Assessing the safety of prescribing for people with mental illness through the development and implementation of prescribing safety indicators

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List of Abbreviations

ACE	Angiotensin-converting enzyme
ADEs	Adverse drug events
ADHD	Attention deficit hyperactivity disorder
ADRs	Adverse drug reactions
AHRQ	Agency for Healthcare Research and Quality
BPSD	Behavioural and psychological symptoms of dementia
BMI	Body mass index
BNF	British National Formulary
CDS	Clinical decision support
CI	Confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CPOE	Computerized provider order entry
CPRD	Clinical practice research datalink
CQC	The Care Quality Commission
CVD	Cardiovascular disease
CYPMHS	Children and young people's mental health services
DDI	Drug-drug interaction
DQIP	Data driven quality improvement in primary care
DRPs	Drug-related problems
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
e-Delphi	Electronic Delphi
EFIPPS	Effective Feedback to Improve Primary Care Prescribing Safety
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
GAD	Generalised anxiety disorder

GBD	Global Burden of Disease
GPs	General practitioners
HMIC	Health Management Information Consortium
HRA	Health Research Authority
ICC	The intraclass correlation coefficient
ICD	International Classification of Diseases
IMD	The Index of Multiple Deprivation
INR	International normalized ratio
IPA	International Pharmaceutical Abstracts
IQR	Interquartile range
MAOIs	Monoamine oxidase inhibitors
MeSH	Medical Subject Headings
MHRA	Medicines and Healthcare Products Regulatory Agency
MOR	Median odds ratio
NHS	National Health service
NHS RECs	NHS Research Ethics Committees
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NGT	Nominal group technique
NPSA	National Patient Safety Agency
NSAIDs	Non-steroidal anti-inflammatory drugs
OCD	Obsessive-compulsive disorder
OR	Odds ratio
OTC	Over-the-counter
PCNs	Primary Care Networks
PDRM	Preventable drug-related morbidity
PIM	Potentially inappropriate medication
PINCER	Pharmacist-led information technology intervention for medication errors
POMH-UK	The Prescribing Observatory for Mental Health

PTSD	Post-traumatic stress disorder
QIPs	Quality Improvement Projects
QOF	The Quality and Outcomes Framework
RAM	RAND/UCLA appropriateness method
RCGP	Royal College of General Practitioners
SD	Standard deviation
SLWG	Short Life Working Group
SMASH	Pharmacist-led safety medication dashboard
SMI	Severe mental illness
SSRIs	Selective serotonin reuptake inhibitors
START	Screening tool to alert to right treatment
STOPP	Screening tool of older people's prescriptions
TCAs	Tricyclic antidepressants
UK	United Kingdom
UREC	University research ethics committee
US	United States
WHO	World Health Organization
YLDs	Years lived with disability

Abstract

Background: Measuring the safety of prescribing is vital to understanding and improving patient care. As a result, several sets of prescribing safety indicators have been developed for use across primary and secondary care settings. Despite the fact that prescribing errors and medication related harm may be common in patients with mental illness, there has been limited research focusing on the development and application of prescribing safety indicators specifically for this vulnerable population. Also, while most patients with mental illness are managed entirely in primary care, there is a lack of data exploring potential prescribing safety issues in this setting for this population.

Aim: The aim of this PhD is to assess the safety of prescribing for people with mental illness through the development and implementation of a suite of prescribing safety indicators related to mental health conditions and medications, and to use the findings to set an agenda for future research, policy and practice to support safety improvement efforts.

