by the FDA warnings in 2003. Accordingly, the SGAs label was updated to cover the warnings about hyperglycaemia and diabetes.(40,191) Supportive findings from a retrospective study exploring the glucose and lipid monitoring rate in people on maintenance SGA therapy revealed that physicians' concerns about the metabolic issues of antipsychotic therapy were associated with significant improvements in testing rates.(208) Nevertheless, increasing awareness regarding the cardiometabolic

liabilities of antipsychotics may not necessarily lead to improving monitoring. For example, records of low metabolic monitoring frequencies were reported in a survey of general practitioners despite their awareness of the associated high metabolic risks of SGAs.(230,231) This suggests that other high-level organisational barriers may interfere with healthcare professionals' monitoring performance.

It is likely that the more frequently an individual's uses medical care services, the more opportunities there are to receive monitoring. A previous work (232) supported this claim by highlighting the fragmentation of care and limited access to the healthcare system as fundamental barriers for patients with mental illness to receive cardiometabolic monitoring. An integrated system of general and mental healthcare should ensure coordination and collaboration between the two services without obscuring the monitoring responsibility at key periods, such as upon admission or before starting antipsychotic medication. Conversely, poor service integration can result in a lack of fundamental resources and equipment. In addition, the poor integration of general and mental healthcare can act as a mediator for other factors related to the healthcare system (e.g., limited access to general care services). It can also result in confusion among primary care providers regarding the monitoring responsibilities around maintaining physical health.

6.2.2.7. Potential role of pharmacists in improving cardiometabolic screening in primary care

In 2018, the Royal Pharmaceutical Society of Great Britain issued a policy document recommending full utilisation of pharmacists' clinical expertise and knowledge to improve the lives of people with mental illness.(233) As discussed in the qualitative review **(Chapter 4)**, the barriers to proper cardiometabolic monitoring include limited access to specialised services and time constraints. Primary care pharmacists can provide innovative patient care

services beyond retailing and dispensing.(234) In cardiometabolic monitoring, for example, pharmacists can perform monitoring for various purposes (see Figure 6-1).

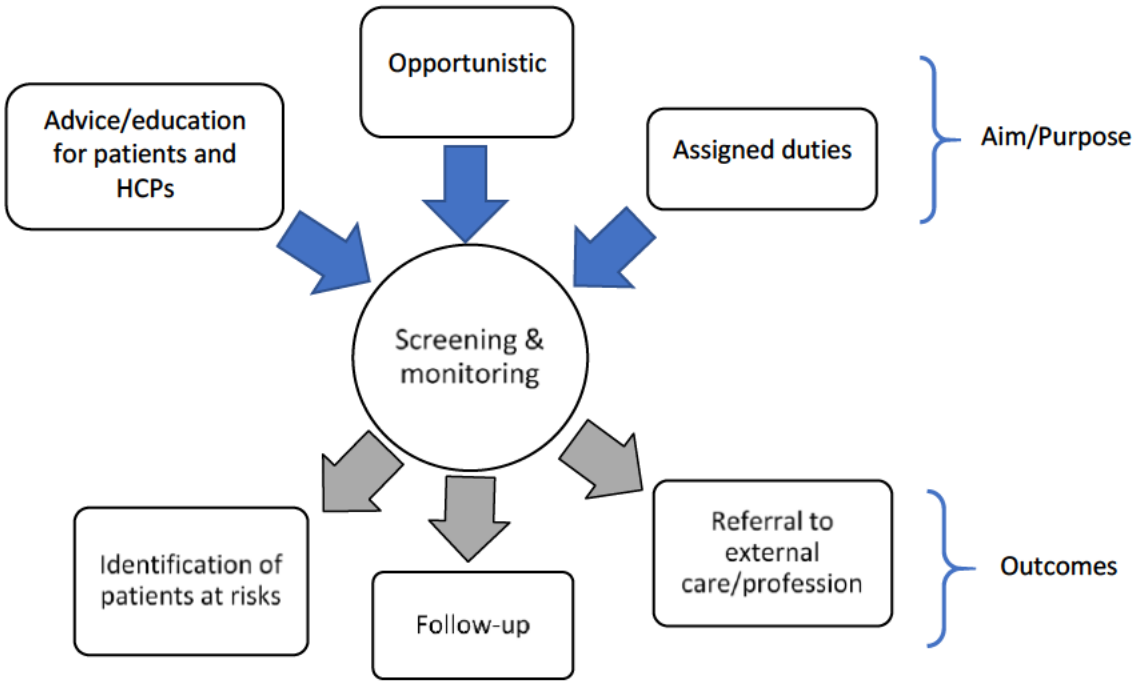


Figure 6-1. Forms and purposes for monitoring activities that pharmacists can offer. HCPs: healthcare providers.(234)

Notably, the monitoring-related activities that can be delivered by pharmacists depend on the context and the setting. Evidence supporting the pharmacist's role in mental healthcare has been mainly applied to inpatients.(235) Few studies have highlighted the role of pharmacists in cardiometabolic monitoring in primary care settings, mainly specialised clinics. The available evidence suggests that pharmacists' role in cardiometabolic monitoring in mental illness has been demonstrated effectively as part of collaborative care (235), in which pharmacists can participate in the cardiometabolic monitoring process either directly or indirectly. On the one hand, the pharmacists' role in monitoring has been investigated in pharmaceutical care programmes in a community pharmacy to manage patients with dyslipidaemia.(236) For example, Gonzalvo (237) assessed the effectiveness of services

provided by a pharmacist as a member of a pharmacist-managed cardiovascular risk-reduction clinic for patients with mental illness. The pharmacists were instructed to obtain blood samples (lipids) and engage in other (teaching/counselling) activities targeting patients' knowledge about the role of cholesterol in CVDs.(237)

Similarly, another study evaluated the value of pharmacists in cardiometabolic monitoring in patients prescribed SGAs in an outpatient community mental health clinic. The pharmacists were allowed to order relevant laboratory tests (plasma glucose and lipids) without a physician's verbal order.(46) However, it is important to note that this study did not clarify whether the intervention was an originally implemented service or was only conducted for the research purpose, even though the study showed positive outcomes with regard to pharmacists' involvement. Such involvement can be beneficial as integrating pharmacists into the primary care workforce can counteract factors that hinder the monitoring process, such as time constraints and the heavy workload. However, the role of pharmacists in cardiometabolic monitoring in antipsychotic users was not fully expanded upon. More evidence is therefore needed to address the effectiveness of pharmacists' interventions in measuring outcomes related to central obesity (WC).

On the other hand, pharmacists can indirectly mediate the monitoring process by signposting and advising other healthcare professionals regarding the monitoring. This was highlighted by a systematic review aimed at identifying the pharmacist's role in monitoring metabolic syndrome among mentally ill patients. (238) The review highlighted an intervention proposed by the pharmacist which was a reminder system (e.g., pop-up alert). The system aimed to alert clinicians to perform screening for metabolic issues in patients with mental illness who needed screening; however, no significant impact was observed in

the screening rate among physicians. This suggests a low uptake rate of such an approach by physicians, highlighting the issue of healthcare stigma raised in the current study **(Qualitative review; Chapter 4),** thus stressing the importance of addressing issues related to stigma when incorporating new services.

Also, pharmacists can mediate the cardiometabolic monitoring of patients by facilitating patient transfer between services. Community pharmacies do not operate on an appointment-based schedule, making them highly accessible to customers.(235,239) Evidence has shown that approximately 90% of the population can access a community pharmacy within a 20-minute parameter.(240) Disadvantaged individuals, including those with mental illness, benefit most from this level of access. (240) In other words, opportunistic and other forms of screening by community pharmacists likely have the potential to improve the continuity of care by increasing the detection rates around cardiometabolic risk factors. This is particularly relevant in the UK, where up to a third of patients with mental illnesses are treated exclusively in primary care.(241)

Nonetheless, some may argue that involving pharmacists in procedures involving blood testing in community settings may be inconvenient and challenging. Unlike hospital pharmacists, community pharmacists work in isolation from the rest of the primary care workforce, making it difficult for them to access clinical patient data.(234,235) Notably, in the previous models (238) the pharmacists were particularly assigned to taking blood samples. Thus, it is crucial to clearly establish responsibilities when integrating pharmacists within the healthcare system.

In addition, the setup of the traditional community-based pharmacy is challenging since it does not facilitate enhanced services. However, several improvements targeting patient care

service delivery have been introduced in community-based pharmacies, including semi-private counselling areas and examination rooms. Another challenge is represented in the competency of pharmacists to deliver such enhanced services. Physical health screening and monitoring services may not be offered by all pharmacies, for example, as they are optional and require further accreditation.(234) Therefore, strategies targeting pharmacists' integration into medical teams and the expansion of their roles need further development to achieve a more comprehensive and collaborative working relationship. The following part discusses the applied methods for this PhD.

Part II: Strengths and limitations of the work

The strength and weaknesses of each programme of work have been presented in relevant chapters. This section presents an overarching discussion of the key strengths and limitations of the thesis. This PhD work was achieved as a result of a collaboration of primary healthcare professionals, and data managers.

The study protocol was developed by the PhD candidate and supervised by the supervisors, who have extensive experience in the field. Also, the study protocol was developed in alliance with an external review panel which was involved in guiding the study design and the development of supportive research materials such as the data extraction tool. Involving the external collaborators allowed for addressing key issues in the research through important feedback on how to proceed and solve any emerging obstacles.

Also, the collaboration helped identify and address fundamental issues during conducting the research such as extracting and handling huge and complex datasets. For example, consulting expert data support was important for data extraction as experienced abstractors were assigned to this work. This is particularly vital to satisfy key quality elements in the

data, enhancing the data integrity using an inter-rater approach and working with field specialists (e.g., health information manager).(199) Also, the collaboration with the data experts allowed the generation of high-quality datasets along with facilitating the extraction process to fit the narrow time frame of the PhD.

Similarly, involving a statistician enabled the support and advice on the selection and conduct of the appropriate analytical approach along with ensuring the accuracy of the findings. Also, the research student was able to conduct the analysis herself through the advice received allowing the execution of key research analysis.

6.3. Strengths and limitations of the systematic reviews (Chapters 3&4)

6.3.1 Strengths of the systematic reviews (Chapters 3&4)

The methodological rigour of the systematic review was enhanced by fulfilling the general elements of validity for systematic reviews throughout the different steps of the review process as proposed by Thompson (242), who emphasised transparency in comprehensive literature search, appropriateness of the selection criteria, and the validity of the selected evidence, with attention to transparency.

The quality of the methods used to conduct the systematic review is also important, as the use of high-quality methods will ensure that the summary of the results is as free of bias as possible to prevent the reporting of false significant findings of benefit or harm. As with any study, this review was conducted as per the protocol that was developed and verified by the review team. A well-designed protocol that is centred on a researchable, focused, and clinically relevant question and that provides for a clear description of the population, intervention or exposure, and outcomes of interest is important. Further bias can be introduced with an inadequately rigorous methodological protocol.

Also, the inclusion and exclusion criteria of studies in this systematic review were clearly defined a priori. The applied eligibility criteria specified the patients, interventions, exposures, and outcomes of interest to be achieved when identifying the studies for inclusion.(242) Another important aspect and defining characteristic of a systematic review is the comprehensive systematic search used to identify studies that are relevant to the research question. The validity of the results of any systematic review is reflected in the search strategy employed to find the extensiveness of the evidence and it is essential to use a broad search strategy when identifying original publications for inclusion. For this purpose, a comprehensive search was conducted using relevant keywords in three databases. The search strategy included both MESH terms and text words.

Furthermore, the quality of the primary studies is considered a major limiting factor in drawing valid conclusions. The validity of the individual studies was checked using comprehensive and reliable tools for assessing quality and susceptibility to bias. Thus, the JBI Critical appraisal checklists were used for this purpose.(242) In this review, the quality assessment was applied to reveal the extent of bias and the resulting uncertainty in the final study pool as detailed in Chapters **3&4**.

An additional value of this review was the integration of quantitative and qualitative evidence. The present review was one of the few reviews that employed mixed methods to highlight different aspects of a single phenomenon (cardiometabolic side effects of antipsychotic drugs). The addition of qualitative studies to quantitative studies helped reveal the reasons behind the heterogeneity of the quantitative studies and the gaps in the current research. Data from qualitative and quantitative studies were combined using an established methodology to increase the richness and robustness of the synthesis. In the present review,

the authors tried to align with the method proposed by the JBI as it is so far recognised as the first gold standard for conducting mixed methods systematic reviews.

Additionally, the results of the review were reported as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.(55,242) The PRISMA guidelines included an item for reporting in conclusion, "a general interpretation of the results in the context of other evidence, and implications for future research". Applying the PRISMA guidelines allowed a defined or transparent process for reporting the evidence gaps.

6.3.2 Limitations of the systematic reviews (Chapters 3&4)

A key weakness of this review was the use of a newly developed approach. The methodology employed in this thesis is complicated regardless of the use of standard guidance (JBI-MMSR), particularly with few published examples using a similar method available.

Another major limitation of this review was related to the quality assessment, which was based on the judgment of the assessors leading to different decisions by different assessors. Moreover, based on the quality assessment for the individual studies, the assessment showed generally low reporting and study quality. This can be problematic because methodological deficiencies of the individual studies limit the validity and reliability of the review findings.

Additionally, the quality evaluation tools (JBI) used in the present research did not discriminate reporting quality from internal or external validity. For instance, the appropriate reporting of subject characteristics, transparency in analytical techniques, and estimates contribute to the quality of the publications but not necessarily reflect the quality of the studies.(243)

Additionally, the quality of the included studies in the review was narratively presented according to the quality features that were proposed by the assessment tools employed in the study (JBI). In this regard, the quality assessment of the included studies demonstrated high risks of bias across the studies. Conducting a sensitivity analysis would be more beneficial to assess the impact of undetected bias across the studies.

An additional limitation of this review was the utilisation of the narrative synthesis approach without the possibility to compare the magnitude of cardiometabolic changes among antipsychotic users, since conducting a meta-analysis was challenging due to the heterogeneity of the included articles. Thus, the narrative approach was considered appropriate considering the high variations across the included studies.

The study involved a comprehensive search of the literature using important databases and including alternative data sources.

A limitation of this systematic review was associated with the broad inclusion criteria that covered a wide range of studies addressing interventions (randomised and non-randomised controlled trials). The inclusion of the non-randomised controlled study designs can not always be reliable to evaluate the effectiveness of the intervention programmes.

A key methodological concern among the included studies was the lack of reflexivity of the authors (the researchers' role was not clearly defined).

6.4. Strengths and limitations of the observational study (Chapter 5)

6.4.1. Strengths of the observational study (THIN study)

To the best of our knowledge, this is the first large study investigating the association between the antipsychotic type and the monitoring pattern for cardiometabolic side effects. In this regard, a key feature related to the used database was the large study sample. The

data source allowed for a very large sample size through the THIN database. Thus, this study was highly powered to detect cardiometabolic monitoring patterns in patients prescribed antipsychotics in primary care.

Another key strength of the present study was the representation of the THIN data to the UK population. Approximately 6% of the UK population are represented in the database, which is made up of anonymised patient records extracted from 744 GPs around the UK.(31) This is important considering the expansion of community mental health services along with the increasing proportion of patients with mental illness that are being treated in community care. Also, the THIN data is collected in a non-interventional way and, therefore, represents real primary care practice (or real-world data). This makes the THIN data a perfect choice to be used to examine features of healthcare delivery in a vulnerable group (patients with mental illness) including quality of care such as the quality of cardiometabolic monitoring.

The anonymity and confidentiality of research participants were maintained by strict governance processes. Data collection for THIN was approved by the South East Multicentre Research Ethics Committee (MREC) in 2003. Therefore, individual studies using THIN data do not require individual ethical approval when using anonymised THIN data. However, the study was reviewed by an independent Scientific Review Committee (SRC) to ensure data is analysed and interpreted appropriately.

One potential reason for the incomplete recording of the THIN data is that practices solely contributing to THIN may be new to the VISION IT software and that the clinical data from their previous software are not coded as well and do not convert correctly to the VISION IT software. Therefore, to reduce underreporting of events and improve the validity of the dataset, all actively recorded patients taking antipsychotic medication should have

been participating in the practice for at least one year. This enabled sufficient time for patients' data transfer between different practices.

Further strengths lay in the design of this study. Firstly, applying a cohort study design enabled the extraction and analysis of multiple cardiometabolic outcomes in a single cohort which was convenient for the PhD time frame and resources. Secondly, the use of observational design enabled us to obtain critical descriptive data reflecting cardiometabolic monitoring practices, as such information could not be obtained from clinical trials due to ethical concerns. Lastly, the applied process of record selection for inclusion in this study was random. The use of such a technique allowed recruiting a representative sample to maximise the study external validity.

6.4.2. Limitations of the observational study (THIN study)

The leverage of having such diverse and large data may have been accompanied by some drawbacks. Notably, the main limitation of this thesis lies in the assumption that a record of a laboratory test was an evidence of monitoring for cardiometabolic outcomes. It is easy to overlook the fact that EHRs are observational databases. Thus, the data reflect not only the health of the patients but also their interactions with the healthcare system. Due to the fact that the data were obtained from a retrospective analysis of the THIN, the assumption for patients who have undertaken cardiometabolic monitoring was based on the existing date records that reflected the date when the test code was ordered by the GP. However, such an assumption does not confirm whether the test was actually conducted. This may lead to either underestimation or overestimation of the outcome of interest (records of cardiometabolic monitoring) leading to misclassification bias. Similarly, the estimation of patients with cardiovascular risk factors at baseline who received cardiometabolic

monitoring in the cohort was based on the presence of the recorded laboratory results but not based on the clinical READ code for the condition. For example, some patients may have recorded high blood pressure just at the time of visit (white coat hypertension), however; based on the recorded blood pressure measurement, the patient would have been classified to have a risk factor.

Along with the limited time and resources, the complexity of the data allowed only the extraction of the baseline value for the outcome measures from the THIN database. Accordingly, the patient's clinical parameters, such as high blood pressure, were estimated based on the entered blood pressure value and were not based on the clinical READ code for hypertension which may have resulted in misclassification bias. Also, the complexity of the data resulted in restricting the antipsychotic to the baseline only. It was not feasible to assess the effect of antipsychotic switching during the trial period. Although the antipsychotic drug codes consisted of all the antipsychotics approved by the FDA, the cohort mainly covered the list of antipsychotics that are prescribed in the UK.

Further key limitations were associated with the study design. Since an observational cohort design was utilised for this work, it is generally held that, to varying degrees, different observational study types are subject to more sources of bias than randomised study designs. Also, despite using the cohort design allowing the extraction of several outcomes in a single study, this came with consequences in that specific details related to the cohort could not be extracted. For example, information on important confounding factors such as mental illness severity, drugs prescribed for other comorbidities (e.g., lipid-lowering agents), body weight and height were also limited. Furthermore, the present data did not allow differentiation between GPs not undertaking cardiometabolic monitoring and patients failing

to attend for monitoring. For instance, data from specialists, as well as events that occur in the hospital, may not have been fully captured in the patient's electronic record.(244) Treatments given in the hospital may also not have been recorded. Thus, it would be advantageous for future studies in this area to link the data from the THIN database with the data of the patients treated in specialised centres, so it would provide a comprehensive picture of the extent of cardiometabolic monitoring among antipsychotic users in different healthcare sectors. However, obtaining such a complex dataset would come at a price of handling a complicated dataset that requires advanced analytical skills.

A further design-related limitation was related to the nature of the cohort, which indirectly affected the estimation of the association between the type of antipsychotic prescribed at the study index and the cardiometabolic monitoring pattern. Since the cohort used in the present study was a dynamic cohort, the selected cohorts differed in terms of the time spent by each subject. To test the effect of antipsychotics prescribed at index on the monitoring pattern for different outcomes, the effect of time variation was controlled by restricting the time variable. This was done by including only patients with a duration of exposure of at least one year, as the study explored the effect of antipsychotic use on the lilelihood of cardiometabolic monitoring for the first year of antipsychotic treatment. Such approch would allow equal exposure time for the included subjects within the first year of antipsychotic treatment. Nevertheless, our findings may be limited by the time frame of the regression analysis (within the first year of antipsychotic therapy), which may have affected the estimation at time points that are earlier than one year (e.g., 3 months).

The last limitation concerns the generalisability of the data. The generalisability of the THIN database may be limited mainly to practices that contributed to the database.

Potential eligible patients receiving care from practices supported by other databases such as the General Practice Research Database (GPRD) along with practices using IT systems other than the VISION (e.g., EMIS web) are likely to be missed from our study.

6.5. Future work

Two main questions have emerged from the findings of this thesis, which imply future recommendations.

Q1: What are the causes for the observed variations in the monitoring patterns associated with cardiometabolic parameters in patients prescribed antipsychotics as identified in this work?

6.5.1. Identifying barriers to cardiometabolic monitoring

For future research, it is crucial to investigate whether patients prescribed SGAs are monitored for cardiometabolic abnormalities following treatment and if such measures in routine care are cost-effective. Also, further work is needed to address the effect of antipsychotic use as a predictor for cardiometabolic monitoring. Furthermore, this study mainly evaluated patients' related predictors for cardiometabolic monitoring in primary care, whereas external factors (either barriers or facilitators) could have affected the likelihood of undergoing monitoring. This would need deep exploration via interviewing or surveying healthcare providers (e.g., GPs) to obtain views regarding the management of these patients.

Q2: What can be done to improve guideline adherence?

6.5.2. Evaluating the practicality and applicability of the implemented guidelines

Healthcare organizations are constantly changing for political reforms and policy initiatives. However, healthcare providers may not feel prepared for the change nor recognize its value.

Therefore, further research should be devoted to assessing the perceptions of healthcare providers regarding the practicality of implemented changes in the NICE monitoring guidelines.

6.5.3. Expanding the human resources

An area worth investigating is identifying the critical components of the healthcare pathways where pharmacists can be involved by providing or facilitating the monitoring process. Further studies are essential for a clear picture of the proper circumstances to install metabolic monitoring services in community-based pharmacy settings. Furthermore, some challenges may relate to factors influencing patients' motivation to seek physical checks from pharmacists in the first place. Measuring patients' acceptability for such service is highly recommended even after service implementation. Future research needs to focus on patients' perspectives as service users before and after the service implementation and the convenience of the service provided.

6.5.4. Integrating health information technology (HIT)

Research targeting electronic infrastructure introducing electronic alerts to enable rapid identification of patients who require or are delayed for monitoring and reminding the prescriber to undertake laboratory monitoring for patients treated with antipsychotics is valuable. Indeed, technology has been widely spread over different industries, and the medical field is no exception. However, the lack of well-designed and implemenTable electronic alerts can contribute to the defects observed in this work. Such a system would be valuable as a reminder system for practitioners regarding the need to monitor patients before and after therapy. It could also be utilised as an alerting system to notify clinicians if

patients miss monitoring visits. Indeed, applying the technology enabled the completion of this work.

6.6. Conclusions

This PhD work investigated the cardiometabolic side effects of antipsychotics from various perspectives, including the prevalence of cardiometabolic side effects; the available interventions to prevent/mitigate these side effects; factors affecting the management and monitoring of cardiometabolic side effects; and the level of adherence to cardiometabolic monitoring guidelines in primary care.

In light of the increased use of second-generation antipsychotics and the consolidating evidence of their cardiometabolic side effects, the unclear cardiometabolic side effects profiles for most antipsychotics are concerning. The limited data indicated that high-potency antipsychotics such as clozapine and olanzapine were associated with an increased prevalence of cardiometabolic side effects. The other SGAs were either less studied or not examined at all. New SGAs identified in RCTs that may have better cardiometabolic profiles should be characterised in future research.

This work identified various interventions to mitigate cardiometabolic side effects among antipsychotic users. However, it was challenging to recommend any specific intervention because both identified approaches seemed to have the potential to counteract the cardiometabolic side effects of antipsychotics. The evidence suggests that some adjunctive pharmacologic strategies may have some promising benefits in managing antipsychotic-induced weight gain, yet issues related to polypharmacy must not be overlooked. The use of adjunctive therapy with non-antipsychotic drugs can be hindered by increased risks of polypharmacy, which in turn can negatively affect patients' adherence to antipsychotic

therapy and hence lead to the worsening of psychotic symptoms. Finally, challenges of the cardiometabolic management and monitoring may be multifactorial. Further research is needed to identify specific barriers related to settings and health systems to monitoring practices.

Although guidelines can increase cardiometabolic monitoring among antipsychotic users, the findings of this study indicate the need for further developments to enhance the monitoring of patients receiving antipsychotics in primary care. The observational study identified an extremely low level of monitoring frequency for central obesity indicators in patients with mental illness taking antipsychotic drugs compared to other outcomes, as the monitoring frequency for WC did not exceed 3% in any given study year. Weight gain, especially when manifested as intra-abdominal obesity, remains a significant long-term health issue in patients taking antipsychotics, even those with normal BMI scores. WC measurement is a simple and sensitive screening tool for determining several metabolic complications. Therefore, more efforts should be dedicated to enhancing WC monitoring in SGA-treated populations. Also, despite published recommendations insisting on the baseline and timely monitoring of blood glucose, a small proportion of patients on antipsychotic treatment have their blood glucose level assessed in this work. These findings are very concerning as they indicate that antipsychotic users are at high risk of diabetes and may not be identified or adequately assessed for treatment alternatives.

Furthermore, this work has shown that antipsychotic prescribing was not a predictor for cardiometabolic monitoring among patients with mental illness, regardless of the vast proportion of patients prescribed agents with high metabolic risks. Data evaluated in this study showed that monitoring frequency in subgroups populations taking antipsychotics

with known cardiometabolic risks (e.g., olanzapine and quetiapine) barely exceeded 50%. This emphasises the importance of routine cardiometabolic monitoring for all individuals receiving antipsychotic therapy at the beginning of the antipsychotic treatment, regardless of the course of illness or type of healthcare services. Finally, the effective involvement of wider healthcare professionals including pharmacists is imperative to improve monitoring practices. This is highly relevant as the present study detected low baseline and follow-up monitoring patterns for cardiometabolic parameters (WC, plasma glucose and lipids) among antipsychotic users.