Methodology: The prescribing safety indicators development process first involved a comprehensive systematic review to identify potential indicators from existing studies. This was followed by a two-stage e-Delphi consensus building study with a panel of 31 mental health experts from across the UK who rated their agreement with the potential indicators identified by the systematic review, suggested new indicators and rated the likelihood of occurrence and the severity of the most likely outcome of each indicator. Finally, high risk prescribing safety indicators relevant to primary health care were selected, operationalised and applied to the Clinical Practice Research Datalink (CPRD) GOLD. 361 general practices with over 3 million patients were included in a cross-sectional analysis up to September 2019 to examine the prevalence of, variations in, and risk factors for the indicators. In addition, 323 general practices with 4.5 million patients were included in a longitudinal analysis between 2009 and 2019 to examine the change in indicator prevalence over time. To examine variation in indicator rates between practices the intraclass correlation coefficient (ICC) and median odds ratio (MOR) were estimated using two-level logistic regression models. The relationship between patient and practice characteristics and the risk of triggering two composite indicators were assessed using odds ratio derived from multilevel logistic regression models. $\chi 2$ tests were used to examine the change in indicators prevalence over time.

Findings: A total of 1386 mental health indicators were identified from 70 studies in the systematic review. After refinement, 101 potential prescribing safety indicators were sent to the e-Delphi expert panel, where 42 prescribing safety indicators were considered to be high or extreme risk for patient care. These indicators covered a broad range of prescribing and medication monitoring problems as well as different mental health related drug classes. Of these, 18 potentially hazardous prescribing and 4 inadequate medication monitoring indicators were operationalised and applied to the CRPD. A total of 9.4% of patients at risk (151,469 out of 1,611,129) received at least one potentially hazardous prescription in the third quarter of 2019, and between practices this varied from 3.2% to 24.1% (ICC 0.03, MOR 1.22). A total of 90.2% of patients at risk (38,671 out of 42,879) were exposed to at least one inadequate medication monitoring episode in the same quarter, with between practice variation of 33.3% to 100% (ICC 0.27, MOR 2.84). Patients aged 35-44, females, those receiving more than 10 repeat prescriptions and those living in the most deprived areas were at greatest risk of triggering a prescribing indicator. Patients aged less than 25, females and those with one or no repeat prescriptions were at greatest risk of triggering a monitoring indicator. Of the 22 indicators, 9 showed significant increase in prevalence over the study period, 9 showed significant reductions and 4 showed no difference.

Conclusion: This programme of research has successfully assessed the safety of prescribing for people with mental illness through the development and implementation of the first suite of mental health specific prescribing safety indicators. It has found that potentially hazardous prescribing and inadequate medication monitoring commonly affect people with mental illness in primary care, and the proportion of patients triggering some indicators have been increasing over time with marked variation between practices. This thesis has identified several recommendations to support the development of safety improvement efforts that align with current national priorities.

Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

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Dedication

*To my beloved wife, **Nermeen**, for her unconditional love, friendship, unwavering support, patience, sacrifice, continued encouragement and for getting me through the challenging times, without which, I most certainly would not have completed this thesis.*

*To my son, **Ahmed**, who was born during the completion of this work. Thank you for the laughs, hugs and kisses that I needed to continue on this journey.*

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The Author

Wael Y. Khawagi graduated from Taif University in 2013 with a Doctor of Pharmacy (Pharm.D.) degree. During his studies he was given the opportunity to research medication-related problems in internal medicine patients which sparked his interest in medication safety. Afterwards, Wael worked as a teaching assistant at the Department of Clinical Pharmacy, Taif University, where he was awarded a scholarship to pursue a Master of Science (MSc) and a Doctor of Philosophy (PhD) degrees in Pharmacy Practice.

Wael completed an MSc degree with distinction in Advancing clinical pharmacy practice with extended placement at the University of Hertfordshire in 2017, where he also worked on a medication safety project for patient on anticoagulants and completed his extended clinical placement in Bedford Hospital NHS Trust. Wael subsequently started his PhD studies at the University of Manchester in September 2017. His research focussed on assessing prescribing safety for people with mental disorders.