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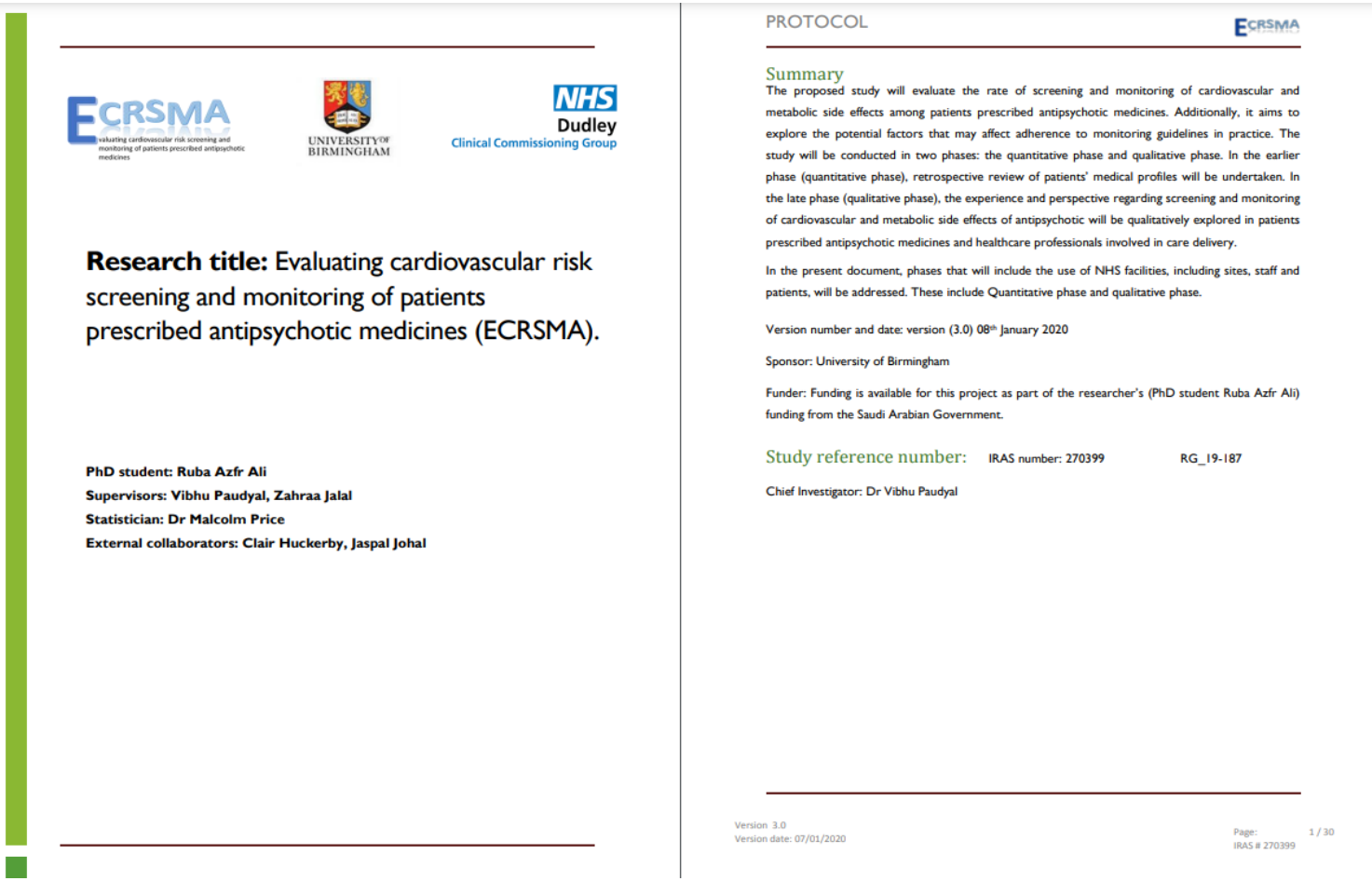
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Appendices

Appendix II (Chapter 2)

A. Study protocol



ECRSMA
evaluating cardiovascular risk screening and monitoring of patients prescribed antipsychotic medicines

UNIVERSITY OF BIRMINGHAM

NHS
Dudley
Clinical Commissioning Group

Research title: Evaluating cardiovascular risk screening and monitoring of patients prescribed antipsychotic medicines (ECRSMA).

PhD student: Ruba Azfr Ali
Supervisors: Vibhu Paudyal, Zahraa Jalal
Statistician: Dr Malcolm Price
External collaborators: Clair Huckerby, Jaspal Johal

PROTOCOL

ECRSMA

Summary

The proposed study will evaluate the rate of screening and monitoring of cardiovascular and metabolic side effects among patients prescribed antipsychotic medicines. Additionally, it aims to explore the potential factors that may affect adherence to monitoring guidelines in practice. The study will be conducted in two phases: the quantitative phase and qualitative phase. In the earlier phase (quantitative phase), retrospective review of patients' medical profiles will be undertaken. In the late phase (qualitative phase), the experience and perspective regarding screening and monitoring of cardiovascular and metabolic side effects of antipsychotic will be qualitatively explored in patients prescribed antipsychotic medicines and healthcare professionals involved in care delivery.

In the present document, phases that will include the use of NHS facilities, including sites, staff and patients, will be addressed. These include Quantitative phase and qualitative phase.

Version number and date: version (3.0) 08th January 2020

Sponsor: University of Birmingham

Funder: Funding is available for this project as part of the researcher's (PhD student Ruba Azfr Ali) funding from the Saudi Arabian Government.

Study reference number: IRAS number: 270399 RG_19-187

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Signature page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to adhere to the signed University of Birmingham's Sponsorship CI declaration.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator:

Signature: ..... Date: ...../……../…….

Name: (please print).....

Name: (please print): Vibhu Paudyal

Sponsor statement:

Where the University of Birmingham takes on the sponsor role for protocol development oversight, the signing of the IRAS form by the sponsor will serve as confirmation of approval of this protocol.

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Summary and Scientific Justifications

Summary of the study

Patients with severe mental health conditions, are associated with an increased prevalence of comorbid physical health conditions especially cardiovascular diseases (CVDs). Although the causes of CVDs in people with mental health conditions are multifactorial, research evidence suggests that antipsychotics have the potential to cause cardiovascular diseases or worsening pre-existing conditions. Recently, the management of cardiovascular and metabolic side effects in patients taking antipsychotics has received considerable attention.

However, undiagnosed and untreated cardiovascular and metabolic diseases among patients prescribed antipsychotics remain high due to suboptimal screening, which leads to missed opportunities for the use of primary preventive measures and hence high in-disposition and death rates.

This study aims to determine the rate of screening and monitoring of patients prescribed antipsychotics and the influences on the uptake of the recommending guidelines in practice.

A mixed-method of quantitative and qualitative research will be used for the present study. The study will involve three phases: quantitative phase and qualitative phase. The outcomes of this research may enable better understanding and highlight how is the current practice, what is required for optimal service and to allow for more inter-professional working.

Synopsis

TABLE 1

Study Title	Evaluating cardiovascular risk screening and monitoring of patients prescribed antipsychotic medicines (ECRSMA)	
Internal ref.	RG_19-187	
Study Design	Mixed method of quantitative and qualitative approaches.	
Study Participants	Patients prescribed antipsychotics medicines Healthcare professionals who are involved in the management of patients prescribed antipsychotic medicines.	
Planned Sample Size	For the quantitative phase we aim to analyse for approximately 120 patients records For the qualitative phase (we aim to recruit approximately 40 participants including 20 healthcare professionals and 20 patients).	
Planned Study Period	Approximately one year and one month starting from February 2020.	
	Objectives	**Outcome Measures**
Quantitative	This phase aims to investigate the level of guideline adherence among health professionals for cardiovascular and metabolic monitoring guidelines in a primary care setting (Dudley CCG).	The main outcomes of interest are the proportion (%) of the sample population who were monitored for cardiovascular and metabolic components according to the local/national guidelines.
Qualitative	This phase aims to investigate factors affecting the uptake of guidelines for monitoring and management of cardiovascular and metabolic side effects of antipsychotics.	Factors associated with the uptake of screening and monitoring guidelines by healthcare professionals along with the perspective of patients prescribed antipsychotic around screening and monitoring practices of cardiovascular and metabolic side effects of antipsychotics.

Key words: Cardiovascular side effects, screening, monitoring, management, antipsychotics.

Role of sponsor and funder

This research is conducted as part of the doctoral degree for (Ruba Azfr Ali), and it is funded by the Saudi Government; however, the funder is purely funding the study and has no conflict of interests with the study outcomes. The study is organised by the University of Birmingham.

Role and responsibilities of study management committees/groups/individuals

Study will be managed by the CI and research team.

Study flow chart

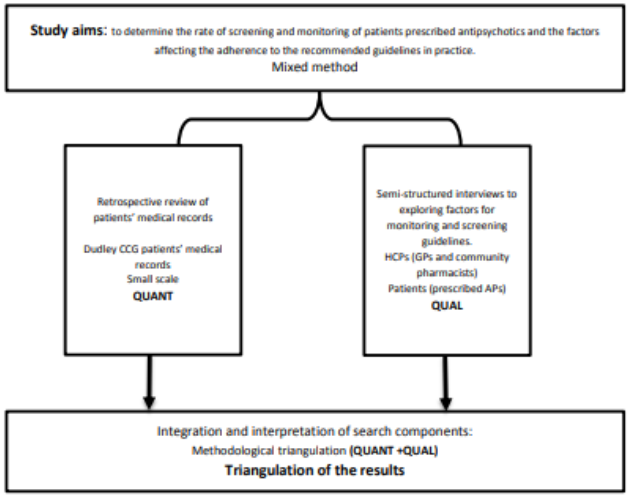


FIGURE 1

HPCs: healthcare professionals

GPs: general practitioners

APs: antipsychotic medicines

QUANT: quantitative approach

QUAL: qualitative approach

Study protocol

Background

Patients with mental illness, including schizophrenia, affective mood disorder and major depressive disorders, are associated with high suicide risk and increased prevalence of comorbid physical health disorders (1). Therefore, they are more like to die prematurely compared to the general population (1,2). A recent review on the causes of deaths in schizophrenic patients Piotrowski et al. (3) estimated that patients experienced around 10 to 20 years reduction in life expectancy compared to the general population. The increased mortality in this group has shown to be due to several aetiologies, mainly cardiovascular diseases (29.2%) and cancer (13.5 %) (2).

Results from a meta-analysis (1) assessing prevalence and incidence of cardiovascular deaths among 3,211,768 patients with severe mental illnesses including psychotic and non-psychotic conditions reported an increased prevalence of cardiovascular diseases (CVDs) with individual rate of 8.4% for people with bipolar disorder (95% CI: 5.4-12.6, 12 studies, N=66,911); 11.7% for those with major depressive disorder (95% CI: 3.6-32.2, 7 studies, N=83,965); 11.8% for those with schizophrenia (95% CI: 7.1-19.0, 13 studies, N=191,982) compared to control groups.

Furthermore, epidemiological studies reported an increased prevalence of cardiovascular risks factors such as metabolic syndrome (MetS) (37-61.1%) among patients with mental illness (4). Although the aetiology of CVDs in people with mental health conditions is multidimensional, research evidence suggests that antipsychotics have the potential to causes cardiovascular risk or accelerate pre-existing conditions (5). According to the results of meta-regression analysis on the prevalence of CVDs among a wide range of patients with severe mental illness there was an increased incidence of CVDs among antipsychotic users (12 studies; β=0.04, 95% CI: 0.01-0.08, p=0.008) compared to control groups (6 studies; β=0.24, 95% CI: 0.06-0.42, p=0.008) (1).

Cardiovascular and metabolic side effects of antipsychotic drugs

Antipsychotics are classified according to their chemical structure into first (FGAs) and second (SGAs) generations (6). The former group is characterized by their effectiveness in relieving positive psychotic symptoms of schizophrenia such as hallucinations. However, they have been proved to be less effective against negative symptoms, which lead to the development of the later generation of antipsychotic drugs (SGAs) (9). Antipsychotics are considered the cornerstone in the management of psychotic disorders (7) along with other non-psychotic conditions such as dementia (8). Despite their extensive use, many antipsychotics have a high tendency to cause metabolic abnormalities,

therefore increasing the risk of CVDs and other metabolic conditions particularly MetS and, type 2 diabetes mellitus (DMT2) (9).

Robust evidence suggests that antipsychotics-induced metabolic side effects were attributed to multiple functional pathways (9). The proposed underlying mechanism that antipsychotics induce metabolic disturbances includes the blockage of histamine H1, dopaminergic (D2 and D3), muscarinic (M2 & M3) and the central 5-HT receptors (6). Activating the central 5-HT receptors leads to changings in the eating behaviour and hence reduce food intake (10). Conversely, inhibiting the central 5-HT receptors by antipsychotics can cause an increase in food intake, and subsequently, weight gain (10). Others (11) suggested a mechanism for antipsychotics inducing weight gain is the inhibition of dopaminergic receptors particularly (D2 and D3), as research on obesity-associated with antipsychotics highlighted the potential association between dopaminergic receptors and feeding behaviour (12). Although all antipsychotics bind to dopaminergic receptors, the binding affinity was reported to vary across different antipsychotics (6). Clear evidence is available on a similar association between the inhibition of muscarinic receptors (M2 and M3) and metabolic side effects of antipsychotics (6). Muscarinic receptors (M3) control cholinergic-dependent insulin release, as they are located on pancreatic β cells (6). It was hypothesised that some antipsychotics (such as clozapine and olanzapine) might possess activity for both cholinergic-dependent and glucose-dependent insulin secretion from pancreatic β cells (13). Furthermore, the degree of antipsychotics affinity for muscarinic receptors appeared to vary across different antipsychotics as antipsychotics with high affinity towards muscarinic receptors (such as clozapine and olanzapine) have high propensity to cause glucose deregulations compared to antipsychotics with a low affinity towards muscarinic receptors such as aripiprazole, risperidone, amisulpride and lurasidone, asenapine (14). Notably, the onset of metabolic abnormalities in serum glucose and lipid-associated with antipsychotics occur even before the onset of weight gain, suggesting an independent relationship between the metabolic changes and weight gain (9).

Consequently, concerns regarding the cardiovascular and metabolic side effects of these drugs have also grown (15). Nevertheless, antipsychotics are well documented of their liabilities to cause metabolic dysregulations. Results from a meta-analysis comparing the metabolic side effects of SGAs (16) showed that risk for metabolic abnormalities was higher among certain drug members of the class, namely olanzapine and clozapine. This was in line with the results of another meta-analysis, which showed that except for haloperidol, ziprasidone, and lurasidone, all antipsychotics are associated with metabolic side effects including weight gain compared to placebo (17). The increasing use of SGAs, which currently forms the primary choice pharmacotherapy for several mental diseases

(18), has run parallel with the rising recognition of cardiovascular and metabolic abnormalities in psychiatric practice (19). Patients with schizophrenia are at the dual disadvantage of being inherently predisposed to metabolic abnormalities, which were reported to be worsened by the subsequent use of antipsychotics (19). Along with highlighting the magnitude of this problem, these findings enlightens how it remains undiagnosed.

Recommendations for monitoring and management of cardiovascular and metabolic side effects of antipsychotic drugs

In 2003, a black box warning was launched by the U.S. Food and Drug Administration (FDA) regarding the diabetogenic effect of antipsychotics (20). In response to these warnings, a panel of regulatory bodies and professional associations including the American Diabetes Association (ADA)/ American Psychiatric Association (APA) published a consensus statement that recommends early and regular monitoring of metabolic side effects among antipsychotics users (21). Consequently, the management of cardiovascular and metabolic dysregulations in patients with mental health conditions has received considerable attention and has been the focus of much clinical guidance and healthcare policy (22).

Effective monitoring and management of cardiovascular and metabolic abnormalities in patients taking antipsychotics aim for two primary purposes: (1) identifying treatable pathology among high-risk populations; (2) tracking cardiovascular and metabolic disturbances among antipsychotics treated population and hence link these abnormalities to APs treatment (23). The results of such assessment would aid the selection of antipsychotics, particularly in the presence of existing risk factors or metabolic abnormalities (23).

Baseline metabolic assessment should be obtained for all patients before starting antipsychotic treatment. Antipsychotic naïve patients (patients who are taking antipsychotic drugs for the first time or being treated for a first episode of schizophrenia) should be assessed for risks factors of cardiovascular diseases including high risks of metabolic abnormalities (23).

In July 2014, the National Institute for Health and Care Excellence (NICE) had updated the guidelines for managing schizophrenia to include management of cardiovascular and metabolic abnormalities in patients with schizophrenia (24). The guidelines recommend that physical health checks should 'pay particular attention to' endocrine disorders such as diabetes and hyperprolactinaemia, to cardiovascular risk factors such as blood pressure and lipids, to the side-effects of medication, and lifestyle factors such as smoking; all of which should be recorded in the patient's notes (24).

Precisely, it recommends that physical monitoring should include baseline monitoring of body compositions such as (body weight and waist circumference), anthropometrics measures (such as heart rate and blood pressure) and biochemical parameters (such as fasting blood glucose and lipids), before starting antipsychotic medication (24). The list of recommendations included: (1) Bodyweight (plotted on a chart); (2) Waist circumference; (3) Pulse and blood pressure; (4) Fasting blood glucose, glycosylated haemoglobin (HbA1c), blood lipid profile and prolactin levels. Additional measures including electrocardiogram (ECG) should be conducted for patients with: (1) Specific cardiovascular risk (such as diagnosis of high blood pressure); (2) Medical history of cardiovascular disease; (3) During hospital admission.

The NICE guidelines recommended baseline measurement of body weight, then weekly for the first 6 weeks, then at 12 weeks, at 1 year and then annually (plotted on a chart). Waist circumference measurement is recommended at baseline then annually (plotted on a chart). Blood pressure is recommended at baseline then at 12 weeks, at 1 year and then annually. Fasting plasma glucose and lipid profile measures are recommended at baseline than at 12 weeks, at 1 year and then annually (24).

Study rationale

Despite the recommendations by the guidelines, appropriate cardiovascular and metabolic monitoring has remained uncommon. Undiagnosed and untreated cardiovascular and metabolic diseases among patients prescribed antipsychotics remains high due to suboptimal screening, which leads to missed opportunities for the use of primary preventive measures. One survey was done in the USA assessing the knowledge of metabolic side effects of antipsychotics along with the use of measures that can guide the clinician in managing risk among psychiatrists, routinely prescribing SGAs for psychotic patients (25). The majority of the participants (58%) reported that they never obtained a waist circumference, while only (21%) reported they measured waist circumference measures. Failure to diagnose cardiovascular and metabolic side effects of antipsychotics in a timely manner associate with consequences including the development of other comorbidities and decreased life span. In other words, the missed opportunities are linked with high in-disposition and death rates.

Because guideline implementation is a complex process, that is shaped by interacting multiple factors including factors related to the guideline, system, professional and the patients; claims are made that interventions to support implementation be multifaceted and contextually relevant (26). To reduce the occurrence of cardiovascular and metabolic side effects of antipsychotics, there is a need for a detailed understanding of how healthcare professionals currently respond to those side effects in

people prescribed antipsychotics. Besides, addressing the factors that influence the practice is critical to intervention design, and hence enrich the knowledge gap about embedding evidence-based practice in mental healthcare.

Research question/aims

For the purpose of present study, cardiovascular and metabolic management was defined according to the definition proposed by Schrijvers (27) who stated that 'disease management refers to the use of an explicit, systematic population-based approach to identify persons at risk, intervene with specific programs of care, and measure clinical outcomes' (Epstein and Sherwood, 1996). This includes early management of cardiovascular issues, including early screening and regular monitoring of these issues. Accordingly, the study' interests will be examining the extent of compliance among health care professionals with the metabolic and monitoring guidelines of cardiovascular risks among patients taking antipsychotics.

Aim: This study aims to determine the rate of screening and monitoring of patients prescribed antipsychotics and the influences on the uptake of the recommending guidelines in practice.

The objectives in the context of patients prescribed antipsychotic medications are

Objectives 1-2 aim to investigate the level of guideline adherence among health professionals for cardiovascular and metabolic monitoring guidelines in a primary care setting (Dudley CCG).

1) To explore the extent to which cardiovascular and metabolic risk factors and diseases are being monitored for patients receiving antipsychotic drugs in primary care.

2) Explore nature of interventions that were provided (e.g. lifestyle or medications for diabetes).

Objective 3-4 aim to investigate factors affecting the uptake of guidelines for monitoring and management of cardiovascular and metabolic side effects of antipsychotics.

3) To investigate barriers for optimal monitoring and management of cardiovascular and metabolic diseases in patients prescribed antipsychotic drugs in primary care

4) To explore potential barriers for optimal uptake of NICE guidelines and recommendations by the health care professionals.

Study design and methods of data collection and data analysis

This study will use a mixed-method approach to analyse quantitative and qualitative data study that will involve three phases. The first phase (quantitative phase) will include retrospective analysis of patients' data that are stored in a national database: The Dudley Clinical Commissioning Group

(CCG) database along with patient medical notes from the Dudley CCG will be used. The next phase will involve a qualitative interview of patients treated with antipsychotic and health care professionals regarding the barriers and facilitators for monitoring and screening cardiovascular and metabolic side effects of antipsychotic drugs.

Quantitative phase; Study of retrospective review of patients' data from medical records at primary healthcare setting, Dudley clinical commissioning group (Dudley CCG)

Objectives of this phase.

This phase will involve the assessment of cardiovascular and metabolic monitoring among patients prescribed antipsychotics. Approximately 120 records of patients prescribed antipsychotic medications will be reviewed.

The setting

Dudley Clinical Commissioning Group (CCG): is part of a local National Health Service (NHS) that is looking to involve local people and organisations in the decisions it makes about healthcare. The group provides different services primarily for Dudley residence including: (1) Elective hospital care; (2) Rehabilitation care; (3) Urgent and emergency care; (4) Most community health services; (5) Mental health and learning disability services.

Inclusion criteria

1) Patients registered with Dudley CCG primary care services prescribed with antipsychotics in the last 12 months will be included.
2) Patients prescribed antipsychotics for mental health conditions, primarily schizophrenia related disorders, effective mood disorders, and depression.

Exclusion criteria

1) Patients who received antipsychotic treatment less than 12 months ago.
2) Patients who are not registered with Dudley CCG primary care services.

Data source

All general practice within Dudley CCGs will be sent an invitation letter requesting to participate in the study. They will be able to respond using a response letter to indicate what aspect of the study they wish to participate in using a response letter. This includes participation in the retrospective review of routinely collected data and qualitative interviews with healthcare professionals and patients.

Patients clinical data stored in the primary care medical records database from approximately 2 general practices will be extracted. A search will be undertaken for patients prescribed antipsychotic medicines through IT search of medical records by clinical staff who have routine access to records and anonymised data will be handed over to the researcher. If more than the required number of eligible patients are identified, a random number generator will be used to extract the relevant patient data.

Data extraction

The data will be extracted by clinical staff who have routine access to records and anonymised data will be handed over to the researcher. Data collected form the Dudley CCG database will include:

- Patients' demographics age and gender, etc.
- Type of prescribed antipsychotic.
- Dates of cardiovascular risk assessments.
- Score of cardiovascular risk assessment and the recommendation given.
- Items within the cardiovascular risk assessment including BMI, waist circumference, systolic and diastolic blood pressures, total cholesterol, high density lipoprotein and low-density lipoprotein (LDL) cholesterols, non-HDL cholesterol, triglycerides, blood glucose, and glycosylated haemoglobin (HbA1c).

Patients' medical records will be also examined to obtain clinical data mainly:

- Psychiatric diagnoses (disease type, status, duration etc.)
- Past medical history of cardiovascular conditions such as hypertension, diabetes, or any other cardiovascular complications such as stroke, or coronary artery diseases.
- Other biological variables such as BMI, waist circumference, systolic and diastolic blood pressures, total cholesterol, high density lipoprotein and low density lipoprotein (LDL) cholesterols, triglycerides, blood glucose, and glycosylated haemoglobin (HbA1c) will be extracted.
- Data will be gathered for psychotropic medications (first and second generation antipsychotics, and antidepressants), antihypertensive medications and, anti-diabetic medications.

Outcomes measures

The main outcomes of interest are the proportion (%) of the sample population who were monitored for cardiovascular and metabolic components according to the local/national guidelines. This include the following:

- Proportion of patients screened for overweight and obesity (body mass index and waist circumference)
- Proportion of patients screened for diabetes mellitus (glucose screening)
- Proportion of patients screened for dyslipidaemia (Lipid screening)
- Proportion of patients assessed for hypertension (any blood pressure assessment)
- Time window for screening rate (every 6 week/bi-annually)
- Glycaemic and lipid profiles of patients treated with clozapine and olanzapine will be compared with those whom treated with other antipsychotic agents to identify the rate of monitoring across different antipsychotic agents.
- Any advice/intervention offered after the monitoring, e.g. smoking cessation, exercise, lifestyle changes.

Complete monitoring is defined as the proportion of patients at high risk (QRISK2 ≥10%), who underwent regular monitoring and assessment of cardiovascular and metabolic components according to the implemented guidelines, regardless the presence of any abnormalities within one year. On the contrary, incomplete monitoring will be defined as the proportion of patients who did not have follow-up monitoring or patients with missing data.

Statistical analysis plan for this phase

Statistical analysis will be done using Statistical Package for Social Sciences (SPSS version23). Means and standard deviations will be calculated for continuous variables, while percentages and proportions will be computed for categorical variables. Descriptive statistics (proportions and percentages) will be applied to report the results. Glycaemic and lipid profiles of patients treated with clozapine and olanzapine will be compared with those treated with other antipsychotic agents to identify the rate of monitoring across different antipsychotic agents. Metabolic profiles among patients treated with different antipsychotic groups will be analysed using ANOVA test for multiple variables.

Ethical and regulatory considerations

The sample identification will involve reviewing of medical records that will be done by clinical staff at the setting, so the researcher will be handed and deal with anonymised data, however, data that can be linked to the patients' identity will not be extracted e.g. practice data.

Informed consent

Individual informed consent is not required as this phase includes analysis of anonymised data. Only the healthcare professionals who have routine access to clinical records will undertake the searching before handing anonymised data to the researchers.

Data protection and Confidentiality of the study data

All data will be collected and stored in accordance with the Data Protection Act and General Data Protection Regulation (GDPR). As the data to be extracted will be anonymous, patients will be given codes that will not be identifiable nor accessible to the research team. Identifiable information, such as practice name will not be extracted to maintain confidentiality. Reliability check of both the data abstraction instrument and the data abstractor. This can be achieved by random check (28). The check will be performed by the data abstractor. The dataset will be extracted as spreadsheet document that will be encrypted with password along with cells locks to ensure the data cannot be altered once it is collected at the end of the study. The password will be known only to the data abstractor.

All electronic data will be stored on a password-protected computer. Electronic-based data files will be encrypted by passwords that are only known to the investigation team. Electronic-based data will be backed-up in to University servers as protection against data loss. Data storage and analysis will be done at the offices of the University of Birmingham. This will be done in accordance with the University of Birmingham's Code of Practice for Research. Specifically, following completion of the study, the data will be accessible for 10 years; after this period, the data will be destroyed as appropriate. The CI will be the data custodian.

Qualitative phase: Qualitative interview.

Objectives of this phase

This phase aims to investigate factors affecting the uptake of guidelines for monitoring and management of cardiovascular and metabolic side effects of antipsychotics.

Study design and participants

This phase will involve face-to-face or telephone interviews with healthcare professionals who are involved in the management of cardiovascular and metabolic side effects of antipsychotics amongst patients prescribed antipsychotic medicines. Additionally, it will include face-to-face or telephone interviews with patients prescribed antipsychotics receiving monitoring and management of cardiovascular and metabolic side effects of antipsychotics. Demographic data will be collected using a demographic questionnaire before the interview.

Inclusion and exclusion criteria:

Inclusion criteria for healthcare professionals:

- General practitioners, primary care nurses, primary care pharmacists and community pharmacists, involved in the management of cardiovascular and metabolic side effects of prescribed antipsychotic medicines

Exclusion criteria for healthcare professionals:

- No specific criteria

Inclusion criteria for patients:

- Adult service users service users (older than 18 years) who are prescribed antipsychotics for at least 12 months who attend general medical practice in Dudley CCG.
- Service users able to give consent.
- Service users who can communicate in English

Exclusion criteria for patients:

- Service users taking antipsychotics as treatment for conditions other than mental health such as dementia and learning disabilities.
- Service users under the age of 18
- Service users who received antipsychotic treatment more than 12 months ago
- Service users lack the capacity to consent.
- Service users who do not communicate in English.

Study setting

This study will be conducted in the Dudley Clinical Commissioning Group. Dudley Clinical Commissioning Group (CCG). The group provides different services primarily for Dudley residence including: (1) Elective hospital care; (2) Rehabilitation care; (3) Urgent and emergency care; (4) Most community health services; (5) Mental health and learning disability services.

Recruitment

Size of recruitment target

Approximately 20 patient participants and 20 healthcare professionals will be recruited. Final sample size will be informed by theoretical saturation, the point at which analysis revealed no new emergent codes and themes (29). Approximately five general practices and five pharmacies will be recruited for this phase.

Recruitment technique

All general practices within Dudley CCGs will be sent an invitation letter requesting to participate in

the study. They will be able to respond using a response letter to indicate what aspect of the study they wish to participate in using a response letter. This includes participation in the retrospective review of routinely collected data (approximately two general practices needed for this phase) and qualitative interviews with healthcare professionals and patients (from approximately five general practices and five pharmacies)

A purposive sampling, which aims for selecting information-rich cases whose study will illuminate the study objectives (29). Such a strategy will help to ensure heterogeneity of the selected sample. Final sample size will be informed by theoretical saturation, the point at which analysis reveals no new emergent codes and themes. Approximately 40 healthcare professionals and 40 patients will be approached considering non-response.

Patient identification

A convenience sample will be applied. Potential participants will be recruited from the general practice and pharmacy services of the Dudley CCG.

Eligible patients' participants will be identified by clinical staff in participating general practices within Dudley CCG. Invitation letters and participant information sheets will be handed over to the participants by the recruiting healthcare professionals in the general practice while presenting for consultation or will be posted to the eligible patients.

Additionally, potential participants will be identified by community pharmacists who will be requested to recruit participants during dispensing of antipsychotic medicines. Pharmacists will be asked to identify eligible patients' prescribed antipsychotic medication and invite them to take part in the study by handing over the invitation letter, information sheet (PIS) and consent form.

The participants will be given a time (maximum 14 days) to allow them to read the PIS and make a decision about taking part. Participants (patients) who express their interests to participate will be asked to contact the LR (Ruba Afzr Ali); contact information will be provided in the invitation letter.

They will also be able to send the consent form to the researcher using the pre-paid return envelope. The researcher will contact the participants to arrange the interviews at the participating practices, pharmacies or through telephone at a mutually agreeable time. University premises will be used for face-to-face interviews. Telephone conversations will be recorded with the applicants' consent using a secure recording device.

Healthcare professional identification

Participants will be recruited from the general practice and pharmacy services of the Dudley CCG, including medical and non-medical practices. All general practice within Dudley CCGs will be sent an invitation letter requesting to participate in the interviews.

Community pharmacies within Dudley will be invited to participate in the qualitative study. List of pharmacies will be extracted from the General Pharmaceutical Council publicly available domain. An invitation pack including an invitation letter, participant information sheet and consent form will be sent to the responsible pharmacist who will be invited to participate in the in-depth interviews.

In case of difficulties in recruiting healthcare professionals, professional acquaintance will be used to invite potential participants to participate in the interviews. Such forums include local practice forums for pharmacists, nurses and doctors. The researcher will attend these forums and will hand over the invitation pack and invite interested healthcare professionals to participate. The local practice forum meetings will be identified through a local acquaintance of the researcher with clinical staff working at the University of Birmingham, College of Medical and Dental Sciences.

Informed consent

The informed consent form will consist of two parts; part (A & B). The former part will be intended to the participant who wishes to undergo face to face interview. The later will be intended for participants who prefer other options (telephone interview). The LR will obtain consent from the participants prior the interview as it will be emailed to potential participants who are interested in the study. Participants who agree to take part will sign the consent forms and posted back to the LR.

Data Collection (interview process)

Semi-structured interviews will be utilised as the primary data collection method. Two different topic guides interview for health professionals and patients will be used. Participants demographic data will be collected before the interviews commence. This will be done by handing specific demographic questionnaires for each participant type. The participants will be given a copy as a reference, and a reminder of the information conveyed.

The interviewer will use the topic guides to stimulate further discussion (HCP interview topic guide & patients' interview topic guide). Each interview will be conducted for approximately 30 minutes (45-60 minutes, including the consent process). The interviews will be digitally recorded after obtaining participants' full consent; then the records will be transcribed verbatim.

Quality Assurance Procedures

The interview topic guides were developed in accordance with the current literature (30). Pilot interviews will be conducted to validate the interview questions and make amendments when necessary.

Outcome of this phase

For this phase, the outcomes will be the factors associated with the uptake of screening and monitoring guidelines by healthcare professionals along with the perspectives of patients prescribed

antipsychotic around screening and monitoring practices of cardiovascular and metabolic side effects of antipsychotics.

Data analysis plan

The interviews will be analysed independently using the thematic method by two researchers who will be comparing, discussing and agree on emerging themes, categories and concepts. An iterative process of data analysis will be employed to identify and categorise concepts into key themes and their relationships with each other. The textual material will be coded in terms of these categories. Disagreements about coding will be resolved through discussion. To facilitate the coding process, the data will be analysed using NVivio software for qualitative analysis.

Data management

Data will be managed in compliance with the Data Protection Act 2018, Good Clinical Practice standards (GCP) and General Data Protection Regulation 2018 (GDPR).

Access to data

Direct access will be granted to authorised representatives from the University and authorised institutions for monitoring or audit of the study to ensure compliance with regulations. Access to the data retrieved from participants (consent forms and paper-based data recording templates) will be restricted to the research team members (the ECRSMA team) who are listed in this protocol. Authorised representatives from the University and authorised institutions would need access to this data too for audition purposes.

The identifiable data to be collected will be restricted to contact details, mainly email and telephone number that are written on consent forms as well as screening tools. Such data will be needed to track participants. Participants will be asked to give explicit consent to their identifiable data being stored at UoB, and the identifiable data needs to be kept separate to any data that is pseudo-anonymised.

Identifiable information that will be obtained electronically (e.g. recruitment tool) will be stored as encrypted spreadsheet files. Identifiable information that will be provided on papers (e.g. consent forms) will be stored as paper-based, and they will be separated from the other documents and stored in a secured cabinet at the University of Birmingham. All paper-based data recording, including paper-based transcriptions, templates and the consent forms will be stored in a secure location (e.g. locked cabinet in a secure locked office) with access limited to the research teams.

Electronic data including interviews transcripts will be stored in an encrypted spreadsheet and stored in a UoB computer, which will be password protected and it's located at the university, and

hence the data will be stored securely on the UoB network. The transcripts will be backed-up onto the university network to prevent data loss. Audio records will be stored in a removal memory stick that will be restricted to be accessed only by the research correspondence (see the research correspondence section). Access to the files and the computer will be restricted to those directly involved in the research.

Data recording and record keeping

Data recording

All processes will be carried out with respect to participant confidentiality. The audio files (source data) will be stored in a memory stick that will be labelled with unidentifiable codes and encrypted with passwords that will be known for to the research team only. The device will be locked in a secure cabinet at the UoB, and it will be accessible only to the CI and the research members who will be involved in the analysis. The audio files (the data) will be uploaded into a password protected PC at the UoB and the files will be encrypted with a password that will be known only to the personnel who involved in the analysis. Informed consent shall be obtained from participants before the recording. The data analysis will be carried out on a password protected UoB PC.

Record keeping and Archiving

It is estimated that the study will take approximately one year to be completed. It is the responsibility of the CI to ensure all essential trial documentation, and source documents (e.g. signed ICFs, interviews manuscripts, and anonymised datasets) at their site are securely retained for 25 years. Original consent forms and relevant documentation will be retained at the study site (University of Birmingham) under the supervision of the CI for 10 years.

Ethical and regulatory considerations

All of the participants will be treated in accordance with the Helsinki declaration (31) and ethical guidelines outlined by the National Research Ethics Service (NRES) and the University Ethics Review System (for staff and postgraduate research projects) at University of Birmingham.

Discontinuation/Withdrawal of participants from study

Participants have the right to withdraw from the study at any time, without giving a reason before the study report is submitted for publication. Interview manuscripts and audio records and all associated documents will be destroyed immediately once participants decide to withdraw according to the university policies. Additionally, the participant can withdraw at any time during the interview. Furthermore, the participant may be excluded from the study at any time if the Investigator considers it necessary for any reason including withdrawal of consent. Data of withdrawn participants will not be included in the analysis and dissemination. However, it is the responsibility of

the investigator to inform participants that they cannot withdraw their data once a manuscript is submitted for publication.

Approval

The study protocol and all supportive materials, including (informed consent, interview topic guide, participant's information leaflet will be submitted to the seek NHS Ethics approval. The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents. The CI will be responsible for ensuring that all the appropriate approvals from participating organisations are in place before patients being enrolled in the study.

Data protection and confidentiality of study data

Measures will be taken to maintain participant anonymity, such as not disclosing individual numbers and institutional names. All electronic data will be stored on a password-protected computer. Electronic-based data will be entered into a computer protected by a password. Electronic-based data files will be encrypted by passwords that are only known to the investigation team.

All paper-based data recording, including paper-based transcriptions, templates and the consent forms will be stored in a secure location (e.g. locked cabinet in a secure locked office) with access limited to the research teams. Records contain any identifiable data (consent forms and screening tools) will be stored separately to paper-based datasheets. All documentation will be locked at the secure filing cabinet in a secure office at the University of Birmingham; this will restrict any unauthorized access. Data analysis will be done at the offices of the University of Birmingham. Data storage will be done in accordance with the University of Birmingham's Code of Practice for Research. Specifically, following completion of the study, the data will be accessible for 10 years; after this period, the data will be destroyed as appropriate.

Peer review

The protocol has been peer reviewed within the research team and by the University clinical research support team. The research team consists of qualified academics who are considered field experts in pharmacy practice and research.

Expenses and benefits

Only patients' participants will receive financial compensation of £10 gift cards for their time at the end of the interview. The general practices which will participate in the anonymised data search and helping with patient recruitment will be offered £500 remuneration.

Finance and insurance

Funding

As the study is part of a doctoral research for Miss Ruba Azfr Ali, it is mainly funded by the Saudi Government. The details of the funding have been drawn up in a separate agreement.

Insurance

As the participants are NHS patients, indemnity is provided through the NHS schemes. The University of Birmingham has in force a Public Liability Policy and/or Clinical Trials policy which provides cover for claims for "negligent harm" and the activities here are included within that coverage.

Dissemination policy

Publication Policy

Results of the study will be submitted for publication in a peer-reviewed journal. The manuscript will be prepared by the primary investigator in collaboration with the research team members (the ECRSMA research team) and authorship will be determined by mutual agreement. Authors must acknowledge that the trial was performed with the support of Saudi Arabian Government.

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B. THIN study protocol

Protocol title: Evaluating the rate and extent of cardiovascular screening and monitoring in antipsychotic users

Aim and objectives

Aim: this study aims to determine the rate of screening and monitoring of patients prescribed antipsychotics and the influences on the uptake of the recommending guidelines in practice in primary care.

The objectives in the context of patients prescribed antipsychotic medications are to investigate the level of guideline adherence among health professionals for cardiovascular and metabolic monitoring guidelines in a primary care setting using primary care databases (THIN database).

a. To explore the extent to which cardiovascular and metabolic risk factors and diseases are being monitored for patients receiving antipsychotic drugs in primary care.

b. Explore the nature of interventions that were provided (e.g. lifestyle or medications for diabetes).

c. Explore the glycaemic and lipid profiles of patients treated with clozapine and olanzapine compared with those whom treated with other antipsychotic agents to identify the rate of monitoring across different antipsychotic agents.

d. Explore the outcomes of the monitoring including their BMI, waist circumference, systolic and diastolic blood pressures, total cholesterol, high density lipoprotein and low density lipoprotein (LDL) cholesterols, non-HDL cholesterol, triglycerides, blood glucose, and glycosylated haemoglobin (HbA1c),

Background:

Patients with mental illness including schizophrenia, effective mood disorder and major depressive disorders which are associated with high suicide risk and increased prevalence of comorbid physical health disorders (1). Therefore, patients are more like to die prematurely compared to the general population (1,2). A recent review on the causes of deaths in schizophrenic patients Piotrowski et al (3) estimated that patients experienced around 10 to 20 years reduction in life expectancy compared to general population. The increased mortality in this group has shown to be due to several aetiologies mainly cardiovascular diseases (29.2%) and cancer (13.5 %) (2).

Results from a meta-analysis (1) assessing prevalence and incidence of cardiovascular deaths among 3,211,768 patients with severe mental illnesses including psychotic and non-psychotic conditions reported an increased prevalence of cardiovascular diseases (CVDs) with individual rate of 8.4% for people with bipolar disorder (95% CI: 5.4-12.6, 12 studies, N=66,911); 11.7% for those with major depressive disorder (95% CI: 3.6-32.2, 7 studies, N=83,965); 11.8% for those with schizophrenia (95% CI: 7.1-19.0, 13 studies, N=191,982) compared to control groups.

Furthermore, epidemiological studies have reported an increased prevalence of cardiovascular risks factors such as metabolic syndrome (MetS) (37-61.1%) among patients with mental illness (4). Although, the aetiology of CVDs in people with mental health conditions is multidimensional in nature, research evidence suggests that antipsychotics have the potential to causes cardiovascular risk or accelerate pre-existing conditions (5). According to the results of meta-regression analysis on the prevalence of CVDs among a wide range of patients with severe mental illness, there was an increase incidence of CVDs among antipsychotic users (12 studies; β=0.04, 95% CI: 0.01-0.08, p=0.008) compared to control groups (6 studies; β=0.24, 95% CI: 0.06-0.42, p=0.008) (1).

Cardiovascular and metabolic side effects of antipsychotic drugs:

Antipsychotics are classified according to their chemical structure into first (FGAs) and second (SGAs) generations (6). The former group is characterized by their

effectiveness in relieving positive psychotic symptoms of schizophrenia such as hallucinations. However, they have been proved to be less effective against negative symptoms, which lead to the development of the later generation of antipsychotic drugs (SGAs) (9). Antipsychotics are considered the corner stone in the management of psychotic disorders (7) along with other non-psychotic conditions such as dementia (8). Despite their wide use, many antipsychotics have a high tendency to cause metabolic abnormalities, therefore increasing the risk of CVDs and other metabolic conditions particularly MetS and, type 2 diabetes mellitus (DMT2) (9).

Robust evidence suggests that antipsychotics-induced metabolic side effects were attributed to multiple functional pathways (9). The proposed underlying mechanism that antipsychotics induce metabolic disturbances includes the blockage of histamine H1, dopaminergic (D2 and D3), muscarinic (M2 & M3) and the central 5-HT receptors (6). Activating the central 5-HT receptors leads to changings in the eating behaviour and hence reduce food intake (10). Conversely, inhibiting the central 5-HT receptors by antipsychotics can cause an increase food intake, and subsequently weight gain (10). Others (11) suggested mechanism for antipsychotics inducing weight gain is the inhibition of dopaminergic receptors particularly (D2 and D3), as a research on obesity associated with antipsychotics highlighted the potential association between dopaminergic receptors and feeding behaviour (12). Although, all antipsychotics bind to dopaminergic receptors, the binding affinity were reported to be varied across different antipsychotics (6). Clear evidence is available on similar association between the inhibition of muscarinic receptors (M2 and M3) and metabolic side effects of antipsychotics (6). Muscarinic receptors (M3) control cholinergic-dependent insulin release, as they are located on pancreatic β cells (6). It was hypothesised that some antipsychotics (such as clozapine and olanzapine) may possess activity for both cholinergic-dependent and glucose-dependent insulin secretion from pancreatic β cells (13). Furthermore, the degree of antipsychotics affinity for muscarinic receptors appeared to vary across different antipsychotics. As antipsychotics with higher affinity towards muscarinic receptors (such as clozapine and olanzapine) have high propensity to cause glucose deregulations compared to antipsychotics with lower affinity towards muscarinic receptors such as aripiprazole, risperidone, amisulpride and lurasidone, asenapine (14).

Notably, the onset of metabolic abnormalities in serum glucose and lipid associated with antipsychotics occur even before the onset of weight gain, suggesting independent relationship between the metabolic changes and weight gain (9).

Consequently, concerns regarding the cardiovascular and metabolic side effects of these drugs has also grown (15). Nevertheless, antipsychotics are well documented of their liabilities to cause metabolic dysregulations. Results from a meta-analysis comparing the metabolic side effects of SGAs (16) showed that risk for metabolic abnormalities were higher among certain drug members of the class, namely olanzapine and clozapine. This was in the line with the results of another meta-analysis, which showed that with the exception of haloperidol, ziprasidone, and lurasidone, all antipsychotics are associated with metabolic side effects including weight gain compared to placebo (17). The increasing use of SGAs, which currently forms the primary choice pharmacotherapy for several mental diseases (18) has run parallel with the increasing recognition of cardiovascular and metabolic abnormalities in psychiatric practice (19). Patients with schizophrenia are at the dual disadvantage of being inherently predisposed to metabolic abnormalities, which were reported to be worsened by the subsequent use of antipsychotics (19). Along with highlighting the magnitude of this problem, these findings enlightens how it remains undiagnosed.

Recommendations for monitoring and management of cardiovascular and metabolic side effects of antipsychotic drugs:

In 2003, a black box warning was launched by the U.S. Food and Drug Administration (FDA) regarding the diabetogenic effect of antipsychotics (20). In response to these warnings, a panel of regulatory bodies and professional associations including the American Diabetes Association (ADA)/ American Psychiatric Association (APA) published a consensus statement that recommend early and regular monitoring of metabolic side effects among antipsychotics users (21). Consequently, the management of cardiovascular and metabolic dysregulations in patients with mental health conditions has received considerable attention, and has been the focus of much clinical guidance and healthcare policy (22).

Effective monitoring and management of cardiovascular and metabolic abnormalities in patients taking antipsychotics aims for two main purposes: (1) identifying treaTable pathology among highly risk populations; (2) tracking cardiovascular and metabolic disturbances among antipsychotics treated population and hence link these abnormalities to APs treatment (23). The results of such assessment would aid the selection of antipsychotic, particularly in the presence of existing risk factors or metabolic abnormalities (23).

Baseline metabolic assessment should be obtained for all patients before starting antipsychotic treatment. Antipsychotic naïve patients (patients who are taking antipsychotic drugs for the first time or being treated for a first episode of schizophrenia) should be assessed for risks factors of cardiovascular diseases including high risks of metabolic abnormalities (23).

In July 2014, the National Institute for Health and Care Excellence (NICE) updated their guidelines for managing schizophrenia to include management of cardiovascular and metabolic abnormalities in patients with schizophrenia (24). The guidelines recommend that physical health checks should 'pay particular attention to' endocrine disorders such as diabetes and hyperprolactinaemia, to cardiovascular risk factors such as blood pressure and lipids, to the side-effects of medication, and to lifestyle factors such as smoking; all of which should be recorded in the patient's notes (24).

Precisely, it recommends that physical monitoring should include baseline monitoring of body compositions (such as body weight and waist circumference), anthropometrics measures (such as heart rate and blood pressure) and biochemical parameters (such as fasting blood glucose and lipids) at the before starting antipsychotic medication (24). The list of recommendations included: (1) Body weight (plotted on a chart); (2) Waist circumference; (3) Pulse and blood pressure; (4) Fasting blood glucose, glycosylated haemoglobin (HbA1c), blood lipid profile and prolactin levels. Additional measures including electrocardiogram (ECG) should be conducted for patients with: (1) Specific cardiovascular risk (such as diagnosis of high blood pressure); (2) Medical history of cardiovascular disease; (3) During hospital admission.

NICE guidelines recommended baseline measurement of body weight, then weekly for the first 6 weeks, then at 12 weeks, at one year and then annually (plotted on a chart). Waist circumference measurement is recommended at baseline then annually (plotted on a chart). Blood pressure is recommended at baseline then at 12 weeks, at one year and then annually. Fasting plasma glucose and lipid profile measures are recommended at baseline than at 12 weeks, at one year and then annually (24).

Project outline:

Despite the recommendations by the guidelines, appropriate cardiovascular and metabolic monitoring has remained uncommon. Undiagnosed and untreated cardiovascular and metabolic diseases among patients prescribed antipsychotics remains high due to suboptimal screening, which leads to missed opportunities for use of primary preventive measures. One survey was done in USA assessing the knowledge of metabolic side effects of antipsychotics along with the use of measures that can guide the clinician in managing risk among psychiatrics, routinely prescribing SGAs for psychotic patients (25). The majority of the participants (58%) reported that they never obtained a waist circumference, while only (21%) reported they were given a waist circumference measures. Failure to diagnose cardiovascular and metabolic side effects of antipsychotics in a timely manner associates with consequences including the development of other comorbidities and decreased life span. In other words, the missed opportunities are linked with high in-disposition and death rates.

Because guideline implementation is a complex process, that is shaped by interacting multiple factors including factors related to the guideline, system, professional and the patients, claims are made that interventions to support implementation be multifaceted and contextually relevant (26). To reduce the occurrence of cardiovascular and metabolic side effects of antipsychotics, there is a need for a detailed understanding of how healthcare professionals currently response to those side effects in people prescribed antipsychotics. Besides, addressing the factors that influence practice is critical to intervention design, and hence enrich the knowledge gap about embedding evidence-based practice in mental healthcare.

Methods

A retrospective cohort study of patients between 1st January 1995- 1st January 2019 taking antipsychotic medications for at least one year (at least 4 or more prescriptions during this period) will be conducted. The study will use patients' data that are stored in the Health Improvement Network (THIN) database.

Retrospective analysis of patients' data from the health Improvement Network (THIN) database:

Data source:

The Health Improvement Network (THIN) database is a large electronic database that contains records of patents collected from approximately 787 general healthcare practices in around the UK. The THIN database is considered a representative data source of the UK population as the data are structured in a way that enable extracting relevant information. Such information including but not limited to patients' demographics, the diagnosed condition, longitudinal records of symptoms, routine clinical care measures, laboratory investigations, written prescriptions by GPs, other treatments and therapies and referrals to specialised care (28).

Inclusion and exclusion criteria for cohort of interest:

All actively recorded patients who have been taking antipsychotic medication for at least one year. We will only include practices at the later of 12 months after they begin using electronic medical records and 12 months after they achieve AMR.

Outcomes measures:

The main outcomes of interest are the proportion (%) of the sample population who were monitored for cardiovascular and metabolic components according to the local/national guidelines. This include the following:

- Total number of patients prescribed any of the antipsychotic medications
- Proportion of patients screened for overweight and obesity (body mass index and waist circumference)
- Proportion of patients screened for diabetes mellitus (glucose screening)
- Proportion of patients screened for dyslipidaemia (lipid screening)
- Proportion of patients assessed for hypertension (any blood pressure assessment)
- Time window for screening rate
- Glycaemic and lipid profiles ((1) Lipid profiles (total cholesterol, high density lipoprotein and low-density lipoprotein (LDL) cholesterols, non-HDL cholesterol and triglycerides; (2) Glycaemic (random/fasting sample of blood glucose, and glycosylated haemoglobin (HbA1c)) of patients treated with clozapine and olanzapine compared with those whom treated with other antipsychotic agents to identify the rate of monitoring across different antipsychotic agents.
- Outcomes of the monitoring including their BMI, waist circumference, systolic and diastolic blood pressures, total cholesterol, high density lipoprotein and low density lipoprotein (LDL) cholesterols, non-HDL cholesterol, triglycerides, blood glucose, and glycosylated haemoglobin (HbA1c),
- Any advice/intervention offered after the monitoring, e.g. smoking cessation, exercise, lifestyle changes.

Complete monitoring is defined as proportion of patients at high risk (QRISK2 ≥10%), who underwent regular monitoring and assessment of cardiovascular and metabolic components according to the implemented guidelines, regardless the presence of any abnormalities within one year period. On the contrary, incomplete monitoring will be defined as proportion of patients who did not have a follow-up monitoring or patients with missing data. Regular monitoring will be defined according to the monitoring criteria stated by the NICE guidelines for cardiovascular monitoring of antipsychotic drugs. The NICE guidelines recommended baseline measurement of body weight, then weekly for the first 6

weeks, then at 12 weeks, at one year and then annually (plotted on a chart). Waist circumference measurement is recommended at baseline then annually (plotted on a chart). Blood pressure is recommended at baseline then at 12 weeks, at one year and then annually. Fasting plasma glucose and lipid profile measures are recommended at baseline then at 12 weeks, at one year and then annually.

Statistical analysis plan:

Statistical analysis will be done using Statistical Package for Social Sciences (SPSS version23) or STATA. Means and standard deviations will be calculated for continuous variables while percentages and proportions will be computed for categorical variables. Descriptive statistics (proportions and percentages) will be applied to report the results. Metabolic profiles among patients treated with different antipsychotic groups will be analysed using chi-squared test to test the difference in terms of proportions between the groups. The term 'metabolic profile' refers to the analysis of blood biochemical parameters including: (1) Lipid profiles (total cholesterol, high density lipoprotein and low-density lipoprotein (LDL) cholesterols, non-HDL cholesterol and triglycerides; (2) Blood sugar (random/fasting sample of blood glucose, and glycosylated haemoglobin (HbA1c). These values will be identified using additional health data recorded in THIN. The study is mainly interested in measuring the adherence to the guidelines in terms of cardiovascular screening and monitoring, however, the recorded values of these parameters will be extracted as they can be used in sub group analysis to stratify patients groups (e.g. pre-diabetic VS diabetic GP). In addition to handle patients who switch drugs, a sub-group analysis will be carried out to identify proportions of screening and monitoring among patients who switch antipsychotic VS patients on stable antipsychotic therapy

Limitations:

- Misclassification bias or under-recording of patients who may actually be eligible for the study. It is possible that some patients who are managed on anti-psychotics may be solely managed in secondary care whom may not be reflected in THIN data. However, we anticipate this group to be small.
- It will not be possible to obtain an in-depth understanding of why certain patients may be inappropriately monitored. This would be need to explored with in-depth work interviewing or surveying GPs to obtain views as to management of these patients.

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C.1. HRA decision letter

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

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22 May 2020

Dear Dr Paudyal

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Evaluating Cardiovascular Risk Screening and Monitoring for Patients Prescribed Antipsychotic Medicines.**
IRAS project ID:	**270399**
REC reference:	**20/WM/0102**
Sponsor	**University of Birmingham**

I am pleased to confirm that HRA and Health and Care Research Wales (HCRW) Approval has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **270399**. Please quote this on all correspondence.

Yours sincerely,
Rekha Keshvara

Approvals Manager

Email: approvals@hra.nhs.uk

Copy to: *Dr Birgit Whitman*

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
Copies of advertisement materials for research participants	2.0	17 December 2019
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)		10 February 2020
GP/consultant information sheets or letters	1.0	11 November 2019
GP/consultant information sheets or letters	1.0	11 November 2019
Interview schedules or topic guides for participants [nterview Topic Guide for Healthcare Professionals]	1.0	11 November 2019
Interview schedules or topic guides for participants [Interview Topic Guide for Patients]	1.0	11 November 2019
IRAS Application Form [IRAS_Form_12022020]		12 February 2020
Letter from sponsor		10 February 2020
Letters of invitation to participant	1.0	11 November 2019
Letters of invitation to participant [Research invitation letter to general practices]	1.0	11 November 2019
Other [REC review response letter]		13 May 2020
Participant consent form	4.0	13 May 2020
Participant consent form	4.0	13 May 2020
Participant information sheet (PIS)	5.0	18 May 2020
Participant information sheet (PIS)	4.0	18 May 2020
Research protocol or project proposal [Study protocol]	3.0	08 January 2020
Summary CV for Chief Investigator (CI) [Summary CV]		01 July 2019
Summary CV for student		08 January 2020
Summary CV for supervisor (student research)		01 July 2019
Summary CV for supervisor (student research)		02 December 2019
Summary of any applicable exclusions to sponsor insurance (non-NHS sponsors only)		10 February 2020
Summary of any applicable exclusions to sponsor insurance (non-NHS sponsors only)		10 February 2020
Summary of any applicable exclusions to sponsor insurance (non-NHS sponsors only)		10 February 2020

IRAS project ID	270399

Information to support study set up

The below provides all parties with information to support the arranging and confirming of capacity and capability with participating NHS organisations in England and Wales. This is intended to be an accurate reflection of the study at the time of issue of this letter.

Types of participating NHS organisation	Expectations related to confirmation of capacity and capability	Agreement to be used	Funding arrangements	Oversight expectations	HR Good Practice Resource Pack expectations
Participating NHS organisations will act as PICs.	Research activities should not commence at participating NHS organisations in England or Wales prior to their formal confirmation of capacity and capability to deliver the study.	mNC-PICA will be used as the study agreement.	No application for external funding has been made.	The research is limited to involvement of PICs and therefore, a Local Collaborator or Principal Investigator is not expected for the study.	The research is limited to involvement of PICs and therefore, HR good practice arrangements are not expected for the study.

Other information to aid study set-up and delivery

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales in study set-up.
The applicant has indicated that they intend to apply for inclusion on the NIHR CRN Portfolio.

C.2. SRC decision letter (Ethical approval for the THIN database use)

SRC Feedback

Researcher Name: Vibhu Paudyal
Organisation: University of Birmingham
SRC Reference Number: 19THIN070
Date: 11th November 2021
Study title: Evaluating the rate and extent of cardiovascular screening and monitoring in antipsychotic users.

Committee opinion: Approved

The following feedback has been supplied by the SRC.

Notes from the Chair:

1. What is the justification for the consideration of only 'at least 4 or more prescriptions during this period'? This will most likely reduce the potential sample size of the stucy as one would expect fewer patients to have at least 4 prescriptions within 12 months for a newly diagnosed condition. Perhaps the emphasis should be more so on limiting to 'two prescriptions or more' to ensure that the first was not an erroneous prescription.

2. The authors state under the 'objective section, first page' that they will explore the 'adherence of healthcare professionals to the guideline' however, the listed objectives seem to explore this indirectly i.e. once the results are in line with the guidelines then the authors would assume that the HCPs are indeed adhering to the guidelines. However, this could be misleading given that no definition to adherence or how it will be measured has been presented – please consider revising the use of 'adherence' as a terminology in relation to the objectives

3. A range of guidelines have been mentioned and the authors indicate that the objectives will be mapped to 'local/national guidelines' however, it is unclear what exactly these guidelines are i.e. NICE guidelines only or hospital or trust guidelines, etc

4. Under objectives, authors aim to evaluate the "Proportion of patients screened for diabetes mellitus, etc" – what is the denominator of these calculations? Perhaps the authors mean 'patient counts or percentage' as opposed to the true 'proportion' in a statistical perspective

5. Will the authors put into consideration patient cohorts that have been screened for more than one diagnosis or metabolic syndrome or otherwise? i.e. patients with diabetes screened for lipid screening and hypertension, etc

6. It remains unclear if the sample of patients of interest for this study are those being screened for conditions such as diabetes, hyperlipidemia, etc that have been triggered by the use of atypical antipsychotics only or otherwise? Some patients could have been screened for such conditions regardless of whether they were receiving antipsychotics or not.

7. For some patients on low doses of antipsychotics, especially those prescribed below the recommended dosages, there is evidence to suggest that some physicians may feel that monitoring is not required Therefore, will the authors put such factors in to consideration in the interpretation or generalisability of the results especially relative to the uptake of guidelines?

8. What is the rationale of focus on 'clozapine and olanzapine' compared to other antipsychotics? I.e. why the mention of only these drugs only if the study wishes to evaluate other antipsychotics currently available to patients within the UK or what is the hierarchy of medications?

9. What is entailed in the "Time window for screening rate" i.e. do the authors refer to the time before initiation of antipsychotics or not?
    a) Authors should also consider that the time window for screening rates will be influenced by a range of factors such as frequency of patient encounters to healthcare and are thus more likely to be screened. Also, patients with pre-existing risk factors are likely to be prioritized for 2 screening and these patients may also be 'sicker' and thus, utilise healthcare services more often. Furthermore, geographical access to medical and mental health services a well as the continuity in care may impact on screening times. Such variables would need to be considered in the interpretation of the study results on time window for screening outcome.

SRC
Scientific Review Committee

Minor comments

- Spell out abbreviations at first use i.e. AMR (see section Inclusion and exclusion criteria for cohort of interest, Line 3).
- Protocol could benefit from 'page numbering' for quick referencing
- Would be great to understand what the implications for clinical practice are relative to the execution of this study? I.e. does it aim to change clinical practice through continued HCP training, awareness etc? – how will the results be disseminated?

Approved documents:

Approved document	Version	Date
SRC_Protocol_19THIN070_v2_30-11-2019	2	30/11/2019
SRC_Protocol_19THIN070_Researcher_response		

We are pleased to inform that your protocol has been approved and you can proceed with the study.

As part of our ongoing commitment to improve transparency and public awareness in the use of patient data in research, all manuscripts, abstracts and posters using IQVIA Medical Research Data (IMRD) are to be reviewed and approved prior to publication.

This is to ensure that:

- The ownership of the data and any acknowledgements are correctly attributed.
- Researchers provide a lay summary of the study for any intended publication.

IQVIA maintain a publicly accessible register / bibliography of research projects using data from IQVIA Medical Research Data.

Please send a copy of your completed manuscript, abstract and (or) poster with lay summary along with the SRC reference number quoted above to UKEthics@IQVIA.com for approval; this step can take up to two weeks.

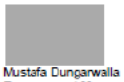
References to all published studies are added to IQVIA's online bibliography found here: https://www.rwebibliography.com/

Please note that the name of IQVIA's Health Research Authority (HRA) approved UK research database is "IQVIA Medical Research Data" which may be abbreviated to "IMRD" if the full name is stated within the publication at first mention. If referencing 'IMRD' where the source of the data is THIN, then the correct citation which **must** be included in all publications (i.e. slides, posters, manuscripts, articles, abstracts etc) is:

"IQVIA Medical Research Data (IMRD) incorporates data from THIN, A Cegedim Database. Reference made to THIN is intended to be descriptive of the data asset licensed by IQVIA."

IQVIA will let the Health Research Authority (HRA REC) know that this study protocol has been approved by the SRC.

I wish you and your team all the best with the study progression.



Mustafa Dungarwalla
Engagement Manager

SRC
Scientific Review Committee

D. Research ethics queries

Dudley CCG study: Comments raised by the health research authority (HRA) review

Comments were mostly concerning adjusting research activities in the participating sites (GP Practices and Community Pharmacies) as per the COVID-19 environment.

Queries:

- ''How will some of the activities be done given the COVID19 environment - both with GP Practices and Community Pharmacies?''
- ''Have you considered changes to administrative arrangements to reduce burden or physical contact with sites?''
- ''Are you looking at changing how you approach participants and how you run interviews? For example, online interviews, via zoom or other platforms?''

Responses: Participant's recruitments were planned to be done by the telephone or by emails. Clinical Staff (GPs and pharmacies were planned to approach the participants). Clinical staff (GPs and pharmacies) will identify potential participants using a list of patients prescribed antipsychotic medicines. All interviews will be undertaken remotely. Where possible we will minimise the need for parcel and paperwork by using web-based information sheets and consent through telephone prior to the interviews. Participant's consent will be obtained by the phone at the day of the interview, and these will be recorded.

***According to the HRA COVID-19 research guide, the presented amendments are considered non-substantial, as the suggested adjustments required to accommodate COVID-19 situation mostly related to social distancing measures and hence has been suggested as non-substantial amendment and not requiring a review. Please see section Changes to site monitoring arrangements or changes to administrative arrangements to reduce burden or physical contact with sites (Appendix X).

Dudley study (data extraction) – queries regarding the anonymised data that would be handed from clinical staff to the research team.

- ''How was this done? Would it be online, via a secure encryption? Or would the researcher visit the site?''
- ''Would the researcher be required to follow local procedure for GP Practice social distancing recontact in non-clinical areas?''
- ''How was the data extraction built? Would it be set-up so that the GP Practice can run it, using set EMIS read codes? Or would this need to be worked out by each Practice from the criteria specified in the Protocol?''

Response: the data extraction will be done by staff with routine access to clinical records. The researcher will not be required to visit the site. The data extraction will be conducted using standardised pre-designed abstraction tool that was designed according to the EMIS medical recording system used by the site.

The model Non-Commercial PIC agreement requires updating with the following:

- ''Add study title and references, make changes required in highlighted sections where applicable.''
- ''Section 2.3 (page 7) - describe the PIC activities - all sections from 2.3.1 - 2.3.4.''
- ''Schedule 1 Section A - Financial Arrangements, you will need to include £500 to GP Practice for Phase 1 Data Extraction, but this only applies to the GP Practice undertaking the data extraction activity.''

Response: amendments were applied to the NC_PIC agreement model in accordance with the HRA guidance (Appendix X).

Dudley CCG study: Comments raised by the University of Birmingham research committee

Queries that were highlighted during the review and the responses are presented below.

Queries:

- *Query* 1: ''how are participants going to consent to their medical records being used for this study (the Dudley study)?''

Response 1: No individual consent was obtained, however, for this to be ethically sound, gate keeper consent was sought from the participating institutions. The study will rely on using anonymised patients' data that will be extracted by a delegated data abstractor from the participating site. No Confidentiality Advisory Group (CAG) approval was necessary.

- The need for AER application form (no need to apply since application for the IRAS has been made).
- The time provided for participants to withdraw from the study.

Response: participants can withdraw from the study at any time, without giving a reason before the study report is submitted for publication. Interview manuscripts and audio records and all associated documents will be destroyed immediately once participants decide to withdraw according to the university policies. Additionally, the participant can withdraw at any time during the interview.

- ''Are you planning on approaching 40 HP and 40 patients who decline to participate or have agreed but not taken part in interviews? It is confusing as the recruitment target is 20 HPs and 20 patients – is this the number you need to complete? Please clarify overall how many will be approached to take part?''

Response: Initially, the plan was to approach 40 of each HCP and patients. This number was considered taken into the account the response rate among participants which was estimated according to the literature by 50% response. Target sample is 20 HCP and 20 patients.

- How will telephone interviews be documented/recorded?

Response: The recording will be done using specific application.

- ''Who will perform the interviews with the health care professionals and patients? If it is a UoB researcher, do they have a research passport?''

Response: the researcher is a doctorate student at the UoB, accordingly the researcher has obtained a research passport from the UoB.

- ''That just leaves the distress protocol, do you have a copy to share? Also if you are happy to advise regarding the data extraction, how sites will run this, training/instructions to site staff etc, a confirmation that this will be in hand with advice from Dudley CCG is fine in terms of evidence I require for the review''.

Response: distress protocol has been designed to be sent to the participants.

Amendments:

- Regarding the consent forms, there are large elements which I would usually expect to see in the participant information sheet rather than the consent form itself, for example the 'how will my data be used', 'what if I have any concerns about this research' and the 'what will happen' sections.
- Insert Name and Address of Participating Site - this is University of Birmingham according to Part C of the IRAS
- Can you add further details to the reimbursement on the Schedule 1 Financial arrangements, please advise you will reimburse administrative time for mailout support at the CRN West Midlands Primary Care suggested hourly rate of £13.29 and consumables covering printing costs, materials, postage etc. As there are number of costs here, it might be best to provide a nominal Figure to cover all these items? Additionally please advise in the schedule of payments, how the GP Practice is to invoice you for the reimbursement and costs.
- You may also need to update the GP reply slips where you've mentioned the £500 reimbursement, and add coverage of administrative costs for support with mail outs or something similar.
- Please include in the protocol your plans to record/document telephone conversations, for example: ''Telephone conversations will be recorded with the applicants consent using a secure recording device.''

Response: amendments to the following documents: study protocol, IRAS form, PIC_NC agreement and the PIS as per the HRA guidance on consent forms and participant information sheets, as well as the transparency wording from the University of Birmingham legal services (Appendix X). Also, GP reply slips were prepared (Appendix X)

THIN database phase: Comments raised by the Scientific Review Committee (SRC)

Issues with the study that needs clarification (Complete in the style of questions to be passed on to the researchers for further clarification)

Queries:

- *Query* A. ''The methods states that the cohort will be patients attending 'an outpatient psychiatric clinic'; I'm not clear how THIN is useful for this? THIN contains general practice/primary care data, not outpatient psychiatric clinic data. Be careful to avoid using inaccurate or misleading descriptions of the dataset.''

Response A. We thank the reviewer for this point. To avoid confusion or misleading information, we have removed reference to outpatient psychiatric data. We are just utilising primary care data.

- *Query* B. Several definitions need to be clarified, e.g.: B.1. ‘’How will 'taking antipsychotic mediation for at least one year' be defined? e.g., a specified number of records of a prescription over a period of a year?’’

Response B.1. The targeted population (patients prescribed antipsychotic for at least 12 months) will be identified by patients who have had 4 or more prescriptions for the medications during a one-year period.

- *Query* B.2. ‘’Complete monitoring is defined as proportion of patients at high risk (QRISK2 ≥10%), who underwent regular monitoring…'- how is 'regular' monitoring defined?’’

Response B.2. Regular monitoring will be defined according to the monitoring criteria stated by the NICE guidelines for cardiovascular monitoring of antipsychotic drugs. The NICE guidelines recommended baseline measurement of body weight, then weekly for the first 6 weeks, then at 12 weeks, at 1 year and then annually (plotted on a chart). Waist circumference measurement is recommended at baseline then annually (plotted on a chart). Blood pressure is recommended at baseline then at 12 weeks, at 1 year and then annually. Fasting plasma glucose and lipid profile measures are recommended at baseline then at 12 weeks, at 1 year and then annually.

- *Query* C. ‘’The outcomes relating to blood tests and physiological measures are not adequately described. What exactly will be calculated and compared with regard to the glycaemic and lipid profiles (7th outcome) and 'Outcomes of the monitoring including the BMI, waist circumference, BP', etc (8th outcome)? Are you simply looking at the proportions of patients who have these measures recorded? Or the values of these measures? Be explicit and clear about exactly what you are investigating. Similarly, the statistical analysis plan states 'Biochemical and metabolic profiles among patients treated with different antipsychotic groups will be analysed using chi-squared test' - this is vague; what is meant by profiles? It suggests to me that you will be looking at the distribution of individual patient measurements, but I think from the rest of the protocol that you mean you will be comparing proportions of patients with records of these measures between different types of treatment. The methods needs to be clarified.’’

Response C. The main outcomes of interest are the proportion (%) of the sample population who were monitored for cardiovascular and metabolic components according to the local/national guidelines. The term ‘metabolic profile’ refers to the analysis of blood biochemical parameters including: (1) Lipid profiles (total cholesterol, high density lipoprotein and low-density lipoprotein (LDL) cholesterols, non-HDL cholesterol and triglycerides; (2) Blood sugar (random/fasting sample of blood glucose, and glycosylated haemoglobin (HbA1c). These values will be identified using additional health data recorded in THIN. The study is mainly interested in measuring the adherence to the guidelines in terms of cardiovascular screening and monitoring, however, the recorded values of these parameters will be extracted as they can be used in sub-group analysis to stratify patients’ groups (e.g. pre-diabetic VS diabetic GP). The reviewer is correct that actually we will be comparing the proportions of these test results rather than distribution of data. Hence, we are using a chi squared

test. To avoid confusion, we have expanded in the protocol the definition of profile and clearly stated the analysis relates to proportions.

- *Query* D. ''QRISK2 score is mentioned towards the end of the outcomes section; this is the first mention of risk scoring - previously it is suggested that monitoring will be investigated in all patients on antipsychotics. Please explain more clearly how risk stratification fits into the analysis. Furthermore, later in this section, 'the presence of any abnormalities' is mentioned without explanation - what are these abnormalities?''

Response D. We thank the reviewer for this comment, the QRISK score is mentioned as it also forms part of the expected metabolic profile score which is meant to be calculated in all patients on anti-psychotics. So rather than assessing for risk stratification, we are actually assessing whether patients had their QRISK scores measured. The abnormalities we are looking for will be any abnormal lab value such as high fasting blood glucose and describing the rate and frequency of this occurrence.

- *Query* E. ''What is the study period? What is the study design (cross-sectional)?''

Response E. The study period will be between January 1995- January 2019. The study design is a retrospective cohort study. This is in order to calculate the proportion of patients who are having their risk factors monitored and also the incidence of interventions used for treatment.

- *Query* F. ''Are there any practice or patient eligibility criteria that need to be met before you will include them in the study? e.g. do practices need to have achieved Acceptable mortality reporting rates, as an indicator of good data quality?''

Response F. We will only include practices at the later of 12 months after they begin using electronic medical records and 12 months after they achieve AMR.

- *Query* G. ''It isn't clear whether the researchers are planning to use outpatient data or not and outpatient data is notoriously badly coded and recorded. How are the researchers going to identify outpatient attendance?''

Response G. Please refer to comment A (no outpatient data will be used).

- *Query* H. ''How is taking medication to be defined? e.g. 1 prescription for antipsychotic or regular prescriptions over a one year period.''

Response H. Please refer to comment B.1

- *Query* I. ''How will the researchers handle patients who have missing prescription data?''

Response I. If a patient did not receive 4 repeat prescriptions of the antipsychotic they will not be included in the study. As primary care manages much mental illness in the UK, after feasibility testing we anticipate that there will be sufficient data to use to conduct the study.

- *Query* J. ''How will the researchers handle patients who switch drugs?''

Response J. Sub-group analysis will be carried out to identify proportions of screening and monitoring among patients who switch antipsychotic VS patients on stable antipsychotic therapy.

- *Query* K. ''Are the researchers going to specify any time limits? e.g., limited to data from 2013 onwards?''

Response K. For this study we will include records from January 1995- January 2019. The purpose of this will provide sufficient time to demonstrate the practice prior to the introduction of the NICE guideline.

- *Query* L. ''Are screenings (glucose, lipid, BP assessment) going to be identified via codes? or by the presence of a result?''
- *Query* M. ''If codes, please identify which codes are to be used.''

Response L & M. Numeric variables will be identified using results coded in additional health data. As the purpose is also to explore the proportion of profiles being taken, even data which has a date for blood test, but no measurement value included will be included.

- *Query* N. ''Can glycaemic and lipid profile be defined please?''

Response N. Please refer to C

- *Query* O. ''I'm assuming the researchers mean how often the patients are monitored rather than what the measurement results are?''

Response O. Although our primary aim is mainly interested in how regularly the patients are monitored for these side effects. We are also interested in the actual values of the measurement results.

- *Query* P. ''By outcomes do the researchers mean the measurement values? How are these outcomes to be used?''

Response P. This question has been answered above (query C).

- *Query* R. ''Are the researchers going to calculate QRISK? what variables will be needed for this? and what will the researchers do if data are missing? What about patients who have a QRISK<10?''

Response R. The researchers will not calculate the QRISK value. However, QRISK data will be extracted where a values have been recorded by the GP.

Mon 7/27/2020, 4:07 PM
IRAS Project ID: 270399
Sponsor amendment reference: Amendment 01

Ruba Azfr Ali (PhD Pharmacy FT Non-Lab (B230))
Flag for follow up. Start by Monday, July 27, 2020. Due by Monday, July 27, 2020.

Thank you for submitting your study amendment. In accordance with the outcome of your completed amendment tool, this amendment requires no further regulatory review. Please now share this amendment with your UK research sites, in accordance

with the instructions in your completed amendment tool.

For studies with more than one UK research site, your amendment will now be automatically shared with the R&D offices of any NHS/HSC research sites in Scotland and Northern Ireland, but you should share the amendment by email directly with those Research team/s.

For all NHS research sites in England and Wales, please now share this amendment by email directly with those sites, including both the R&D offices and research teams.

Do not reply to this email as this is an unmonitored address and replies to this email cannot be responded to or read.

This message may contain confidential information. If you are not the intended recipient please inform the sender that you have received the message in error before deleting it. Please do not disclose, copy or distribute information in this e-mail or take any action in relation to its contents. To do so is strictly prohibited and may be unlawful. Thank you for your co-operation..

E. Research passport



F. Documents related to the qualitative study

F.1. Healthcare Participant information sheet (HPIS)





Participant Information Sheet- Healthcare Professionals

Research project title: Evaluating cardiovascular risk screening and monitoring of patients prescribed antipsychotic medicines (ECRSMA).

Dear Participant,

My name is Ruba Azfr Ali. I am undertaking a PhD study at the University of Birmingham. This study aims to identify ways to enable healthcare professionals to better identify and manage the cardiovascular and metabolic side effects of antipsychotic medicines. Thank you for showing an interest in our study. Please read this information sheet and do not hesitate to contact us using details provided overleaf. Also feel free to discuss any aspects of this research with your family, friends and acquaintances.

Who is organising the research?

This project is funded by the University of Birmingham and it is part of a PhD thesis for Ruba Azfr Ali. The study is being managed by University of Birmingham and Dudley Clinical Commissioning Group (CCG).

Why am I being invited to take part?

We are writing to primary healthcare professionals involved in the care of patients taking antipsychotic medicines with at least two years' experience.

What does participation involve?

Participation in this study will only involve taking part in an interview that will last no more than 45 minutes. The interview will be conducted by the primary researcher (Ruba Azfr Ali) and they will take place at the University facilities (e.g. meeting rooms).

Alternatively, we can also modify it according to your needs (e.g. by telephone).

At the day of the interview, you will be asked to complete a short anonymous questionnaire. This questionnaire will collect your demographic data including job title, clinical speciality etc. Before commencing the interview, we will ask for your permission to record the interview onto a secure recording device.

If you are a community pharmacist, we would like to invite you to recruit eligible patients (see attached recruitment tool for community pharmacist), you will be asked to pass the invitation letter (the one intended the patient) to the potential participants. Once they decide to participate, they will contact the researcher later.

Do I have to take part?

No. participation in this study is voluntary, and you may withdraw at any time. You will be given some time to decide to take part, minimum of one week after receiving this document.

If you change your mind after you have taken part, you can still withdraw at any time without given any reason. To inform us about your change of mind after the interview, simply let the researchers on-site know if they are available or by emailing [redacted] or contact Dr Vibhu Paudyal at 01214142538. Alternatively, you could also phone your GP practice or pharmacy from where you were asked to take part. Your relationship with the practice or the researcher won't be affected by decision not to participate. If at any point during interview you feel uncomfortable or unable to continue, the interview will be ceased immediately.

How do I benefit from participation?

There is no direct benefit to you from participation in this study. However, it is possible that by sharing your thoughts and experiences with us, you will be helping our research team and the University of Birmingham to better understand the possible factors for effective physical health care delivery in people taking antipsychotic medications.

What are the possible risks and disadvantages of taking part in the study?

We do not believe that there are risks involved in taking part in the study. If you have any concerns about the study, please discuss raise those with a member of the research team. Alternatively, you may contact your healthcare professionals or family and friends.

Will my taking part in the study be kept confidential?

All data will be treated as per the Data Protection Act 2018 and General Data Protection Regulation (GDPR). All personal information will be anonymised i.e. a unique code will be given to your participation in the research. We will not identify you in any reports or publications. Your personal data will be treated with strict confidence. We will not share your data with any third party.

Non-identifiable paper-based data will be stored in a locked filing cabinet in the primary researcher's office.

All electronic data will be stored on a password-protected computer for analysis purposes located at the University of Birmingham. Data will only be accessed by the primary researcher and the members of the research team. When necessary, representatives from University of Birmingham and regulatory authorities will be able to access the information for audit and compliance purposes. The consent form will include statement states the forms will be stored at University of Birmingham. In line with the University's guidelines on records management, transcript of your interviews will be retained intact for 25 years from the date of collection. We will destroy the audio recording as per the University research governance policies after we have transcribed the recordings.

In case you withdraw from the study at any time after the interview, your research data will be destroyed, and subsequently, your data will not be used in the study. If a transcript has been submitted for publication and you decided to withdraw from the study, it may not be possible to delete the quotation from your interview.

What will happen to the results of the research?

The full findings of the study may be published in a health care journal and presented at a conference and as an academic thesis for the researcher's PhD. You will not be identified in any report or publication. We will use your direct quotations in the publication but you will not be identified. If you wish to be given a copy of any reports resulting from the research, please ask us to put you on our circulation list.

Who has reviewed and approved this study?

This study was reviewed and approved by the NHS Research Ethics Committee (REC). This study has also been reviewed by the Clinical Research Compliance Team (CRCT) and the Research Governance (RG) and subsequently endorsed by the ethics procedures of University of Birmingham.

Who can I contact if I have a complaint?

If you want to complain about how researchers have handled your information, you should contact the research team. Alternatively, you can contact the Patient Liaison Services (PALS) at the NHS Trust where the research is being conducted on the following email: dgft.pals@nhs.net

If you are not happy after that, you can contact the University's Data Protection Officer at;

Email: Legalservices@contacts.bham.ac.uk

Telephone: 01214143916

You can also contact the sponsor's point of contact Dr Birgit Whitman at researchgovernance@contacts.bham.ac.uk

If you are not happy with their response or believe they are processing your data in a way that is not right or lawful, you can complain to the Information Commissioner's Office (ICO) (www.ico.org.uk or 0303 123 1113).

Who has sponsored this study?

This study is sponsored by the University of Birmingham.

What do I do next?

If you feel you would like to be involved in our study, please send the consent form back using the pre-paid envelope provided. You may contact Ruba Azfr Ali on the following email: [redacted]. The researcher will call you or arrange to meet you at your convenient time for the interview.

Contact and further information: If you want any further information about this particular study, you can contact the researcher team.

Miss Ruba Azfr Ali

Phone: [redacted] (mobile)

Email: [redacted]

Dr Vibhu Paudyal

Phone: (0)121 4142538 (office)

Email: [redacted]

For further questions, please contact the Head of Research Governance and Ethics at UoB:

Dr. Birgit Whitman, Head of Research Governance and Integrity

Email: researchgovernance@contacts.bham.ac.u

F.2. Patients Participants Information Sheet

ECRSMA
valuating cardiovascular risk screening and monitoring of patients prescribed antipsychotic medicines

UNIVERSITY OF BIRMINGHAM

NHS Dudley Clinical Commissioning Group

Patients' Participant Information Leaflet: Patients

Research project title: Evaluating cardiovascular risk screening and monitoring of patients prescribed antipsychotic medicines (ECRSMA).

Dear Participant,

Dear Participant,

My name is Ruba Azfr Ali. I am undertaking a PhD study at the University of Birmingham. This study aims to identify ways to enable healthcare professionals to better identify and manage the cardiovascular and metabolic side effects of antipsychotic medicines. Thank you for showing an interest in our study. Please read this information sheet and do not hesitate to contact us using details provided overleaf. Also feel free to discuss any aspects of this research with your family, friends and acquaintances.

Who is organising the research?

This project is funded by the University of Birmingham as it is part of a PhD thesis for Ruba Azfr Ali. The study is being managed by University of Birmingham and Dudley Clinical Commissioning Group (CCG).

Who can take part?

We are looking for individuals who are aged 18 or over and taking antipsychotic medicines such as aripiprazole for the last 12 months.

What does participation involve?

Participation in this study will only involve taking part in an interview that will last no more than 45 minutes. The interview will be conducted by the primary researcher (Ruba Azfr Ali) and they will take place at the University facilities (e.g. meeting rooms). Alternatively, we can also conduct it over the phone.

At the day of the interview, you will be asked to complete a short anonymous questionnaire. This questionnaire will request your age, employment status and current medications. Before commencing the interview, we will ask for your permission to record the interview onto a secure recording device.

Do I have to take part?

No. participation in this study is voluntary, and you may withdraw at any time. You will be given some time to decide to take part, minimum of one week after receiving this document.

If you change your mind after you have taken part, you can still withdraw at any time without given any reason. To inform us about your change of mind after the interview, simply let the researchers on-site know if they are available or by emailing [redacted] or contact Dr Vibhu Paudyal at 01214142538. Alternatively, you could also phone your GP practice or pharmacy from where you were asked to take part. Your relationship with the practice or the researcher won't be affected by decision not to participate. If at any point during interview you feel uncomfortable or unable to continue, the interview will be ceased immediately.

How do I benefit from participation?

By sharing your thoughts and experiences with us, you will be helping our research team and the University of Birmingham to better understand the possible factors for effective physical health care delivery in people taking antipsychotic medications.

Participants who attend the interview will be given a £10 gift card which will be given to you on the day of interview or it can be posted to you after participation in appreciation of the time and effort you have taken to attend.

What are the possible risks and disadvantages of taking part in the study?

We do not believe that there are risks involved in taking part in the study. If you have any concerns about the study, please discuss raise those with a member of the research team. Alternatively, you may contact your healthcare professionals or family and friends.

Will my taking part in the study be kept confidential?

All data will be treated as per the Data Protection Act 2018 and General Data Protection Regulation (GDPR). All personal information will be anonymised i.e. a unique code will be given to your participation in the research. We will not identify you in any reports or publications. Your personal data will be treated with strict confidence. We will not share your data with any third party.

Non-identifiable paper-based data will be stored in a locked filing cabinet in the primary researcher's office.

All electronic data will be stored on a password-protected computer for analysis purposes located at the University of Birmingham. Data will only be accessed by the primary researcher and the members of the research team. When necessary,

representatives from University of Birmingham and regulatory authorities will be able to access the information for audit and compliance purposes. The consent form will include statement states the forms will be stored at University of Birmingham. In line with the University's guidelines on records management, transcript of your interviews will be retained intact for 25 years from the date of collection. We will destroy the audio recording as per the University research governance policies after we have transcribed the recordings.

In case you withdraw from the study at any time after the interview, your research data will be destroyed, and subsequently, your data will not be used in the study. if a transcript has been submitted for publication and you decided to withdraw from the study, it may not be possible to delete the quotation from your interview.

What will happen to the results of the research?

The full findings of the study may be published in a health care journal and presented at a conference and as an academic thesis for the researcher's PhD. You will not be identified in any report or publication. We will use your direct quotations in the publication but you will not be identified. If you wish to be given a copy of any reports resulting from the research, please ask us to put you on our circulation list.

Who has reviewed and approved this study?

This study was reviewed and approved by the NHS Research Ethics Committee (REC). This study has also been reviewed by the Clinical Research Compliance Team (CRCT) and the Research Governance (RG) and subsequently endorsed by the ethics procedures of University of Birmingham.

Who can I contact if I have a complaint?

If you want to complain about how researchers have handled your information, you should contact the research team. Alternatively, you can contact the Patient Liaison Services (PALS) at the NHS Trust where the research is being conducted on the following email: dgft.pals@nhs.net

If you are not happy after that, you can contact the University's Data Protection Officer at;

Email: Legalservices@contacts.bham.ac.uk

Telephone: 01214143916

You can also contact the sponsor's point of contact Dr Birgit Whitman at researchgovernance@contacts.bham.ac.uk

If you are not happy with their response or believe they are processing your data in a way that is not right or lawful, you can complain to the Information Commissioner's Office (ICO) (www.ico.org.uk or 0303 123 1113).

Who has sponsored this study?

This study is sponsored by the University of Birmingham.

What do I do next?

If you feel you would like to be involved in our study, please send the consent form with your contact details using the prepaid envelope provided. You may contact Ruba Azfr Ali on the following email: rxa774@student.bham.ac.uk. The researcher will call you or arrange to meet you at your convenient time for the interview.

Contact and further information: If you want any further information about this particular study, you can contact the researcher team.

Miss Ruba Azfr Ali

Phone: [redacted] (mobile)

Email: [redacted]

Dr Vibhu Paudyal

Phone: (0)121 4142538 (office)

Email: [redacted]

For further questions, please contact the Head of Research Governance and Integrity at UoB:

Dr Birgit Whitman, Head of Research Governance and Integrity

Email: researchgovernance@contacts.bham.ac.uk

F.3.Consent form (patients)

ECRSMA valuating cardiovascular risk screening and monitoring of patients prescribed antipsychotic medicines

UNIVERSITY OF BIRMINGHAM

NHS Dudley Clinical Commissioning Group

Patient Interview Consent Form

All information is strictly confidential and will be kept on paper only. An audio record will be obtained in case of a telephone interview.

Researcher name_____ Location: _____

Participant's ID _____ (to be complete by the researcher)

Research title: Evaluating cardiovascular risk screening and monitoring for patients prescribed antipsychotic medicines (ECRSMA).

Section (A) Agreement

By signing this form, I agree that **Please initial box**

1. I confirm that I have read the information sheet version (4.0) dated 18/05/2020 for the study named above. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily. ☐
2. I understand that my identifiable personal data, including contact details, will be collected and stored securely at the University of Birmingham, and my data will be stored according to the UoB policies. ☐
3. I understand that my participation is voluntary and that I am free to withdraw from the study at any time, without giving any reason, without my care or my legal rights being affected. ☐
4. I agree with my consent form to be stored at secure premises at the UoB. I understand only the authorised personnel from the research team will have access to the consent form. ☐
5. I understand that I cannot withdraw my data once a manuscript was produced and submitted for publication. ☐
6. I agree that my demographic data will be collected and stored for the purpose of the study ☐
7. I agree for my interview to be audio-recorded. I understand that this recording will be stored securely at the University of Birmingham and will be retained intact for ten years from the date of the collection according with The Data Protection Act and General Data Protection Regulation (GDPR) ☐
8. I understand that data collected during the study will be used for research purposes, including publication of anonymised findings and quotations. I grant copyright permission on the understanding that my confidentiality will be protected. ☐
9. I agree to representatives of the sponsor (University of Birmingham), ☐

NHS and regulatory agencies having access to my data for review and audit purposes.

10. I agree to take part in the study. ☐

Printed Name_____

Participant's Signature _____Date _____

Researcher's Signature _____Date _____

Optional: Section (B). Please complete this section only if you prefer to participate in the study through a telephone interview:

Please contact me on my telephone number (mobile or landline) _____ during the following times _____

(Example Weekdays lunch time between 1 and 2 etc.)

Note: Please send the form back to the researcher using the pre-paid envelope provided. Consent for the telephone interview will be taken by the phone on the day of the interview.

Contact Information:

Miss Ruba Azfr Ali

Phone: [redacted] (mobile). Email: [redacted]

Dr Vibhu Paudyal

Phone: (0)121 4142538 (office). Email: [redacted]

Dr Zahraa Jalal

Phone: (0)121 414 4042 (office). Email: [redacted]

To be completed by the researcher on the date of the telephone interview:

Interview Date:_____
Signed:_____

Researcher's Signature

When completed: 1 copy of this document will be made for researcher site file to be kept in a secure cabinet at the UoB. The original copy of the patient's consent is to be filed in their medical records.

F.4. Consent form (HCPs)







Healthcare Professional Interview Consent Form

All information is strictly confidential and will be kept on paper only. An audio record will be obtained in case of a telephone interview.

Researcher name_____ Location: _____

Participant's ID _____ (to be complete by the researcher)

Research title: Evaluating cardiovascular risk screening and monitoring for patients prescribed antipsychotic medicines (ECRSMA).

Section (A) Agreement

By signing this form, I agree that **Please initial box**

1. I confirm that I have read the information sheet version (5.0) dated 18/05/2020 for the study named above. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily. ☐
2. I understand that my identifiable personal data, including contact details, will be collected and stored securely at the University of Birmingham, and my data will be stored according to the UoB policies. ☐
3. I understand that my participation is voluntary and that I am free to withdraw from the study at any time, without giving any reason, without my care or my legal rights being affected. ☐
4. I agree with my consent form to be stored at secure premises at the UoB. I understand only the authorised personnel from the research team will have access to the consent form. ☐
5. I understand that I cannot withdraw my data once a manuscript was produced and submitted for publication. ☐

6. I agree that my demographic data will be collected and stored for the purpose of the study ☐

7. I agree for my interview to be audio-recorded. I understand that this recording will be stored securely at the University of Birmingham and will be retained intact for ten years from the date of the collection according with The Data Protection Act and General Data Protection Regulation (GDPR) ☐

8. I understand that data collected during the study will be used for research purposes, including publication of anonymised findings and quotations. I grant copyright permission on the understanding that my confidentiality will be protected. ☐

9. I agree to representatives of the sponsor (University of Birmingham), NHS and regulatory agencies having access to my data for review and audit purposes. ☐

10. I agree to take part in the study. ☐

Printed Name_____

Participant's Signature _____Date _____

Researcher's Signature _____Date _____

Optional: Section (B). Please complete this section only if you prefer to participate in the study through a telephone interview:

Please contact me on my telephone number (mobile or landline) _____ during the following times _____

(Example Weekdays lunch time between 1 and 2 etc.)

Note: Please send the form back to the researcher using the pre-paid envelope provided. Consent for the telephone interview will be taken by the phone on the day of the interview.

Contact Information:

Miss Ruba Azfr Ali

Phone: [redacted](mobile).

Email: [redacted]

Dr Vibhu Paudyal

Phone: (0)121 4142538 (office). Email:

Dr Zahraa Jalal

Phone: (0)121 414 4042 (office). Email:

To be completed by the researcher on the date of the telephone interview:

Interview Date:_____
Signed:_____

Researcher's Signature

When completed: 1 copy of this document will be made for researcher site file to be kept in a secure cabinet at the UoB. The original copy of the patient's consent is to be filed in their medical records.

F.5. Interview topic guide (Patients)

ECRSMA valuating cardiovascular risk screening and monitoring of patients prescribed antipsychotic medicines

UNIVERSITY OF BIRMINGHAM

NHS Dudley Clinical Commissioning Group

Qualitative interview (Approximately 45-60 min)

Study objectives (for researcher reference)

1. 1. To explore the extent to which cardiovascular and metabolic risk factors and diseases are being monitored for service users receiving antipsychotic drugs in primary care.
2. Explore nature of interventions that are provided (e.g. lifestyle or medications for diabetes).
3. To investigate barriers for optimal monitoring and management of cardiovascular and metabolic diseases in service users prescribed antipsychotic drugs in primary care
4. To explore potential barriers for optimal uptake of NICE guidelines and recommendations by the health care professionals.

Background information:

Invite interviewee to briefly tell about him/herself: general information about the background mostly about the duration of treatment with the antipsychotics.

To start with, I would like to know you a little, can you tell me more about yourself?

Questions:

Knowledge and experience of using their antipsychotic medications

- ☐ How long have you been taking your medication (the antipsychotic)?

  [Prompt: check their understanding of the reasons for prescribing the antipsychotics]

- ☐ Tell me how you currently feeling, do you feel that the medicines work for you?

- ☐ Have you ever experienced any problem while taking your medicines (the antipsychotic one)?

  [Prompt: refer to the issue they faced (any possible side effect?)]

- ☐ As you previously mentioned, you use this medicine (medicine name) for your mental health condition, I would like to know what else do you know about the medication you take?

  [Prompts: refer to any side effects e.g. weight gain, blood sugar levels, blood pressure and blood lipids]

- ☐ What do you see as the benefit of knowing the side effects of the drugs you are using?

- ☐ How did they know about them? [Prompt: refer to the source of information e.g. doctor/drug leaflet, internet etc...]

Screening and monitoring of cardiovascular/metabolic side effects of antipsychotics:

Question:

- ☐ Can you tell me who firstly prescribed the antipsychotic drugs for you?

  [Prompt: refer to healthcare professionals (e.g. psychiatric)]

- ☐ How often do you check your general health when you go to the GP [or your prescriber who prescribed/prescribes you antipsychotic medicines]?

  [Prompt: refer to the side effects they mention (e.g. blood pressure/weight gain etc...]

[Note for interviewer: (1) if patients have been previously screened and monitored, proceed to the following questions.]

- ☐ When was the last time you have checked for your general health?

  [Prompt: refer to blood lipid level, blood glucose, etc…]

- ☐ Can you take me through what happened the last time you visited your GP to check your general health or your last visit in relation to your antipsychotic medications?
- ☐ In your opinion how connected (integrated) do you find different clinics that look after your mental health?

[Note for interviewer (2): if the patient HAS NEVER BEEN screened and monitored for cardiac cardiovascular issues, proceed to the next question to identify potential barriers for screening.]

- ☐ In your opinion, what are the possible difficulties that you face and hence prevent you from checking up on your general health?

[Prompt: whether patient ever advised, and by whom]

Prevention and management of cardiovascular and metabolic side effects of antipsychotics:

Questions:

- ☐ Are you aware of any side effects of antipsychotic medicines that you are taking?
- ☐ Have you been advised of the side effects of the medicine by any healthcare professional? If so by whom and where?
- ☐ In your opinion who should be monitoring you for the side effects of the antipsychotic medicines?
- ☐ Could you please describe if you have been advised any life style modifications for preventing or managing cardiovascular health conditions?
  [Prompt: exercise, smoking cessation, healthy diet…]
- ☐ Could you please elaborate on your experience of participating in any such lifestyle modification programme?
  [Prompt: prompt: exercise, smoking cessation, healthy diet…]?
- ☐ Have you been prescribed medicines to manage your [lipid, blood pressure…..]?
  [Prompts: Who prescribed such medications to you?……]
- ☐ How satisfied are you in relation to your care of your [blood pressure, lipid….]?
- ☐ What barriers do you face in adopting the advice from your GP/health care professionals in relation to maintaining your [blood pressure, lipid…]?
- ☐ How motivated you are in relation to making the changes (e.g. implement lifestyle changes for managing or prevent cardiovascular health conditions) or adherence to medicines for cardiovascular health)?
- ☐ From your views, what would a good lifestyle programme to manage your cardiovascular health look like?
  [Prompts: peer led- support groups …]

Closing:

A. Is there anything else you did not tell me yet but think may be of interest?

F.6. Interview topic guide (HCPs)

Qualitative interview (Approximately 45-60 min)

Study objectives (for researcher reference)

5. To explore the extent to which cardiovascular and metabolic risk factors and diseases are being monitored for service users receiving antipsychotic drugs in primary care.
6. Explore nature of interventions that are provided (e.g. lifestyle or medications for diabetes).
7. To investigate barriers for optimal monitoring and management of cardiovascular and metabolic diseases in service users prescribed antipsychotic drugs in primary care
8. To explore potential barriers for optimal uptake of NICE guidelines and recommendations by the health care professionals.

Background information:

Invite interviewee to briefly tell about him/herself: general information about the background mostly about their experience with prescribing/management of patients taking antipsychotic medications.

Exploring the knowledge/attitude of the participants toward the cardiovascular/metabolic side effects of antipsychotic medications.

Questions:

- ☐ How often do you prescribe antipsychotic drugs? Or manage patients taking antipsychotic drugs (if not prescribing)
- ☐ What are the key issues managing patients taking antipsychotic medicines?
- ☐ How knowledgeable do you feel about side effects caused by antipsychotic drugs?

  [Prompt: refer to the most common reported side effect, e.g. weight gain, hypotension, etc…]

  [Prompt: Refer to the drug that most commonly reported, e.g. clozapine]

- ☐ How knowledgeable do you feel about cardiovascular and metabolic side effects caused by antipsychotic drugs?
- ☐ In your opinion, is it important to regularly monitoring cardiovascular/metabolic side effects in people taking antipsychotics?

- ☐ Are you aware of the guidelines that have been recommended for screening and monitoring of cardiovascular/metabolic side effects of antipsychotics?

  In your opinion who do you think should be monitoring these side effects or why[prompt: which clinic or healthcare professional)
- ☐ How well do you find primary care, mental health clinics and secondary care integrated for screening these patients?[prompt: NICE guidelines]

- ☐ What recommendations do you have to improve care integration to screen/monitor these patients?

Screening and monitoring of cardiovascular/metabolic side effects of antipsychotics.

Questions:

- ☐ How often do you screen patients taking antipsychotics for cardiovascular/metabolic issues?

  [Prompt if: they don't screen for cardiovascular/metabolic side effects of antipsychotics, ask for any possible causes]

- ☐ In your opinion, who should be prioritized for the screening?

  [Prompt: refer to any particular groups, e.g. drug naïve/chronically treated, patients on certain antipsychotics etc…]

- ☐ Who should do the screening in your opinion?
  [Prompt: refer to other health care professionals/services/settings]
- ☐ What barriers do you find to screen and monitor the physical health of patients with mental illness?
  [Prompt: refer to possible barriers, e.g. psychotic symptoms, low attendance rate, difficulties to communicate effectively with your patients with mental health conditions etc…]
- ☐ What enablers help you screen and monitor your patients for cardiovascular and metabolic side effects of antipsychotic drugs? What would you like to suggest to improve screening and monitoring practices of cardiovascular and metabolic side effects in people taking antipsychotics in your setting?

  [Prompt*:* refer to plans like, using guidance tool, etc…]

  [prompt: If you were to change one thing to improve practice, what would that be and why?]

Management of cardiovascular and metabolic side effects in patients taking antipsychotic medications:

Questions:

- ☐ What are your experiences of managing cardiovascular and metabolic side effects in patients taking antipsychotics?

  [Prompt: refer to different strategies available to manage cardiovascular and metabolic side effects for antipsychotics]

- ☐ What are the key barriers to manage these side effects?
- ☐ What are they key enablers to manage these side effects?
- ☐ Let's talk about a particular antipsychotic side effect for example, weight gain, what kind of strategy do you often recommend to manage it?
  [Prompt: refer to care/interventions for the particular issue, e.g. prescribing weight losing medications for weight gain]
- ☐ Which interventions are followed well by patients and which are not?

- ☐ In your opinion, what makes it difficult for patients to access and utilize care/treatment for co-prevalent mental and physical health?

  [Prompt: refer to possible barriers [e.g. inaccessible facilities, patients from remote areas, etc...]

- ☐ In the future, what would you wish to improve regarding the management of cardiovascular side effects of antipsychotics at your setting?

  [Prompt: refer to particular training needs or programmes].

- ☐ Do you believe the WHO/NICE should develop treatment guidelines for managing these side effects…?
  [Prompt: If you were to change one thing to improve practice, what would that be and why?]

  In your opinion who do you think should be managing these side effects or why? [prompt: which clinic or healthcare professional)

- ☐ How well do you find primary care, mental health clinics and secondary care integrated for management these patients? [prompt: NICE guidelines]
- ☐ What recommendations do you have to improve care integration to manage these patients?

Closing:

Is there anything else you did not tell me yet but think may be of interest?

F.7. Advertising materials: (Invitation poster for patients & Research logo)





F.8.Research invitation letter for general practitioners







Dear Lead General Practitioner/Practice manager

Research title: Evaluating cardiovascular risk screening and monitoring of patients prescribed antipsychotic medicines (ECRSMA).

We are writing to invite you to take part in the ECRSMA research which we are carrying out to determine current practice of screening and monitoring of patients prescribed antipsychotics and the uptake of the recommending guidelines in practice. The study is organised by the University of Birmingham.

I would be grateful if your practice would consider participating in this study.

This study has been reviewed by West Midlands - Solihull Research Ethics Committee
and University of Birmingham Research Ethics Committee. The study will be conducted in two phases.

Phase 1: The first phase involves retrospective review of medical records for patients' prescribed with antipsychotic medications by one of your clinical staff and extract information on the current practices in risk monitoring and management. The anonymised data will then be passed on to the researcher for analysis. **Your practice will be reimbursed £500 for participation in this phase of the study.** The practice will not be identified in any reports or publications arising from this work.

Phase 2: The second part of the study will involve interviews with interested healthcare professionals (general practitioners, nurses and pharmacists) to investigate incentives and barriers for cardiovascular and

metabolic screening and monitoring in people taking antipsychotic medications. admin time and the consumables

Participation will be voluntary and participation in phase 1 above will not bind to your practice participating in phase 2. **Resources spent in this phase including the admin time and the consumables will be reimbursed.** If you would be willing to take part in the study I would appreciate it if you could sign the enclosed agreement form and then return them in the envelope provided. The researcher will contact you to make further arrangements with the project. Many thanks in advance for your consideration of this project. Please let me know if you require further information.

If you have any questions about the study then please do contact us.

Miss Ruba Azfr Ali, PhD Student, Institute of Clinical Sciences, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK, phone: [redacted] (mobile).

Email: [redacted]

Study supervisor: Dr Vibhu Paudyal, Senior Lecturer in Clinical Pharmacy, 3rd floor, Institute of Clinical Sciences, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK, Phone: (0)121 4142538 (office).
Email: [redacted]

Thank you!

On behalf of the ECRSMA research team*.

*Research team: Ruba Afzr Ali, Dr Vibhu Paudyal, Dr Zahraa Jalal, Dr Malcolm Price, Ms Clair Huckerby (Dudley CCG), Mr Jaspal Johal (Dudley CCG).

F.9 Research invitation letter for pharmacies







Research title: Evaluating cardiovascular risk screening and monitoring of patients prescribed antipsychotic medicines (ECRSMA).

Date:

Pharmacy name:

Address:

We are writing to invite you to take part in the ECRSMA research which we are carrying out to determine current practice of screening and monitoring of patients prescribed antipsychotics and the uptake of the recommending guidelines in practice. The study is organised by the University of Birmingham. We contacted you because your pharmacy was recommended to us as eligible site.

I would be grateful if your pharmacy would consider participating in this study

Part of the study will involve interviews with community pharmacists and patients prescribed antipsychotic medications. The interviews aim to investigate barriers and facilitators for cardiovascular and metabolic screening and monitoring in people taking antipsychotic medications.

Furthermore, as community pharmacies are known to be accessible for patients, we would like to ask your assistance to recruit eligible patients for interviews. You will be requested to hand in invitation letter and the information sheet to any patients dispensed antipsychotic medicines for them to directly contact the researcher.

Please send this form back to the researcher using the pre-paid envelope provided.

If you would like to participate, I would appreciate it if you could sign the enclosed form (response letter) and it return it in the envelope provided. Many thanks in advance for your consideration of this project. Please let me know if you require further information.

If you have any questions about the study then please do contact us.

Miss Ruba Azfr Ali, Institute of Clinical Sciences, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK, phone: [redacted] Email: [redacted]

Study supervisor: Dr Vibhu Paudyal, Senior Lecturer in Clinical Pharmacy, 3rd floor, Institute of Clinical Sciences, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK, Phone: (0)121 4142538 (office). Email: [redacted]

Thank you!

On behalf of the ECRSMA research team.

F.10. Response slip for general practicies







Response letter for (name of the setting) to take part in the study.

Date:

GP practice name:

Address:

We _____ (NAME OF THE PRCATICE) agree to participate in

the ECRSMA study in relation to the invitation letter version_____dated_____.

We would like to participate in (tick as appropriate)

◯ Phase 1- retrospective review of patient records to identify the extent of screening and monitoring of patients prescribed antipsychotic medicines. Participation will also include inviting eligible patients to participate in an interview with the researcher. I understand that if we participate in this phase, **the practice will be reimbursed £500**. I also understand that neither the patients nor the practice will not be identified in any reports or publications arising from this work.

◯ Phase 2- Interviews with health care professionals and patients. We have some healthcare professionals who would like to take part in the interviews. I have access to their information sheet enclosed within this invitation pack. I understand that a separate consent will be obtained with the healthcare professionals participating in the interviews. I understand that if we participate in this phase **, resources spent in this phase including the admin time and the consumables will be reimbursed.**

◯ Both- Phase1 and Phase 2

Name: ……

Role:……

Signature: ……

Date: ……

Please send the form back to the researcher using the pre-paid envelope provided.

F.11.Response slip for pharmacies







Response letter for (name of the setting) to take part in the study.

Date:

Pharmacy name:

Address:

We _____ (name of the pharmacy) agree to participate in

the ECRSMA study in relation to the invitation letter version_____dated_____.

We would like to participate by identifying eligible patients in the study (i.e. adult patients who are prescribed antipsychotic medicines) and handing over the invitation pack on behalf of the researcher. I understand that the pharmacy nor the patients will not be identified in any reports or publications arising from this work.

Name: ……

Role:……

Signature: ……

Date: ……

<u>Please send the form back to the researcher using the pre-paid envelope provided.</u>

Appendix III (Chapter 3)

A. Literature search strategy

Medline 18.07.2018

POPULAION AND (CONDETION/CONTEXT)

1. Schizophrenia/ or Psychotic Disorders/
2. Psychotic symptom*.mp. or Hallucinations/
3. Mental illness/dt, mo [Drug Therapy, Mortality]
4. Antipsychotic Agents/ae [Adverse Effects]
5. ANTIPSYCHOTIC drug*.mp.
6. Antipsychotic medication*.mp.
7. First-generation antipsychotic*.mp.
8. Second-generation antipsychotic*.mp.
9. Neuroleptic drug*.mp.
10. Neuroleptic agent*.mp.
11. Neuroleptic medication*.mp.
12. Antipsychotic medicine*.mp.
13. Depressive Disorder/dt, mo [Drug Therapy, Mortality]
14. DEPRESSION/dt, mo [Drug Therapy, Mortality]
15. Antidepressive Agents, Second-Generation/ or Serotonin Uptake Inhibitors/ or Antidepressive Agents/ or antidepressant*.mp. or Antidepressive Agents, Tricyclic/
16. Selective serotonin re-uptake inhibitor*.mp.
17. Tricyclic related antidepressant*.mp.
18.(Serotonin and Noradrenaline Reuptake Inhibitor*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
19. Cardiovascular Diseases/di, ep, pc [Diagnosis, Epidemiology, Prevention & Control]
20. Heart Diseases/co, di, ep, pc [Complications, Diagnosis, Epidemiology, Prevention & Control]
21. Coronary Disease/ or Heart Failure/ or cardiac complication*.mp. or Myocardial Ischemia/ or Myocardial Infarction/
22. Cardiovascular complication*.mp.
23. Cardiovascular effect*.mp.
24. Cardiac effect*.mp.
25. Cardiovascular side effect*.mp.
26. Hypertension/ or Obesity/ or Cardiovascular risk factor*.mp. or Diabetes Mellitus, Type 2/
27. Metabolic Syndrome/di, pc [Diagnosis, Prevention & Control]
28. Insulin Resistance/ or Metabolic disturbance*.mp.
29. Glucose Intolerance/di, pc [Diagnosis, Prevention & Control]
30.(glucose intolerance adj4 schizophrenia).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
31.(glucose intolerance adj4 depression).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
32. Metabolic dysregulation*.mp.
33. cardiometabolic*.mp.
34. Cardiovascular risk.mp.
35. Cardiovascular event*.mp.
36. Major adverse cardiovascular event*.mp.
37. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
38. 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
39. 37 and 38

40. Limit 39 to (English language and yr="2003 -Current")

B. research key terms used in MEDLINE database.

Data base: MEDLINE			
Search terms	**Concept**	MeSH terms	Key words/free text
	Concept 1: patients taking antipsychotic drugs. Free texts: Antipsychotic medications/drugs/ agents.	**Mental health or mental disorder** **ANTIPSYCHOTIC AGENTS** antipsychotic agent*/drug*/effect* antipsychotics drugs, antipsychotic drugs, neuroleptic neuroleptic agent* neuroleptic* second generation antipsychotic*	**Antipsychotic** medication*/medicine* People with Psychotic symptom* **First generation antipsychotic***
	Concept	MeSH	Key words
	Concept 2: Cardiovascular/metabolic effects/side effect/complications ✓ **Cardiovascular effects/side effects/complications**	Cardiovascular disease* **HYPER/HYPOTENSION** **HYPOTENSION, ORTHOSTATIC** hypotension, orthostatic hypotension, postural orthostatic hypotension postural hypotension	Cardiac disease*/disorder* Cardiac effect* **Cardiac** dysrhythmia/s **Coronary heart** disease* Dysrhythmia/s **Cardio**vascular risk factor* Cardio- metabolic risk factor* Cardiovascular side effect* Cardiovascular effect*
	✓ **Metabolic effects/side effect/complications**	**DIABETES MELLITUS** **Metabolic disease*** Obesity Metabolic syndrome Glucose intolerance Insulin resistance Dyslipidaemia* Hyperlipidaemia* Hypercholesterolemia **HYPERTRIGLYCERIDEMIA/** **Weight Gain/** Over weight	Metabolic disorder* Metabolic dysregulation Metabolic abnormal* Metabolic risk factor* Lipid disorder Impaired lipid profile Decreased HDL Abnormal lipid profile. Increased Wight Increased body mass index Increased waist circumference. Excess weight Obese patient*

C.1. JBI assessment tool for prevalence study



JBI Critical Appraisal Checklist for Studies Reporting Prevalence Data

Reviewer_____Date_____.

Author _____Year_____Record Number_____.

	Yes	No	Unclear	Not applicable
1. Was the sample frame appropriate to address the target population?	☐	☐	☐	☐
2. Were study participants sampled in an appropriate way?	☐	☐	☐	☐
3. Was the sample size adequate?	☐	☐	☐	☐
4. Were the study subjects and the setting described in detail?	☐	☐	☐	☐
5. Was the data analysis conducted with sufficient coverage of the identified sample?	☐	☐	☐	☐
6. Were valid methods used for the identification of the condition?	☐	☐	☐	☐
7. Was the condition measured in a standard, reliable way for all participants?	☐	☐	☐	☐
8. Was there appropriate statistical analysis?	☐	☐	☐	☐
9. Was the response rate adequate, and if not, was the low response rate managed appropriately?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

_____

_____

_____

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C.2. JBI assessment tool for randomised controlled studies



JBI Critical Appraisal Checklist for Randomized Controlled Trials

Reviewer_____Date_____

Author _____Year_____Record Number_____

		Yes	No	Unclear	NA
1.	Was true randomization used for assignment of participants to treatment groups?	☐	☐	☐	☐
2.	Was allocation to treatment groups concealed?	☐	☐	☐	☐
3.	Were treatment groups similar at the baseline?	☐	☐	☐	☐
4.	Were participants blind to treatment assignment?	☐	☐	☐	☐
5.	Were those delivering treatment blind to treatment assignment?	☐	☐	☐	☐
6.	Were outcomes assessors blind to treatment assignment?	☐	☐	☐	☐
7.	Were treatment groups treated identically other than the intervention of interest?	☐	☐	☐	☐
8.	Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	☐	☐	☐	☐
9.	Were participants analyzed in the groups to which they were randomized?	☐	☐	☐	☐
10.	Were outcomes measured in the same way for treatment groups?	☐	☐	☐	☐
11.	Were outcomes measured in a reliable way?	☐	☐	☐	☐
12.	Was appropriate statistical analysis used?	☐	☐	☐	☐
13.	Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

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C.3.JBI assessment tool for non-randomised controlled studies



JBI Critical Appraisal Checklist for Quasi-Experimental Studies (non-randomized experimental studies)

Reviewer_____Date_____

Author _____Year_____Record Number_____

		Yes	No	Unclear	Not applicable
1.	Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?	☐	☐	☐	☐
2.	Were the participants included in any comparisons similar?	☐	☐	☐	☐
3.	Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	☐	☐	☐	☐
4.	Was there a control group?	☐	☐	☐	☐
5.	Were there multiple measurements of the outcome both pre and post the intervention/exposure?	☐	☐	☐	☐
6.	Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	☐	☐	☐	☐
7.	Were the outcomes of participants included in any comparisons measured in the same way?	☐	☐	☐	☐
8.	Were outcomes measured in a reliable way?	☐	☐	☐	☐
9.	Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

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D.1 Quality assessments for studies reporting prevalence data

Study ID / Criteria	Hyun Kang. et al, 2015.(85)	Vinberg et la, 2012	Misawa et al, 2011.	Owusu–Ansah et al, 2018.	Coakley et al, 2012.	Yang et al, 2016	Miller et al, 2005	Shakeri et al, 2016	Y. K. Ko et al, 2013.	Said et al, 2012.	Pallava et al, 2012
Q 1 Was the sample size adequate?	N	U	U	U	U	N	U	N	U	N	N
Q 2 Was the sample frame appropriate to address the target population?	U	Y	U	Y	U	U	Y	N	U	Y	U
Q 3 Were the study subjects and the setting described in detail?	Y	N	Y	N	U	Y	Y	Y	U	N	N
Q 4 Was the data analysis conducted with sufficient coverage of the identified sample?	U	U	U	U	U	U	U	U	U	U	U
Q 5 Was the condition measured in a standard, reliable way for all participants?	Y	Y	U	Y	U	U	U	U	U	U	Y
Q 6 Was there appropriate statistical analysis?	U	U	Y	U	U	Y	Y	U	U	N	U
Q 7 Were they recruited appropriately?	U	Y	U	U	U	U	U	N	Y	Y	U
Q 8 Was the response rate adequate, and if not, was the low response rate managed appropriately?	U	U	U	U	U	U	U	U	U	U	U
Q 9 Were valid methods used for the identification of the condition?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Overall quality rating	Low	Low	Low	Low	Low	Low	Fair	Low	Low	Low	Low

Study ID / Criteria	Bell et al, 2009	Grover et al, 2012	Argo et al, 2011 (	Kim et al,2010.	Gardner-Sood et al, 2015	Arango et al, 2008	Lamberti et al, 2006.	Hägg et al,2006.	Zhang et al, 2011	Deuschle et al, 2013	Chukwuma et al,2008
Q 1 Was the sample size adequate?	Y	U	N	N	N	Y	N	N	N	U	N
Q 2 Was the sample frame appropriate to address the target population?	U	U	N	U	U	U	U	Y	U	Y	U
Q 3 Were the study subjects and the setting described in detail?	N	Y	U	N	N	Y	N	N	N	U	Y
Q 4 Was the data analysis conducted with sufficient coverage of the identified sample?	U	U	Y	U	U	Y	U	U	U	U	U
Q 5 Was the condition measured in a standard, reliable way for all participants?	U	U	Y	U	Y	Y	U	U	U	U	U
Q 6 Was there appropriate statistical analysis?	N	N	N	N	U	Y	N	N	U	U	N
Q 7 Were they recruited appropriately?	U	U	N	U	U	Y	Y	U	U	U	Y
Q 8 Was the response rate adequate, and if not, was the low response rate managed appropriately?	U	U	N	U	U	U	U	U	U	U	U
Q 9 Were valid methods used for the identification of the condition?	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Overall quality rating	Low	Low	Low	Low	Low	Good	Low	Low	Low	Low	Low

Y: Yes, N: No, U: Unclear (insufficient information available to make a judgement)

D.2 Quality assessment of pharmacological studies (RCTs) part 1

Study ID / Criteria	Henderson et al, 2009	Wang, et al, 2012	Baptista et al, 2008.	Henderson et al, 2005.	Gross et al, 2010	Assunção et al, 2006.
Q1 1. Was true randomization used for assignment of participants to treatment groups?	Unclear	Unclear	Unclear	Unclear: No detailes not provided	Yes	Yes
Q2 Was allocation to treatment groups concealed?	Unclear	Unclear	Unclear	Unclear	Yes	Unclear
Q3 Were treatment groups similar at the baseline?	Yes	Yes	No	Yes	Yes	Yes
Q4. Were participants blind to treatment assignment?	NA	Yes	Unclear	Yes	Yes	Yes
Q5 Were those delivering treatment blind to treatment assignment?	Unclear	Unclear	Unclear	Unclear: it says double blinded	Unclear: it says double blinded	Unclear
Q6 Were outcomes assessors blind to treatment assignment?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Q7. Were treatment groups treated identically other than the intervention of interest?	Unclear	Unclear	Unclear	Unclear	Yes	Unclear
Q8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	Yes	Unclear	Yes	Unclear	Unclear	Unclear
Q9. Were participants analyzed in the groups to which they were randomized?	Unclear	Yes	Unclear	Unclear	Yes	Yes
Q10. Were outcomes measured in the same way for treatment groups?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Q11. Were outcomes measured in a reliable way?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Q12. Was appropriate statistical analysis used?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

Q13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	Unclear	Unclear	Unclear	Unclear	Yes	Unclear
Overall quality rating	Low	Low	low	Low	Fair	fair

Y: Yes, N: No, U: Unclear (insufficient information available to make a judgement)

D.3 Quality assessment of pharmacological studies (RCTs) part 2

Criteria \ Study ID	Meyer et al, 2005.	Chiu et al, 2016.	Strzelecki et al, 2015.	Joffe, et al, 2008.	Larsen et al, 2017,	Baptista, et al 2007.
Q1 1. Was true randomization used for assignment of participants to treatment groups?	Yes: no information provided	Yes: in a 1:1:1 ratio	Yes: 1:1 ratio	Yes	Yes: no information provided	Unclear
Q2 Was allocation to treatment groups concealed?	Unclear	Yes	Unclear	Unclear	Unclear	Yes: identical placebo pills
Q3 Were treatment groups similar at the baseline?	Yes	Yes	Yes	No	Yes	Unclear
Q4. Were participants blind to treatment assignment?	NA	Yes	Yes	Yes	Yes: double blind	Yes: state double blind
Q5 Were those delivering treatment blind to treatment assignment?	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Q6 Were outcomes assessors blind to treatment assignment?	Yes:rater blinded	Unclear	Unclear	Unclear	Unclear	Unclear
Q7. Were treatment groups treated identically other than the intervention of interest?	Unclear	Unclear	Unclear	Yes	Unclear	Yes
Q8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	Unclear	Unclear	Yes	Yes	Yes	Unclear
Q9. Were participants analyzed in the groups to which they were randomized?	Yes	Yes	Yes	Unclear	Yes	Yes

Q10. Were outcomes measured in the same way for treatment groups?	Yes	Yes	Yes	Yes	Yes	Yes
Q11. Were outcomes measured in a reliable way?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Q12. Was appropriate statistical analysis used?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Q13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	Yes	Yes	Yes	Unclear	Unclear	Yes
Overall quality rating	Fair	Fair	Good	Good	Fair	Fair

Y: Yes, N: No, U: Unclear (insufficient information available to make a judgement)

D.4 Qaulity assessment of pharmacological studies (RCTs) part 3

Study ID / Criteria	Henderson, et al 2011.	Tchoukhine, et al 2011.	Carrizo et al, 2009	Ball, et al 2011.	Brar et al, 2005.	Wu et al, 2008.	Fleischhacker, et al 2010.
Q1 1. Was true randomization used for assignment of participants to treatment groups?	Yes: in a 1:1	Yes	Yes : Computerised rnadomisation	Unclear: No detailes not provided	Yes	Yes	Yes: fixed block (block size=4) randomization schedule
Q2 Was allocation to treatment groups concealed?	Unclear	NA	Yes	Unclear	NA	Yes	Yes
Q3 Were treatment groups similar at the baseline?	Yes	Yes	Yes	Yes	Unclear	Yes	Yes
Q4. Were participants blind to treatment assignment?	Yes:double blind	Yes: double blind	Yes	Yes: it says double blinded	NA	Unclear	Yes
Q5 Were those delivering treatment blind to treatment assignment?	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
Q6 Were outcomes assessors blind to treatment assignment?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

Q7. Were treatment groups treated identically other than the intervention of interest?	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Yes
Q8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	Unclear	Yes	Unclear	Unclear	Yes	Unclear	Yes: number needed to treat was mentioned
Q9. Were participants analyzed in the groups to which they were randomized?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Q10. Were outcomes measured in the same way for treatment groups?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Q11. Were outcomes measured in a reliable way?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Q12. Was appropriate statistical analysis used?	Unclear	Unclear	Unclear	Yes	Yes: power was calculated> not adequatly powered	Yes	Yes
Q13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes
Overall quality rating	Fair	Fair	Fair	Fair	Fair	Fair	Good

Y: Yes, N: No, U: Unclear (insufficient information available to make a judgement)

D.5 Quality assessment of non-pharmacological interventions (RCTs): part 1

Criteria \ Study ID	Looijmans et al,2017.	Wu, et al, 2007.	Khazaal et al, 2007.	Osborn et al, 2018.	McKibbin et al, 2006/10.
Q1 1. Was true randomization used for assignment of participants to treatment groups?	Yes: block was used	Yes	Yes	Yes: 1:1 ratio	Yes: no details
Q2 Was allocation to treatment groups concealed?	Unclear	Yes	Unclear	Yes	Unclear
Q3 Were treatment groups similar at the baseline?	No	Yes	No	Yes	Yes
Q4. Were participants blind to treatment assignment?	Unclear	Yes: it states double blind	Unclear	NA	Unclear
Q5 Were those delivering treatment blind to treatment assignment?	Unclear	Unclear	Unclear	NA	Unclear
Q6 Were outcomes assessors blind to treatment assignment?	Unclear	Unclear	Unclear	Yes	Unclear
Q7. Were treatment groups treated identically other than the intervention of interest?	Unclear	Unclear	Unclear	Unclear	Unclear
Q8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	Unclear	Yes	No	Unclear	Unclear: no information if pts who dropped included in the analysis
Q9. Were participants analysed in the groups to which they were randomized?	Unclear	Unclear	Unclear	Yes	Unclear
Q10. Were outcomes measured in the same way for treatment groups?	Unclear	Unclear	Unclear	Unclear	NA
Q11. Were outcomes measured in a reliable way?	Unclear	Unclear	Unclear	Unclear	Unclear
Q12. Was appropriate statistical analysis used?	Unclear	Unclear	Unclear	Unclear	Unclear

Q13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	Yes	Yes	Yes	Yes	Yes
Overall quality rating	Low	Fair	Low	Good	Low

Y: Yes, N: No, U: Unclear (insufficient information available to make a judgement)

D.6 Quality assessment of non-pharmacological interventions (RCTs): part 2

Criteria \ Study ID	Bartels et al, 2013.	Kilbourne et al, 2017.	Weber et al, 2006.	Brar et al, 2005.	Littrell et al, 2003
Q1 1. Was true randomization used for assignment of participants to treatment groups?	Unclear	Yes	No	Yes	Unclear
Q2 Was allocation to treatment groups concealed?	Unclear	Unclear	Unclear	NA	Unclear
Q3 Were treatment groups similar at the baseline?	Yes	Yes	Unclear	Unclear	Yes
Q4. Were participants blind to treatment assignment?	Unclear	Yes	Unclear	NA	NA
Q5 Were those delivering treatment blind to treatment assignment?	Unclear	No	Unclear	Yes	Unclear
Q6 Were outcomes assessors blind to treatment assignment?	Yes	No	Yess	Unclear	Unclear
Q7. Were treatment groups treated identically other than the intervention of interest?	Unclear		Unclear	Unclear	Unclear
Q8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	No	No	Yes	Yes	Unclear
Q9. Were participants analysed in the groups to which they were randomized?	Yes	Unclear	Unclear	Yes	Yes
Q10. Were outcomes measured in the same way for treatment groups?	Yes	Yes	Yes	Unclear	Unclear
Q11. Were outcomes measured in a reliable way?	Unclear	Unclear	Unclear	Unclear	Unclear

Q12. Was appropriate statistical analysis used?	Yes	Yes	Yes: power was calculated	Yes	Yes
Q13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	Yes	Yes	Yes	Yes	Yes
Overall quality rating	Fair	Fair	Fair	Fair	Fair

Y: Yes, N: No, U: Unclear (insufficient information available to make a judgement)

D.7 Quality assessment of studies using non-RCT design

Study ID / Criteria	Hansen et al, 2016	Chen et al, 2008	Bruno et al, 2017	Li Ch, et al, 2013	Meyer et al, 2005	Chen et al,2012	Giannopoulou ,et al 2014.	Poulin, et al 2007.	Henderson,et al 2006.	Lin ,et al 2009.
Q1:Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes (low risk)	Yes
Q2:Were the participants included in any comparisons similar?	NA	NA	NA	Yes	Yes	NA	NA	No (high risk)	Unclear	No
Q3: Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Unclear	NA	NA	Unclear	Unclear	Yes	NA	Unclear	Unclear	Unclear
Q4: control/ was there a control group?	No	NA	No	No	No	No	No	Yes	No (high risk)	Yes
Q5: Were there multiple measurements of the outcome both pre and post the intervention/exposure?outcomes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes

Q6: Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	Unclear: results not shown	Unclear	No	Yes	yes	Yes	Unclear: only mentioned number of pts dropped	Unclear	Unclear	Unclear
Q7: Were the outcomes of participants included in any comparisons measured in the same way?	NA	NA	NA	Yes	Yes	Yes	NA	Yes	NA	Unclear
Q8: outcomes measuring/ were the outcomes measured in reliable way?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Q9: statistical methods used and their appropriateness	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Overall scoring	Low	Low	Low	Fair	Fair	Fair	Low	Fair	Low	Low

E. Criteria for the metabolic syndrome definition.(1,2)

WHO (1998)	NCEP-ATP III (2001, modified in 2003)	IDF (2006)	Japanese Committee of the Metabolic Syndrome Diagnostic Criteria
(A) and any two of (B),(C),(D) or (E)	≥3 of any (A),(B),(C),(D) or (E)	(A) and any two of (B),(C),(D) or (E)	(A) and at least two of (B),(C),(D) or (E)
(A) High insulin levels, impaired glucose tolerance or impaired fasting glucose	(A) WC: >102 cm for men >88 cm for women	(A) Abdominal obesity: BMI ≥ 30 kg/m², WC ≥ 94 cm for men, ≥ 80 cm for women (of European descent)	(A) visceral fat obesity: waist circumference: ≥85 cm for males ≥90 cm for females
(B) Abdominal obesity: waist-to-hip ratio > 0.9 BMI ≥ 30 kg/m² WC > 94 cm	(B) Raised TGs ≥150 mg/dl	(B) Raised TGs ≥150 mg/dl	(B) fasting glucose level ≥110 mg/dl)
(C) TGs: >150 mg/dl	(C) Reduced HDL: <40 mg/dl for men, <50 mg/dl for women	(C) Reduced HDL <40 mg/dl for men <50 mg/dl for women	(C) raised TGs ≥150 mg/dl
(D) Reduced HDL cholesterol: <35 mg/dl	(D) Raised BP: ≥130/85 mmHg	(D) Raised BP: systolic BP ≥ 130 mmHg diastolic BP ≥ 85 mmHg	(D) reduced HDL <40 mg/dl
(E) Raised BP: >140/90 mmHg	(E) FBG: ≥110 mg/dl; from 2003 onwards ≥100 mg/dl	(E) Raised fasting plasma glucose: ≥100 mg/dl or existing diagnosis of DMT2	(E) elevated BP SBP ≥130 mmHg DBP ≥85 mmHg

1. Papanastasiou E. The prevalence and mechanisms of metabolic syndrome in schizophrenia: a review. Ther Adv Psychopharmacol [Internet]. 2013 Feb 22 [cited 2018 Nov 30];3(1):33–51. Available from: http://journals.sagepub.com/doi/10.1177/2045125312464385
2. Samara MT, Klupp E, Helfer B, Rothe PH, Schneider-Thoma J, Leucht S. Increasing antipsychotic dose versus switching antipsychotic for non response in schizophrenia. Cochrane Database Syst Rev [Internet]. 2018 May 11 [cited 2018 Dec 5];(5). Available from: http://doi.wiley.com/10.1002/14651858.CD011884.pub2

F. Summary of the study characteristics addressing pharmacological interventions

Study ID	country of origin	aims	study design	setting	№ of participants	population	age range	outcomes measured
Bruno et al, 2017.	Italy	To evaluate the efficacy and safety of adjunctive BPF to atypical antipsychotics thera py.	Pilot study, open label	Outpatients of psychiatric unit in general care	13 patients	15 total outpatients, 9 men and 6 women. The patients did not receive any antidepressant or anticonvulsant drugs for a period of 2 months before the study.	20-58 years	Visceral fat mass
Larsen et al, 2017.	Denmark	To determine the effects of liraglutide among subjects treated with clozapine or olanzapine.	Randomized clinical double-blind trial	Not reported	Total 96 participants : 46 treatment group VS placebo group.	Prediabetes, schizophrenia patients on stable treatment with clozapine or olanzapine with BMI > 27 kg/m2.	18-65 years	Change in glucose metabolism parameters, body compositions and cardio metabolic parameters.
Chiu et al, 2016.	Germany	To determine the effect of different dosing of metformin at 500 mg/d and 1000 mg/d for improving the metabolic profiles of clozapine-treated patients with pre-existing metabolic abnormalities.	Randomized, double-blind, placebo-controlled trial	Not reported	55 patients: metformin 500 mg/d (n = 18), metformin 1000 mg/d (n = 19), or placebo (n = 18) groups	Patients diagnosed with schizophrenia whom taking clozapine for ≥ 3 months after initiating therapy.	20–65 years	Changes in metabolic traits.
Strzelecki et al, 2015.	Poland	To determine the effects of add-on treatment with sarcosine in patients with schizophrenia in metabolic parameters	Randomized double blind, placebo-controlled and parallel group study	Not reported	Total 60: (n=30) or placebo (n=29)	Patients treated for psychiatric condition on stable treatment for ≥3 months prior to the enrolment.	18–60 years	Changes in metabolic measures

Study ID	country of origin	aims	study design	setting	№ of participants	population	age range	outcomes measured
Li Ch, et al, 2013.	China	To assess the effects of switching from clozapine to ziprasidone on weight, safety and effectiveness subjects with schizophrenia and metabolic disorders.	Open label study	Outpatients in specialised psychiatric hospital	194 cases completed the study, including (68 ziprasidone) VS (126 combination group).	Patients with schizophrenia and having been treated with clozapine in a conventional dose range for ≥ 2 years and with confirmed diagnosis of metabolic syndrome.	18-60 year	Changes in the outcomes measures
Wang et al, 2012.	China	To evaluate the efficacy of metformin for treatment of antipsychotic-induced weight gain.	A randomized, placebo-controlled study (RCT)	Schizophrenia outpatient clinic of specialised psychiatry department of two hospitals (general care hospitals)	66 subjects	Patients with first psychotic episode of schizophrenia treated with clozapine, olanzapine, risperidone, or sulpiride who experiencing > 7% their pre-treatment body weight within one year of initiating therapy.	18 - 60 years	Changes in body weight and body mass index
Chen et al, 2012.	USA	To test the effects of switching antipsychotic drug-treated patients with schizophrenia treated with different SGAs on metabolic side effects	Prospective, randomized, open label.	Outpatients form general care hospital	52 patients	Patients with schizophrenia, schizoaffective disorder, or bipolar disorder Receiving antipsychotic treatment (quetiapine, risperidone and olanzapine) Had a fasting TG/HDL ratio ≥ 3.5 at screening.	18-64 years	Anthropometric and metabolic measures and quality of life.
Tchoukhine et al, 2011.	Finland	To explore long term effect of orlistat in obese or over weight adult patients using olanzapine	Open label	Not reported	44 patients	Schizophrenic patients treated with olanzapine.	> 18 years	Changes in body weight and lipid profile. ≥ 5% weight reduction

Study ID	country of origin	aims	study design	setting	№ of participants	population	age range	outcomes measured
Fleischhacker et al, 2010	Austria	To evaluate the effect of adjunctive therapy of aripiprazole with clozapine vs. Clozapine monotherapy on body weight and clinical efficacy in patients with schizophrenia.	The main study was a 16-wk, multicentre, randomized, double-blind, placebo-controlled trial	Outpatients	207 patients: Aripiprazole (n=108) Placebo (n=99)	Outpatients with schizophrenia, who were not optimally controlled while on stable dosage of clozapine for 3 months and had experienced weight gain of o2.5 kg while taking clozapine, were randomized		
Gross et al, 2010.	USA	To evaluate the efficacy and safety of mifepristone in preventing weight gain induced by risperidone over 28 days.	Three arms double-blind, placebo-controlled study (rct)	Inpatients.	76 patients (three arms): risperidone alone (n = 30), risperidone plus mifepristone (n = 30) or mifepristone alone (n = 16).	Lean, healthy men (bmi 18–23 kg/m) diagnosed with schizophrenia and taking risperidone.	18–40 years	Changes in weight from the baseline to day 28
Carrizo, et al 2009. (105)	Venezuela	To test the effect of metformin among clozapine-treated subjects	Double-blind, parallel group, placebo-controlled study (RCT)	Specialised psychiatric centre	61 clozapine-treated patients; metformin (n= 31;VS placebo (n= 30) group	Patients with chronic and severe schizophrenia treated with clozapine ≥ 3 consecutive months.	>18 years	Changes in the primary and secondary outcomes; BW. Secondarily, we evaluated an insulin resistance index (HOMAIR), blood lipids, Hba1c.
Lin ,et al 2009	Taiwan	To investigate the effects of switching SGA to amisulpride treatment on body weight and other metabolic profiles	prospective, open-label	Specialised psychiatric hospital	46 patients: The done group (n=18) consists of risperidone and ziprasidone, and the pine group (n=28) consists of olanzapine, quetiapine, and zotepine.	Patients with schizophrenia or schizoaffective disorder; psychiatrically stable for at least 3 months and with a Clinical Global Impression of Severity Scale (CGI-S) score of 4 or lower; and a BMI > 27 kg/m_2 receiving an SGA treatment	18 -60 years	Changes in body compositions and metabolic parameters.

Study ID	country of origin	aims	study design	setting	№ of participants	population	age range	outcomes measured
						other than amisulpride at a stabilized dose for at least 3 months.		
Chen et al, 2008 .	Taiwan	The goal of this study was to evaluate the effect of metformin treatment on the olanzapine-induced metabolic disturbance in schizophrenic patients.	Open-label, prospective, multicentre study (interrupted time series)	Four general care hospitals	24 schizophrenic subjects (16 men, 8 women) who had received olanzapine treatment at least 3 months were included in the study.	Inpatient subjects were . They had fasting glucose level of 126 mg/dl or less and did not have personal or family history of diabetes.	18–60 years	Changes in metabolic parameters
Baptista et al, 2008.	Venezuela	To evaluate the effect of metformin plus sibutramine for olanzapine-associated weight gain and metabolic dysfunction in schizophrenia	A 12-week double-blind, placebo-controlled pilot study	Not reported	28 subjects receiving olanzapine	Subjects receiving olanzapine only.	> 18 years	Changes in the primary and secondary outcomes
Baptista et al, 2007-8	Venezuela	To assess the effect of metformin in preventing or reverses weight gain among schizophrenia and bipolar patients treated with olanzapine.	Multicentre, double-blind, placebo-controlled trial	Out- and inpatients in specialised psychiatric hospital	72 participants	Patients who were treated with olanzapine monotherapy for > 4 months.	> 18 years	Change in body weight, waist circumference and body mass index. Change in glucose, insulin, the HOMA-R index, glycated haemoglobin, leptin.
Joffe et al, 2008.	Finland	To investigate the weight reducing efficacy of orlistat for obesity induced by clozapine or olanzapine.	Randomised double blind placebo controlled trial	General care hospital	63 participants: orlistat (n=35)' placebo (n=36)	Patients on stable dose of clozapine or olanzapine and no compliance with non-pharmacologic intervention	18-65 years.	Changes in metabolic syndrome components

Study ID	country of origin	aims	study design	setting	№ of participants	population	age range	outcomes measured
Assunção et al, 2006.	Brazil	To evaluate the effect of nizatidine in schizophrenic patients who have already gained weight.	Randomized, double-blind, 12-week placebo controlled trial. (RCT)	Outpatient subjects	45 subjects: (27 nizatidine) and (27 placebo)	(Male or female, with schizophrenia treated with olanzapine (5 to 20 mg/day) for > 2 months and < 6 months, who experienced ≥ 5% weight gain after initiating therapy with olanzapine.	18-65 years	Primary outcome measure (i.e. Mean changes in total body weight from baseline to endpoint)
Henderson et al, 2005.	NR	Unclear	Double-blind, placebo-controlled, randomized trial (RCT)	Outpatients from specialised psychiatric centre	37 subjects : Placebo (N=18) or Sibutramine (N=19)	Patients on stable dose of olanzapine for ≥ 4 months. With BMI of ≥30 kg/m2 or a body mass index of 27 kg/m2 plus another risk factor for cardiovascular diseases.	18–65 years	Changes in anthropometric measures

G. Description of the pharmacologic interventions applied among the different studies

Study ID	Applied intervention	Dose (frequency)	Purpose of the intervention	Control	Duration of intervention	Follow up	Outcomes assessed
Bruno et al, 2017.	BPF [Bergamot Polyphenolic Fraction]	1000 mg/day (500 mg twice daily): capsules/orally	Treatment	Placebo	12-week	No	Body weight (kg) BMI score (kg/m2) TG (mg/dl) Total cholesterol (mg/dl) HDL (mg/dl) LDL (mg/dl) Glucose (mg/dl) HbA1c (%)

Study ID	Applied intervention	Dose (frequency)	Purpose of the intervention	Control	Duration of intervention	Follow up	Outcomes assessed
Larsen et al, 2017.	Liraglutide injection	NR	Treatment	Placebo	16 weeks	No	Body weight (kg) WC (cm) BMI score (kg/m2) Impaired glucose tolerance FPG, mg/dL, median (IQR) HbA1c (%) Visceral fat (mean/SD) LDL, median (IQR), mg/dL HDL ,median (IQR), [mg/dl] VLDL , median (IQR), [mg/dl] TGs, median (IQR), [mg/dL]
Chi ue et al, 2016.	Metformin (low dose vs high dose)	(500mg/d) vs (1000 mg/d)	NR	Placebo	12 weeks	No	Body weight (kg) BMI score (kg/m2) WC (cm) TGs, mg/dL HDL, mg/dl FPG, mg/dL
Li CH et al, 2013 .	Switching from ziprasidone	(20mg)	Treatment	Placebo	14 weeks	No	BMI score (kg/m2) FPG (mmol/L) HDL-c (mmol/L) TG (mmol/L)
Chen et al, 2012.	Switching between antipsychotic drugs: ARIP or ZIP	ARIP (5–30mg/day) or ZIP (40–160mg/day)	Treatment	Before the switching process	24 weeks	No	BMI score (kg/m2) Body weight (lbs.) TG (mg/dL) HDL (mg/dL) Total cholesterol (mg/dL) HgbA1c (%)
Wang et a, 2012.	Metformin	1000 mg/d	NR	NA	8-weeks	No	Body weight (kg) BMI score (kg/m2) FBG (mg/dl)
Ball et al, 2011	Atomoxetine	40-120 mg/d	Treatment	Placebo	24-week	No	Body weight (kg) BMI score (kg/m2) SBP, mmHg DBP, mmHg
Henderson et al, 2011	Modafinil	up to 300 mg/day	Treatment	Placebo	8-week	No	SBP, mmHg DBP, mmHg, Body weight (kg), BMI score (kg/m2)

Study ID	Applied intervention	Dose (frequency)	Purpose of the intervention	Control	Duration of intervention	Follow up	Outcomes assessed
							laboratory assays
Tchoukhine et al, 2011.	Orlistat	360 mg/day	Treatment	Placebo	28 days (one month)	No	Body weight (kg) Total cholesterol (mmol/L) LDL (mmol/L) TGs (mmol/L) Fasting glucose (mmol/L)
Gross et al, 2010.	Three arms; (risperidone plus placebo, risperidone plus mifepristone, or mifepristone plus placebo.		Prevention	Placebo	12-weeks	No	Body weight (kg) Triglycerides (mg/dl)
Fleischhacker et al, 2010	Adjunctive treatment with aripiprazole	5–15 mg/d	Treatment	Placebo	16 weeks	Open-label extension phase of 12 weeks	Weight (kg) BMI score (kg/m2) WC (cm)
Carrizo et al, 2009.	Metformin (extended release)	(500 -1000 mg/ daily)	NR	Placebo	12 weeks	No	Body weight (kg) BMI score (kg/m2) WC (cm) Glucose (mg/dl) Hb-A1c (%) HDL (mg/dl) Non-HDL (mg/dl) TGs (md/dl)
Henderson et al, 2009.	Ziprasidone	160 mg/day	Treatment	Placebo	6 weeks	No	Body weight (kg) BMI score (kg/m2) Fasting glucose (mg/dL) TGs (mg/dL) Total cholesterol (mg/dL) HDL (mg/dl) LDL (mg/dl)
Lin ,et al 2009	Switching between antipsychotic drugs: SGAs to Amisulpride	400 mg/d	Treatment	Unclear	12 months	No	Body weight (kg) BMI score (kg/m2) Fasting glucose (mg/dL) TGs (mg/dL) Total cholesterol (mg/dL)

Study ID	Applied intervention	Dose (frequency)	Purpose of the intervention	Control	Duration of intervention	Follow up	Outcomes assessed
							HDL (mg/dl) LDL (mg/dl)
Chen et al, 2008.	Metformin	1500 mg/day	NR	No control	24-weeks	No	Body weight (kg) BMI score (kg/m2) Fasting glucose (mg/dL) TGs (mg/dL) Total cholesterol (mg/dL) HDL (mg/dl) LDL (mg/dl)
Baptista et al, 2008.	Metformin (combination of metformin and sibutramine)	metformin 1700 mg + sibutramine 20 mg/day	NR	Placebo	12 weeks	No	Body weight (kg) BMI score (kg/m2) Glucose (mg/dl) Hb1c (%) TC (mg/dl) LDL (mg/dl) HDL (mg/dl) TG (mg/dl)
Joffe et al, 2008.	Orlistat	150mg/BID	Treatment	Placebo	16 weeks	No	Body weight (kg) Total cholesterol (mg/dl) LDL HDL Fasting glucose (mmol/L)
Baptista et al, 2007.	Metformin	(850 to 2550 mg/daily)	NR	Placebo	12 weeks	No	Body weight (kg) BMI score (kg/m2) Glucose (mg/dl) Hb1c (%) TC (mg/dl) LDL (mg/dl) HDL (mg/dl) TG (mg/dl)
Assunção et al, 2006.	Nizatidine (NIZ)	600 mg/day	Treatment	Placebo	Two phases (32 weeks)	Extension follow-up phase (16 weeks)	Body weight (kg)
Henderson et al, 2006	Aripiprazole	15-30 mg/d	Treatment	NA	6-weeks	No	Body weight (kg) BMI (kg/m2) Glucose (mg/dl) Hb1c (%)

Study ID	Applied intervention	Dose (frequency)	Purpose of the intervention	Control	Duration of intervention	Follow up	Outcomes assessed
							TC (mg/dl) LDL (mg/dl) HDL (mg/dl) TG (mg/dl)
Meyer et al, 2005	Switching between antipsychotic drugs: olanzapine or risperidone	Not reported	Treatment	NA	12 months	No	body weight (kg) BMI, kg/m 2 WC (cm) HDL (mg/dl) TGs, mg/dL FPG, mg/dL SBP, mm Hg DBP, mm Hg

H. Summary of the study characteristics addressing non-pharmacological interventions

Study ID	year	country of origin	Goal of intervention	study design	setting	№ of participants	Baseline characteristics participants	age range	outcomes measured
Osborn et al, 2018.	2018	UK	to compare the clinical effectiveness and cost effectiveness of the intervention versus treatment as usual for people with severe mental illnesses.	cluster randomised control trial	76 general practices from diverse regions across England	287 completed baseline assessments and 245 completed 12-month follow-up assessments.	patients diagnosed with schizophrenia, bipolar affective disorder, or other non-organic psychosis who had disturbed lipid profile or ≥ one cardiovascular risk factor.	30–75 years	Difference in mean total cholesterol concentration for participants between groups at the 12-month follow-up.
Looijmans et al, 2017.	2017	Holland	To determine the effectiveness of 12 months life style intervention on body weight and other metabolic parameters	Multicentre cluster RCT	Two specialised mental health hospitals	61 patients; CBT(31) vs BNE (30)	Not specific	> 18 years	Changes in body compositions mainly waist circumference measurements
Kilbourne et al, 2017.	2017	USA	To the assess effectiveness of the proposed intervention (LG-CC) in the improving physical and mental health	single-blind randomized controlled effectiveness study	outpatients from specialised psychiatric clinic	Total:245 Intervention (Life Goals): (N=146) or usual care (N=147).	patients diagnosed with schizophrenia, bipolar disorder, or major depressive disorder (single or recurrent), with a confirmed	< 18 years	controlling of cardiovascular risk factors at endpoint

Study ID	year	country of origin	Goal of intervention	study design	setting	№ of participants	Baseline characteristics participants	age range	outcomes measured
			outcomes among patients with chronic mental disorders who are at risk for CVD.				diagnosis of ≥ 1 CVD risk factors.		
Giannopoulou et al, 2014.	2014	Greece	To assess the effects of a 3-month exercise and dietary intervention on the aerobic capacity and body composition of obese adults with SMI taking Olanzapine,	Not reported	General care hospital	Total 327: Primrose intervention group (n=38 with 155 patients) vs treatment-as-usual group (n=38 with 172 patients)	Participants on stable dose of olanzapine.	18-55 years	Changes in anthropometric measures of body weight.
Bartels et al, 2013.	2013	NR	to evaluate the effectiveness of modified fitness health program in improving physical fitness and weight loss among overweight and obese adults with serious mental illness	randomized controlled trial	community specialised psychiatric centre	Total: 133 Intervention: SHAPE (N=67) compared with fitness club membership and education (N=66)	Patients diagnosed with major depression, bipolar disorder, schizoaffective disorder, or schizophrenia who had (BMI) ≥ 25. in addition to being on stable pharmacologic treatment which was defined as receiving the same psychotropic drug over the last 2 months.	≥ 21years	Changes in body compositions mainly body weight and BMI.
McKibbin et al, 2010.	2010	USA	The purpose of this study was to test the sustained impact of a 6-month diabetes management intervention in middle-aged and older adults with schizophrenia and type 2 diabetes mellitus.	A randomized pre-test, post-test control group design	general care hospital	57 participants	Patients diagnosed with schizophrenia or schizoaffective disorder and concomitant diabetes mellitus.	≥ 40 years	Changes in body compositions mainly body weight and BMI.

Study ID	year	country of origin	Goal of intervention	study design	setting	№ of participants	Baseline characteristics participants	age range	outcomes measured
Khazaal et al, 2007.	2007	Canada		Randomized controlled study	unclear	57 total: study group (DART; n= 32) VS control group (UCI; n= 32).	Patients with schizophrenia taking antipsychotic drugs and months and with a reported weight gain of > 2 kg during their treatment for > 6 months after initiating the treatment.	18 -65 years	changing in body compositions including body weight and BMI
Poulin et al, 2007.	2007	Canada	To determine the potential effectiveness of a behavioural weight control programme plus physical exercise in the prevention of antipsychotic-induced weight gain.	A prospective, comparative, open and naturalistic study	psychiatric department of general care hospital	133 participants were randomly assigned to the SHAPE (N=67) and to fitness club membership and education (N=66) conditions.	patients diagnosed with schizophrenia, schizoaffective or bipolar disorder on current treatment with second generation antipsychotic drugs as mono or combined with other psychotropic agents.	< 18 years	changes in the metabolic anthropometric and biochemical measures : plasma lipid, protein profile, and fasting plasma glucose concentrations and Hb1C
McKibbin et al, 2006.	2006	USA	to test the efficacy of a novel, manualized 24-week lifestyle intervention to reduce obesity in middle-aged and older persons with schizophrenia and type-2 DM.	A randomized pre-test–post-test control group design	general care hospital	57 participants	patients diagnosed with schizophrenia and concomitant DM.	< 18 years	changes in metabolic anthropometric and biochemical parameters
Weber et al, 2006.	2006	USA	examined the effectiveness of a behavioural intervention, among patients with schizophrenic disorders treated with atypical antipsychotics	pilot A randomized, placebo-controlled study	large urban public mental health clinic	17 patients	Patients diagnosed with schizophrenia or schizoaffective disorder, taking only one oral atypical antipsychotic and have a BMI ≥ 25.	18-65 years	Body compositions including body weight, BMI, waist–hip ratios, and biochemical measures mainly FBG.

Study ID	year	country of origin	Goal of intervention	study design	setting	№ of participants	Baseline characteristics participants	age range	outcomes measured
Brar et al, 2005.	2005	USA	To evaluate the effect of behavioural therapy for obese patients on stable dose antipsychotic (olanzapine) and to investigate the effect of switching from olanzapine to risperidone.	Multicentre open label, rater blinded, randomised study. Two phases: switching phase and weight managing phase.	not specified	72 patients: BT (35) vs UC (37).	patients with schizophrenia or schizoactive disorder using olanzapine	18-65 years	changes in body weight
Littrell et al, 2003.	2003	USA	To assess the effect of an educational intervention on antipsychotic-induced weight gain among patients with schizophrenia.	Open-label Quasi-experimental.	Local community mental health centres and private practice psychiatrists.	110 total : study group (59) VS control group (51)	Patients diagnosed with schizophrenia or schizoaffective disorder Treated with conventional antipsychotics therapy. On medications for ≥ 3 months just before enrolment.	>18 years	changes in body weight: BMI

I. Description of the non-pharmacologic interventions applied among the different studies

Study ID	Applied intervention	Description of the intervention	Purpose of the interventi on	Delivery provider	Mode of delivery	Control	Duration of intervention	Follow up period	Outcomes measured
Osborn et al, 2018	Behaviour change	The intervention based on current evidence aiming to identify eight key behaviour change strategies to reduce cardiovascular disease	NR	41 professionals who were trained on two occasions to use the behaviour change strategies.	In person mode; face to face	Treatment as usual	12 months	No	Body weight (lb) WC (cm) Lipids Total (mg/dl) HDL (mg/dl) LDL (mg/dl)

Study ID	Applied intervention	Description of the intervention	Purpose of the interventi on	Delivery provider	Mode of delivery	Control	Duration of intervention	Follow up period	Outcomes measured
		risk among severely mentally ill patients.							TGs (mg/dl) HbA1c (%)
Kilbourne et al, 2017.	Behaviour change	Life-style changes based on five weekly sessions aiming to promote healthy behaviours.	NR	The interventionist (masters-level in health education) was trained over a 2-day period in LG-CC by study investigators	In person mode; face to face	No control	12 months	12 months	Body weight (kg) BMI (kg/m2)
Looijmans et al, 2017.	Physical activity and diet	three phases intervention: preparation, implementation and monitoring	Preventive	healthcare providers who have professional training: life-style coaches and nurses	In person; face to face	Usual care	12 months (9 months monitoring phase)	No	Body weight (kg) WC (cm)
Hansen et al,2016.	Behavioural changing: adopting healthy life-style.	individual consultations including monitoring of the weight circumference	NR	NR	NR	No control	12 months	12 months	Body weight (kg) BMI (kg/m2) WC (cm) Blood glucose (mg/dl) Total cholesterol (mg/dl)
Giannopou lou et al, 2014	Physical activity and diet	The dietary intervention was based on the principles of the Mediterranean diet. Physical exercise plan with different intensity	NR	NR	In person; face to face	No control	3 months	No	Body weight (kg) BMI (kg/m2)

Study ID	Applied intervention	Description of the intervention	Purpose of the interventi on	Delivery provider	Mode of delivery	Control	Duration of intervention	Follow up period	Outcomes measured
Bartels et al, 2013	Physical activity	Free membership in a fitness programme along with mentoring services.	NR	Health mentors in a community mental health. The mentor received two-day training in healthy eating from a community nutrition educator and three-day training in nutrition education from a doctoral candidate in nutrition science	In-person mode; group based	Usual care	24-weeks	12-months	Body weight (lb) BMI (kg/m2)
Khazaal et al, 2007.	Cognitive/ behaviour treatment (CB)	Cognitive and behavioural therapy (CBT): motivational group interview intended to enhance self-care and promote healthy life-style. Education based interventions for patients about the diff type of food and the daily calorie needs for each food type along with recommendations to be given at the end.	Treatment	Two senior psychologists with master's level training and 2 years of clinical experience in CBT led each CBT group. A registered dietician led the BNE group. Therapists provided training and supervision.	Mixed delivery model; in person(group based) and print based	Standard care (Brief Nutritional Education) : informative 2hrs/session.	12 months	6 months follow-up period)	Weight (kg) BMI (kg/m2)

Study ID	Applied intervention	Description of the intervention	Purpose of the intervention	Delivery provider	Mode of delivery	Control	Duration of intervention	Follow up period	Outcomes measured
Poulin et al, 2007	Behaviour changes and physical exercise	Weight control programme that included an educational activity about dietary and physical activity counselling as well as a structured, supervised, facility-based exercise programme.	Preventive	NR	NR	Standard care group or usual care (UC)	18 months	no	Body weight (kg) BMI (kg/m2) WC (cm) Fasting glucose (mg/dL) Glycosylated haemoglobin (%) TGs (mg/dL) Total cholesterol (mg/dL)
Wu et al, 2007	Physical activity and diet	Restricted calories diet plus regular moderate intensity exercise for 6 months.	Preventive	Dietary plan was implemented by a registered dietitian.	in person; face to face	Standard care group or usual care (UC)	14 weeks	No	
McKibbin et al, 2006	Cognitive/ behaviour treatment (CB)	Educational materials were adapted for middle-aged and older patients with schizophrenia by 1) flexible sessions (1 or 2 topics/ session), 2) implementing a teach-and query training method, 3) using mnemonic aids, and 4) printed materials with large font and limiting text.	NR	Participants' providers (non-specific)	In person, group based	Usual Care plus Information (UCI)	24 weeks	No	Body weight (kg) BMI (kg/m2) WC (cm) Fasting glucose (mg/dL) Glycosylated haemoglobin (%) TGs (mg/dL) Total cholesterol (mg/dL) HDL (mg/dl) LDL (mg/dl)

Study ID	Applied intervention	Description of the intervention	Purpose of the interventi on	Delivery provider	Mode of delivery	Control	Duration of intervention	Follow up period	Outcomes measured
Weber et al, 2006.	Cognitive/ behaviour treatment (CB)	role plays based sessions. Sessions include: goal setting, motivational scaling, problem solving, risk vs. benefits comparisons, discussions on barriers to change, presentations on low-fat diets, and plans to increase activities such as walking. Participants record diaries of the food and activity they perform.	Treatment	A Psychiatric Nurse Practitioner (PMHNP) provided the intervention. The PMHNP was trained over 2 weeks and seen weekly by the first author for content validity. Sessions were monitored each week.	In person: group based	Treatment as usual (TAU) group.	12 months	No	BMI (kg/m2) Weight (lb) Fasting glucose (mg/dL)
Brar et al, 2005	Behavioural treatment (BT)	BT included 20 sessions where patients were trained to reduce calory intake.	Treatment	NR	In person: group based	Usual care (UC)	14-weeks	No	BMI (kg/m2) Weight (kg)
Littrell et al, 2003	Healthy life-style (diet)	The program consists of two written modules: “Nutrition, Wellness, and Living a Healthy Lifestyle” and “Fitness and Exercise.”	Treatment	Practice nurses	Mixed: printed based and face to face (group based)	Standard care group	16 weeks)	No	BMI (kg/m2) Weight (kg)

Appendix IV (Chapter 4)

A. Literature search strategy (Medline 09 Oct 2019)

Population and (condition/context)

1. Schizophrenia/ or Psychotic Disorders/
2. psychotic symptom*.mp. or Hallucinations/
3. Mental illness/dt, mo [Drug Therapy, Mortality]
4. Antipsychotic Agents/ae [Adverse Effects]
5. ANTIPSYCHOTIC drug*.mp.
6. Antipsychotic medication*.mp.
7. First-generation antipsychotic*.mp.
8. Second-generation antipsychotic*.mp.
9. Neuroleptic drug*.mp.
10. Neuroleptic agent*.mp.
11. Neuroleptic medication*.mp.
12. Antipsychotic medicine*.mp.
13. Depressive Disorder/dt, mo [Drug Therapy, Mortality]
14. DEPRESSION/dt, mo [Drug Therapy, Mortality]
15. Antidepressive Agents, Second-Generation/ or Serotonin Uptake Inhibitors/ or Antidepressive Agents/ or antidepressant*.mp. or Antidepressive Agents, Tricyclic/
16. selective serotonin re-uptake inhibitor*.mp.
17. tricyclic related antidepressant*.mp.
18. (Serotonin and Noradrenaline Reuptake Inhibitor*).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy]
19. Cardiovascular Diseases/di, ep, pc [Diagnosis, Epidemiology, Prevention & Control]
20. Heart Diseases/co, di, ep, pc [Complications, Diagnosis, Epidemiology, Prevention & Control]
21. Coronary Disease/ or Heart Failure/ or cardiac complication*.mp. or Myocardial Ischemia/ or Myocardial Infarction/
22. cardiovascular complication*.mp.
23. Cardiovascular effect*.mp.
24. Cardiac effect*.mp.
25. Cardiovascular side effect*.mp.
26. Hypertension/ or Obesity/ or Cardiovascular risk factor*.mp. or Diabetes Mellitus, Type 2/
27. Metabolic Syndrome/di, pc [Diagnosis, Prevention & Control]
28. Insulin Resistance/ or Metabolic disturbance*.mp.
29. Glucose Intolerance/di, pc [Diagnosis, Prevention & Control]
30. (glucose intolerance adj4 schizophrenia).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy]
31. (glucose intolerance adj4 depression).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy]
32. Metabolic dysregulation*.mp.
33. cardiometabolic*.mp.
34. cardiovascular risk.mp.
35. cardiovascular event*.mp.
36. major adverse cardiovascular event*.mp.
37. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
38. 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
39. 37 and 38
40. perspective*.mp.
41. experience*.mp.
42. *PERCEPTION/
43. view.mp.
44. believe.mp.
45. *PATIENT PREFERENCE/ or preference*.mp.
46. incentive*.mp.
47. barrier*.mp.
48. *"Surveys and Questionnaires"/ or facilitator*.mp.

49. *QUALITATIVE RESEARCH/
50. "QUALITATIVE STUDY".mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy]
51. "content analysis"/ or "thematic analysis"/ or phenomenology.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy]
52. interview*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy]
53. "indepth interview*".mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy]
54. "focus group*".mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy]
55. 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54
56. 39 and 55
57. limit 56 to english language
58. limit 57 to yr="2006 -Current"

limit 58 to human

B. PRISMA checklist

Section/topic	#	Checklist item	Reported on section
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract page
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Background
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Background
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Title page and Methodology
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Methodology
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Methodology
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplement A
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Methodology
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Methodology

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Methodology
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Methodology
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Methodology
Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Methodology
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Results
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Results
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Results
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	NA
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Results
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Discussion
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

C. Quality assessment of the selected studies.

Criteria	Mwebe H, 2017.[8]	Blixen et al, 2016.[9]	Yarborough et al ,2016.[10]	Kristiansen et al ,2015.[11]	Wärdig et al,2015.[12]	Graham et al ,2014.[13]	Rastad et al ,2014.[14]	Pearsal et al ,2014.[15]	Bergqvist et al, 2013.[16]	Happell et al,2013.[17]	Hultsjö et al ,2013.[18]
1. Is there congruity between the stated philosophical perspective and the research methodology?	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Is there congruity between the research methodology and the research question or objectives?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Is there congruity between the research methodology and the methods used to collect data?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Is there congruity between the research methodology and the representation and analysis of data?	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Is there congruity between the research methodology and the interpretation of results?	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
6. Is there a statement locating the researcher culturally or theoretically?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

7. Is the influence of the researcher on the research, and vice- versa, addressed?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
8. Are participants, and their voices, adequately represented?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Is the research ethical according to current criteria or, for recent studies, and is there evidence of ethical approval by an appropriate body?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Do the conclusions drawn in the research report flow from the analysis, or interpretation, of the data	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Conserns regarding the methodological limitations	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low

C. Quality assessment of the selected studies. Contd.

Criteria	Mangurian et al, 2013.[19]	Robson et al,2013.[20]	Hultsjö et al ,2012.[21]	Vandyk et al 2012.[22]	McDonell et al, 2011.[23]	Pitman et al,2011.[24]	Yarborough et al ,2011.[25]	Wheeler et al,2010.[26]	Johnstone et al ,2009.[27]	McDevitt et al ,2006.[28]	Hyland et al ,2003.[29]
1. Is there congruity between the stated philosophical perspective and the research methodology?	Unclear	Yes	Yes	Yes	No	Unclear	Unclear	Yes	Unclear	Unclear	Unclear
2. Is there congruity between the research methodology and the research question or objectives?	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No
3. Is there congruity between the research methodology and the methods used to collect data?	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No
4. Is there congruity between the research methodology	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No

and the representation and analysis of data?											
5. Is there congruity between the research methodology and the interpretation of results?	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
6. Is there a statement locating the researcher culturally or theoretically?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
7. Is the influence of the researcher on the research, and vice- versa, addressed?	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
8. Are participants, and their voices, adequately represented?	Yes	No	Yes	Yes	NA	Yes	No	Yes	Yes	Yes	Yes
9. Is the research ethical according to current criteria or, for recent studies, and is there evidence of ethical approval by an appropriate body?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Do the conclusions drawn in the research report flow from the analysis, or interpretation, of the data	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Conserns regarding the methodological limitations	Low	Low	Low	Low	Moderate	Low	Low	Low	Low	Low	Moderate

Appendix V (Chapter 5)

A. Drug Code List of Antipsychotic drugs used for the THIN database searching

Drug	BNF code
Amisulpride	(0402010A0)
Aripiprazole	(0402010AD)
Benperidol	(0402010B0)
Cariprazine	(0402010AJ)
Chlorpromazine Hydrochloride	(0402010D0)
Chlorprothixene	(0402010F0)
Clozapine	(0402010C0)
Flupentixol Hydrochloride	(0402010H0)
Fluphenazine Hydrochloride	(0402010I0)
Haloperidol	(0402010J0)
Levomepromazine Hydrochloride	(0402010L0)
Levomepromazine Maleate	(0402010K0)
Loxapine Succinate	(0402010M0)
Lurasidone	(0402010AI)
Melperone Hydrochloride	(0402010AF)
Olanzapine	(40201060)
Paliperidone	(0402010AE)
Pericyazine	(0402010P0)
Perphenazine	(0402010Q0)
Pimozide	(0402010R0)
Promazine Hydrochloride	(0402010S0)
Quetiapine	(0402010AB)
Risperidone	(40201030)
Sulpiride	(0402010U0)
Thioridazine	(0402010W0)
Trifluoperazine	(0402010X0)
Ziprasidone Hydrochloride	(0402010AG)
Zotepine	(0402010AC)
Zuclopenthixol Acetate	(40201010)
Zuclopenthixol Hydrochloride	(0402010T0)

B. READ codes list for mental conditions used for the THIN database searching

Medical code	Description
E102.00	Catatonic schizophrenia
E102000	Unspecified catatonic schizophrenia
E102100	Subchronic catatonic schizophrenia
E102200	Chronic catatonic schizophrenia
E102300	Acute exacerbation of subchronic catatonic schizophrenia
E102400	Acute exacerbation of chronic catatonic schizophrenia
E102500	Catatonic schizophrenia in remission
E102z00	Catatonic schizophrenia NOS
E10..00	Schizophrenic disorders
E100.00	Simple schizophrenia
E100.11	Schizophrenia simplex
E100000	Unspecified schizophrenia
E100100	Subchronic schizophrenia
E100200	Chronic schizophrenic
E100300	Acute exacerbation of subchronic schizophrenia
E100400	Acute exacerbation of chronic schizophrenia
E100500	Schizophrenia in remission
E100z00	Simple schizophrenia NOS
E101.00	Hebephrenic schizophrenia
E101000	Unspecified hebephrenic schizophrenia
E101100	Subchronic hebephrenic schizophrenia
E101200	Chronic hebephrenic schizophrenia
E101300	Acute exacerbation of subchronic hebephrenic schizophrenia
E101400	Acute exacerbation of chronic hebephrenic schizophrenia
E101500	Hebephrenic schizophrenia in remission
E101z00	Hebephrenic schizophrenia NOS
E103.00	Paranoid schizophrenia
E103000	Unspecified paranoid schizophrenia
E103100	Subchronic paranoid schizophrenia
E103200	Chronic paranoid schizophrenia
E103300	Acute exacerbation of subchronic paranoid schizophrenia
E103400	Acute exacerbation of chronic paranoid schizophrenia
E103500	Paranoid schizophrenia in remission
E103z00	Paranoid schizophrenia NOS
E104.00	Acute schizophrenic episode
E104.11	Oneirophrenia
E105.00	Latent schizophrenia
E105000	Unspecified latent schizophrenia
E105100	Subchronic latent schizophrenia
E105200	Chronic latent schizophrenia
E105300	Acute exacerbation of subchronic latent schizophrenia

E105400	Acute exacerbation of chronic latent schizophrenia
E105500	Latent schizophrenia in remission
E105z00	Latent schizophrenia NOS
E106.00	Residual schizophrenia
E106.11	Restzustand - schizophrenia
E107.00	Schizo-affective schizophrenia
E107.11	Cyclic schizophrenia
E107000	Unspecified schizo-affective schizophrenia
E107100	Subchronic schizo-affective schizophrenia
E107200	Chronic schizo-affective schizophrenia
E107300	Acute exacerbation subchronic schizo-affective schizophrenia
E107400	Acute exacerbation of chronic schizo-affective schizophrenia
E107500	Schizo-affective schizophrenia in remission
E107z00	Schizo-affective schizophrenia NOS
E10y.00	Other schizophrenia
E10y.11	Cenesthopathic schizophrenia
E10y000	Atypical schizophrenia
E10y100	Coenesthopathic schizophrenia
E10yz00	Other schizophrenia NOS
E10z.00	Schizophrenia NOS
146H.00	H/O: psychosis
212T.00	Psychosis, schizophrenia + bipolar affective disord resolved
212X.00	Psychosis resolved
2229.13	O/E - senility - no psychosis

8G13100	CBTp - cognitive behavioural therapy for psychosis
8HHs.00	Referral to psychosis early intervention service
E00y.11	Presbyophrenic psychosis
E011000	Korsakov's alcoholic psychosis
E011100	Korsakov's alcoholic psychosis with peripheral neuritis
E01y.00	Other alcoholic psychosis
E01yz00	Other alcoholic psychosis NOS
E01z.00	Alcoholic psychosis NOS
E02z.00	Drug psychosis NOS
E03y300	Unspecified puerperal psychosis
E040.11	Korsakoff's non-alcoholic psychosis
E04z.00	Chronic organic psychosis NOS
E110300	Single manic episode, severe without mention of psychosis
E110400	Single manic episode, severe, with psychosis
E111300	Recurrent manic episodes, severe without mention psychosis
E111400	Recurrent manic episodes, severe, with psychosis
E112300	Single major depressive episode, severe, without psychosis
E112400	Single major depressive episode, severe, with psychosis
E113300	Recurrent major depressive episodes, severe, no psychosis
E113400	Recurrent major depressive episodes, severe, with psychosis
E114300	Bipolar affect disord, currently manic, severe, no psychosis

E114400	Bipolar affect disord, currently manic,severe with psychosis
E115300	Bipolar affect disord, now depressed, severe, no psychosis
E115400	Bipolar affect disord, now depressed, severe with psychosis
E116300	Mixed bipolar affective disorder, severe, without psychosis
E116400	Mixed bipolar affective disorder, severe, with psychosis
E117300	Unspecified bipolar affective disorder, severe, no psychosis
E117400	Unspecified bipolar affective disorder,severe with psychosis
E11zz00	Other affective psychosis NOS
E121.00	Chronic paranoid psychosis
E12z.00	Paranoid psychosis NOS
E130.00	Reactive depressive psychosis
E131.00	Acute hysterical psychosis
E134.00	Psychogenic paranoid psychosis
E13y100	Brief reactive psychosis
E13z.00	Nonorganic psychosis NOS
E141.00	Disintegrative psychosis
E141z00	Disintegrative psychosis NOS
E14y100	Borderline psychosis of childhood
E14z.00	Child psychosis NOS
E1z..00	Non-organic psychosis NOS
Eu02z12	[X] Presenile psychosis NOS
Eu02z15	[X] Senile psychosis NOS
Eu03.11	[X]Korsakov's psychosis, nonalcoholic

Eu04.13	[X]Acute / subacute infective psychosis
Eu05212	[X]Schizophrenia-like psychosis in epilepsy
Eu05y11	[X]Epileptic psychosis NOS
Eu0z.11	[X]Organic psychosis NOS
Eu0z.12	[X]Symptomatic psychosis NOS
Eu10514	[X]Alcoholic psychosis NOS
Eu10611	[X]Korsakov's psychosis, alcohol induced
Eu22011	[X]Paranoid psychosis
Eu23012	[X]Cycloid psychosis
Eu23112	[X]Cycloid psychosis with symptoms of schizophrenia
Eu23312	[X]Psychogenic paranoid psychosis
Eu23z11	[X]Brief reactive psychosis NOS
Eu23z12	[X]Reactive psychosis
Eu25011	[X]Schizoaffective psychosis, manic type
Eu25012	[X]Schizophreniform psychosis, manic type
Eu25111	[X]Schizoaffective psychosis, depressive type
Eu25112	[X]Schizophreniform psychosis, depressive type
Eu25212	[X]Mixed schizophrenic and affective psychosis
Eu25z11	[X]Schizoaffective psychosis NOS
Eu26.00	[X]Nonorganic psychosis in remission
Eu2y.11	[X]Chronic hallucinatory psychosis
Eu2z.00	[X]Unspecified nonorganic psychosis
Eu2z.11	[X]Psychosis NOS
Eu31.12	[X]Manic-depressive psychosis
Eu32312	[X]Single episode of psychogenic depressive psychosis

Eu32314	[X]Single episode of reactive depressive psychosis
Eu33213	[X]Manic-depress psychosis,depressd,no psychotic symptoms
Eu33312	[X]Manic-depress psychosis,depressed type+psychotic symptoms
Eu33314	[X]Recurr severe episodes/psychogenic depressive psychosis
Eu33316	[X]Recurrent severe episodes/reactive depressive psychosis
Eu3z.11	[X]Affective psychosis NOS
Eu44.14	[X]Hysterical psychosis
Eu53111	[X]Puerperal psychosis NOS
Eu84013	[X]Infantile psychosis
Eu84111	[X]Atypical childhood psychosis
Eu84312	[X]Disintegrative psychosis
Eu84314	[X]Symbiotic psychosis
R20..00	[D]Senility, without mention of psychosis
R20z.00	[D]Senility, without psychosis NOS
ZV11111	[V]Personal history of manic-depressive psychosis
ZV11112	[V]Personal history of manic-depressive psychosis
212W.00	Schizophrenia resolved
E14z.11	Childhood schizophrenia NOS
Eu05200	[X]Organic delusional [schizophrenia-like] disorder
Eu2..00	[X]Schizophrenia, schizotypal and delusional disorders
Eu20.00	[X]Schizophrenia
Eu20000	[X]Paranoid schizophrenia
Eu20011	[X]Paraphrenic schizophrenia

Eu20100	[X]Hebephrenic schizophrenia
Eu20111	[X]Disorganised schizophrenia
Eu20200	[X]Catatonic schizophrenia
Eu20300	[X]Undifferentiated schizophrenia
Eu20311	[X]Atypical schizophrenia
Eu20500	[X]Residual schizophrenia
Eu20511	[X]Chronic undifferentiated schizophrenia
Eu20600	[X]Simple schizophrenia
Eu20y00	[X]Other schizophrenia
Eu20y11	[X]Cenesthopathic schizophrenia
Eu20z00	[X]Schizophrenia, unspecified
Eu21.12	[X]Borderline schizophrenia
Eu21.13	[X]Latent schizophrenia
Eu21.14	[X]Prepsychotic schizophrenia
Eu21.15	[X]Prodromal schizophrenia
Eu21.16	[X]Pseudoneurotic schizophrenia
Eu21.17	[X]Pseudopsychopathic schizophrenia
Eu23111	[X]Bouffee delirante with symptoms of schizophrenia
Eu23200	[X]Acute schizophrenia-like psychotic disorder
Eu25211	[X]Cyclic schizophrenia
ZV11000	[V]Personal history of schizophrenia
285..11	Psychotic condition, insight present
286..11	Poor insight into psychotic condition
38C1300	Assessment of psychotic and behavioural symptoms of dementia
38C1400	Assessment of cause of psychotic and behavioural symptoms
38Qh.00	Glasgow Antipsychotic Side-effect Scale

69DD.00	Antipsychotic medication physical health check
8BM0100	Antipsychotic medication review
8BPa.00	Antipsychotic drug therapy for dementia
8BPf.00	Oral antipsychotic therapy
E0...00	Organic psychotic conditions
E00..00	Senile and presenile organic psychotic conditions
E130.11	Psychotic reactive depression
E13z.11	Psychotic episode NOS
E2...00	Neurotic, personality and other nonpsychotic disorders
E2A..00	Nonpsychotic mental disorders following organic brain damage
E2Az.00	Nonpsychotic mental disorder post-organic brain damage NOS
Eu10500	[X]Mental & behav dis due to use alcohol: psychotic disorder
Eu11500	[X]Mental & behav dis due to use opioids: psychotic disorder
Eu12500	[X]Mental & behav dis due to cannabinoids: psychotic disordr
Eu13500	[X]Mental & behav dis due to seds/hypntcs: psychotic disordr
Eu14500	[X]Mental & behav dis due to use cocaine: psychotic disorder
Eu15500	[X]Mental/behav dis oth stims inc caffeine: psychotic dis
Eu16500	[X]Mental & behav dis due to hallucinogens: psychotic disord

Eu17500	[X]Mental & behav dis due to use tobacco: psychotic disorder
Eu18500	[X]Mental & behav dis due to vol solvents: psychotic disordr
Eu18700	[X]Mnt/bh dis vol solvents: resid & late-onset psychotic dis
Eu1A500	[X]Mental behav disord due crack cocaine: psychotic disorder
Eu23.00	[X]Acute and transient psychotic disorders
Eu23300	[X]Other acute predominantly delusional psychotic disorders
Eu23y00	[X]Other acute and transient psychotic disorders
Eu23z00	[X]Acute and transient psychotic disorder, unspecified
Eu24.13	[X]Induced psychotic disorder
Eu2y.00	[X]Other nonorganic psychotic disorders
Eu30100	[X]Mania without psychotic symptoms
Eu30200	[X]Mania with psychotic symptoms
Eu30211	[X]Mania with mood-congruent psychotic symptoms
Eu30212	[X]Mania with mood-incongruent psychotic symptoms
Eu31100	[X]Bipolar affect disorder cur epi manic wout psychotic symp
Eu31200	[X]Bipolar affect disorder cur epi manic with psychotic symp
Eu32200	[X]Severe depressive episode without psychotic symptoms
Eu32211	[X]Single episode agitated depressn w'out psychotic symptoms

Eu32212	[X]Single episode major depression w'out psychotic symptoms
Eu32213	[X]Single episode vital depression w'out psychotic symptoms
Eu32300	[X]Severe depressive episode with psychotic symptoms
Eu32311	[X]Single episode of major depression and psychotic symptoms
Eu32313	[X]Single episode of psychotic depression
Eu32700	[X]Major depression, severe without psychotic symptoms
Eu32800	[X]Major depression, severe with psychotic symptoms
Eu33211	[X]Endogenous depression without psychotic symptoms
Eu33212	[X]Major depression, recurrent without psychotic symptoms
Eu33214	[X]Vital depression, recurrent without psychotic symptoms
Eu33311	[X]Endogenous depression with psychotic symptoms
Eu33313	[X]Recurr severe episodes/major depression+psychotic symptom
Eu33315	[X]Recurrent severe episodes of psychotic depression
SL93.00	Other antipsychotics/neuroleptics/tranquilliser poisoning
SLX..00	Poisoning by oth & unspec antipsychotics & neuroleptics

SyuFL00	[X]Poisoning by oth & unspec antipsychotics & neuroleptics
E11..11	Bipolar psychoses
E11..13	Manic psychoses
E110.00	Manic disorder, single episode
E110.11	Hypomanic psychoses
E110000	Single manic episode, unspecified
E110100	Single manic episode, mild
E110200	Single manic episode, moderate
E110500	Single manic episode in partial or unspecified remission
E110600	Single manic episode in full remission
E110z00	Manic disorder, single episode NOS
E111.00	Recurrent manic episodes
E111000	Recurrent manic episodes, unspecified
E111100	Recurrent manic episodes, mild
E111200	Recurrent manic episodes, moderate
E111500	Recurrent manic episodes, partial or unspecified remission
E111600	Recurrent manic episodes, in full remission
E111z00	Recurrent manic episode NOS
E114.00	Bipolar affective disorder, currently manic
E114.11	Manic-depressive - now manic
E114000	Bipolar affective disorder, currently manic, unspecified
E114100	Bipolar affective disorder, currently manic, mild
E114200	Bipolar affective disorder, currently manic, moderate

E114500	Bipolar affect disord,currently manic, part/unspec remission
E114600	Bipolar affective disorder, currently manic, full remission
E114z00	Bipolar affective disorder, currently manic, NOS
E115.00	Bipolar affective disorder, currently depressed
E115.11	Manic-depressive - now depressed
E115000	Bipolar affective disorder, currently depressed, unspecified
E115100	Bipolar affective disorder, currently depressed, mild
E115200	Bipolar affective disorder, currently depressed, moderate
E115500	Bipolar affect disord, now depressed, part/unspec remission
E115600	Bipolar affective disorder, now depressed, in full remission
E115z00	Bipolar affective disorder, currently depressed, NOS
E116.00	Mixed bipolar affective disorder
E116000	Mixed bipolar affective disorder, unspecified
E116100	Mixed bipolar affective disorder, mild
E116200	Mixed bipolar affective disorder, moderate
E116500	Mixed bipolar affective disorder, partial/unspec remission
E116600	Mixed bipolar affective disorder, in full remission
E116z00	Mixed bipolar affective disorder, NOS
E117.00	Unspecified bipolar affective disorder
E117000	Unspecified bipolar affective disorder, unspecified
E117100	Unspecified bipolar affective disorder, mild
E117200	Unspecified bipolar affective disorder, moderate
E117500	Unspecified bipolar affect disord, partial/unspec remission
E117600	Unspecified bipolar affective disorder, in full remission
E117z00	Unspecified bipolar affective disorder, NOS
E11y.00	Other and unspecified manic-depressive psychoses
E11y000	Unspecified manic-depressive psychoses
E11y100	Atypical manic disorder
E11y300	Other mixed manic-depressive psychoses
E11yz00	Other and unspecified manic-depressive psychoses NOS
E112.11	Agitated depression
E112.12	Endogenous depression first episode
E112.13	Endogenous depression first episode
E112.14	Endogenous depression
E113.11	Endogenous depression - recurrent
E113700	Recurrent depression
E12..00	Paranoid states
E120.00	Simple paranoid state
E121.11	Sander's disease
E122.00	Paraphrenia
E123.00	Shared paranoid disorder
E123.11	Folie a deux
E12y.00	Other paranoid states
E12y000	Paranoia querulans
E12yz00	Other paranoid states NOS

E13..00	Other nonorganic psychoses
E13..11	Reactive psychoses
E132.00	Reactive confusion
E133.00	Acute paranoid reaction
E133.11	Bouffee delirante
E135.00	Agitated depression
E13y.00	Other reactive psychoses
E13y000	Psychogenic stupor
E13yz00	Other reactive psychoses NOS
E21..00	Personality disorders
E21..11	Neurotic personality disorder
E210.00	Paranoid personality disorder
E210.11	Fanatic personality
E211.00	Affective personality disorder
E211000	Unspecified affective personality disorder
E211100	Hypomanic personality disorder
E211200	Depressive personality disorder
E211300	Cyclothymic personality disorder
E211z00	Affective personality disorder NOS
E212.00	Schizoid personality disorder
E212000	Unspecified schizoid personality disorder
E212100	Introverted personality
E212200	Schizotypal personality
E212z00	Schizoid personality disorder NOS
E213.00	Explosive personality disorder
E213.11	Aggressive personality
E213.12	Quarrelsome personality
E214.00	Compulsive personality disorders
E214.11	Anancastic personality
E214000	Anankastic personality

E214100	Obsessional personality
E214z00	Compulsive personality disorder NOS
E215.00	Histrionic personality disorders
E215.11	Hysterical personality disorders
E215000	Unspecified histrionic personality disorder
E215100	Munchausen's syndrome
E215200	Emotionally unstable personality
E215300	Psychoinfantile personality
E215z00	Histrionic personality disorder NOS
E216.00	Inadequate personality disorder
E216.11	Asthenic personality
E216.12	Dependent personality
E216.13	Labile personality
E217.00	Antisocial or sociopathic personality disorder
E217.11	Amoral personality
E21y.00	Other personality disorders
E21y000	Narcissistic personality disorder
E21y100	Avoidant personality disorder
E21y200	Borderline personality disorder
E21y300	Passive-aggressive personality disorder
E21y400	Eccentric personality disorder
E21y500	Immature personality disorder
E21y600	Masochistic personality disorder
E21y700	Psychoneurotic personality disorder
E21y711	Neurotic personality
E21yz00	Other personality disorder NOS
E21yz11	Manipulative personality
E21z.00	Personality disorder NOS
E21z.11	Psychopathic personality
Eu20211	[X]Catatonic stupor

Eu20212	[X]Schizophrenic catalepsy
Eu20213	[X]Schizophrenic catatonia
Eu20214	[X]Schizophrenic flexibilatis cerea
Eu20400	[X]Post-schizophrenic depression
Eu20512	[X]Restzustand schizophrenic
Eu20y12	[X]Schizophreniform disord NOS
Eu20y13	[X]Schizophrenifrm psychos NOS
Eu21.00	[X]Schizotypal disorder
Eu21.11	[X]Latent schizophrenic reaction
Eu21.18	[X]Schizotypal personality disorder
Eu22.00	[X]Persistent delusional disorders
Eu22000	[X]Delusional disorder
Eu22012	[X]Paranoid state
Eu22013	[X]Paraphrenia - late
Eu22014	[X]Sensitiver Beziehungswahn
Eu22015	[X]Paranoia
Eu22100	[X]Delusional misidentification syndrome
Eu22111	[X]Capgras syndrome
Eu22200	[X]Cotard syndrome
Eu22300	[X]Paranoid state in remission
Eu22y00	[X]Other persistent delusional disorders
Eu22y11	[X]Delusional dysmorphophobia
Eu22y12	[X]Involutional paranoid state
Eu22y13	[X]Paranoia querulans
Eu22z00	[X]Persistent delusional disorder, unspecified
Eu23000	[X]Acute polymorphic psychot disord without symp of schizoph
Eu23011	[X]Bouffee delirante
Eu23100	[X]Acute polymorphic psychot disord with symp of schizophren
Eu23211	[X]Brief schizophreniform disorder
Eu23212	[X]Brief schizophrenifrm psych
Eu23213	[X]Oneirophrenia
Eu23214	[X]Schizophrenic reaction
Eu24.00	[X]Induced delusional disorder
Eu24.11	[X]Folie a deux
Eu24.12	[X]Induced paranoid disorder
Eu25.00	[X]Schizoaffective disorders
Eu25000	[X]Schizoaffective disorder, manic type
Eu25100	[X]Schizoaffective disorder, depressive type
Eu25200	[X]Schizoaffective disorder, mixed type
Eu25y00	[X]Other schizoaffective disorders
Eu25z00	[X]Schizoaffective disorder, unspecified
Eu30.00	[X]Manic episode
Eu30.11	[X]Bipolar disorder, single manic episode
Eu30000	[X]Hypomania
Eu30213	[X]Manic stupor
Eu30y00	[X]Other manic episodes
Eu30z00	[X]Manic episode, unspecified
Eu30z11	[X]Mania NOS
Eu31.00	[X]Bipolar affective disorder
Eu31.11	[X]Manic-depressive illness
Eu31.13	[X]Manic-depressive reaction
Eu31000	[X]Bipolar affective disorder, current episode hypomanic
Eu31300	[X]Bipolar affect disorder cur epi mild or moderate depressn
Eu31400	[X]Bipol aff disord, curr epis sev depress, no psychot symp

Eu31500	[X]Bipolar affect dis cur epi severe depres with psyc symp
Eu31600	[X]Bipolar affective disorder, current episode mixed
Eu31700	[X]Bipolar affective disorder, currently in remission
Eu31800	[X]Bipolar affective disorder type I
Eu31900	[X]Bipolar affective disorder type II
Eu31911	[X]Bipolar II disorder
Eu31y00	[X]Other bipolar affective disorders
Eu31y11	[X]Bipolar II disorder
Eu31y12	[X]Recurrent manic episodes
Eu31z00	[X]Bipolar affective disorder, unspecified
Eu32.00	[X]Depressive episode
Eu32.11	[X]Single episode of depressive reaction
Eu32.12	[X]Single episode of psychogenic depression
Eu32.13	[X]Single episode of reactive depression
Eu32000	[X]Mild depressive episode
Eu32100	[X]Moderate depressive episode
Eu32400	[X]Mild depression
Eu32500	[X]Major depression, mild
Eu32600	[X]Major depression, moderately severe
Eu32900	[X]Single major depr ep, severe with psych, psych in remiss
Eu32A00	[X]Recurr major depr ep, severe with psych, psych in remiss
Eu32B00	[X]Antenatal depression
Eu32y00	[X]Other depressive episodes
Eu32y11	[X]Atypical depression
Eu32y12	[X]Single episode of masked depression NOS
Eu32z00	[X]Depressive episode, unspecified
Eu32z11	[X]Depression NOS
Eu32z12	[X]Depressive disorder NOS
Eu32z13	[X]Prolonged single episode of reactive depression
Eu32z14	[X] Reactive depression NOS
Eu33.00	[X]Recurrent depressive disorder
Eu33.11	[X]Recurrent episodes of depressive reaction
Eu33.12	[X]Recurrent episodes of psychogenic depression
Eu33.13	[X]Recurrent episodes of reactive depression
Eu33.14	[X]Seasonal depressive disorder
Eu33.15	[X]SAD - Seasonal affective disorder
Eu33000	[X]Recurrent depressive disorder, current episode mild
Eu33100	[X]Recurrent depressive disorder, current episode moderate
Eu33200	[X]Recurr depress disorder cur epi severe without psyc sympt
Eu33300	[X]Recurrent depress disorder cur epi severe with psyc symp
Eu33400	[X]Recurrent depressive disorder, currently in remission
Eu33y00	[X]Other recurrent depressive disorders
Eu33z00	[X]Recurrent depressive disorder, unspecified
Eu33z11	[X]Monopolar depression NOS
Eu3z.00	[X]Unspecified mood affective disorder

C. Domains and the types of data elements to be captured by the abstraction tool

Table: Description of data elements collection in abstraction tool
Demographic information • Age, gender, ethnicity, marital status
Family and social history • past/current smoking status and alcohol use and family history of CVD or DM.
Medication history • Antihypertensive medications, lipid lowering medications and, anti-diabetic medications.
General medical history • Non-cardiac condition (diabetes, chronic kidney disease [CKD], dyslipidaemias) • Pre-existing cardiovascular conditions (transient ischemic attack [TIA], prior AMI, angina, atrial fibrillation [AF], hypertension, and heart failure [HF], hypotension, cardiogenic shock, major bleed, and stroke) • Anthropometric parameters such as BMI; waist circumference; systolic and diastolic blood pressures. • Biochemical parameters: blood glucose (glycosylated haemoglobin [HbA1c] & fasting blood glucose [FBG]) and lipid panel (high density lipoprotein [HDL] & non high-density lipoprotein [non-HDL]) cholesterols; triglycerides; was extracted. • Dates and scores of cardiovascular risk assessments.
Psychotic condition • Psychiatric diagnoses (disease type, status, duration etc.) • The prescribed antipsychotic and drug class • Data for other prescribed psychotropic medications (first and second-generation antipsychotics, and antidepressants)