Dissemination of Research

Published journal articles

- **Khawagi, W. Y.,** Steinke, D., Carr, M., Wright, A., Ashcroft, D., Avery, A., & Keers, R. Evaluating the safety of mental health related prescribing in UK primary care: a cross-sectional study using the Clinical Practice Research Datalink (CPRD). BMJ Quality and Safety (Epub ahead of print) http://dx.doi.org/10.1136/bmjqs-2021-013427 **(Chapter 6)**

- **Khawagi, W. Y.**, Steinke, D. T., Nguyen, J., Pontefract, S., & Keers, R. N. (2020). Development of prescribing safety indicators related to mental health disorders and medications: modified e-Delphi study. British Journal of Clinical Pharmacology. https://doi.org/10.1111/bcp.14391 **(Chapter 5)**

- **Khawagi WY**, Steinke DT, Nguyen J, Keers RN (2019) Identifying potential prescribing safety indicators related to mental health disorders and medications: A systematic review. PLoS ONE 14(5): e0217406. https://doi.org/10.1371/journal.pone.0217406 **(Chapter 4)**

Published Conference abstracts

- **Khawagi, W. Y.,** Steinke, D., Carr, M., Wright, A., Ashcroft, D., Avery, A., & Keers, R. (2021) Measuring mental health prescribing safety indicators in UK primary care. Pharmacoepidemiology and Drug Safety, 30(S1): 117-118. https://doi.org/10.1002/pds.5305 **(Chapter 6)**

- **Khawagi, W. Y.**, Steinke, D., Pontefract, S., & Keers, R. N. (2020). Development of indicators to assess the safety of prescribing for populations with mental illness using a modified Delphi approach. Pharmacoepidemiology and Drug Safety*, 29*(S2), 12-12. https://doi.org/10.1002/pds.4977 **(Chapter 5)**

- **Khawagi, W.**, Steinke, D., Nguyen, J., & Keers, R. (2019). Identifying indicators of potentially hazardous prescribing related to mental health disorders and medications: A systematic review. Pharmacoepidemiology and Drug Safety (Vol. 28, pp. 5). https://doi.org/10.1002/pds.4732 **(Chapter 4)**

Oral presentations

- **Khawagi, W. Y.,** Steinke, D., Carr, M., Wright, A., Ashcroft, D., Nguyen, J., Pontefract, S., Avery, A., & Keers, R. Developing and implementing mental health prescribing safety indicators using a mixed-method approach. 11th CMHP Annual Conference, (Manchester, UK); 8-9 October 2021 **(Chapter 4, 5 and 6)**

- **Khawagi, W. Y.,** Steinke, D., Carr, M., Wright, A., Ashcroft, D., Avery, A., & Keers, R. Measuring mental health prescribing safety indicators in UK primary care. ICPE 2021, (Virtual); 23-25 August 2021 **(Chapter 6)**

- **Khawagi, W. Y.,** Steinke, D., Carr, M., Wright, A., Ashcroft, D., Avery, A., & Keers, R. Potentially hazardous prescribing and inadequate medication monitoring related to mental health in UK primary care. HSRUK 2021, (Virtual); 6-8 July 2021 **(Chapter 6)**

- **Khawagi, W. Y.,** Steinke, D., Pontefract, S., & Keers, R. Using an eDelphi consensus technique to develop mental health related indicators to assess prescribing safety. EuroDURG 2020 Conference, (Szeged, Hungary); 4-7 March 2020 **(Chapter 5)**

Poster presentations

- **Khawagi, W. Y.,** Steinke, D., Pontefract, S., & Keers, R. Development of indicators to assess the safety of prescribing for populations with mental illness using a modified Delphi approach. PRIMM 31st Annual Scientific Meeting "Medication Without Harm - WHO is Responsible?", (Manchester, UK); 17 January 2020 **(Chapter 5)**

- **Khawagi, W**., Steinke, D., Nguyen, J., & Keers, R. Identifying mental health related potentially hazardous prescribing indicators: a systematic review. 8th Clinical Pharmacy Congress, (London, UK); 7-8 June 2019 **(Chapter 4)**

- **Khawagi, W.,** Steinke, D., Nguyen, J., & Keers, R. Identifying indicators of potentially hazardous prescribing related to mental health disorders and medications: a systematic review. PRIMM 30th Annual Scientific Meeting "Person-Centred Care in the Digital Age: Nudge Nudge, Tweet Tweet", (London, UK); 14 December 2018 **(Chapter 4)**

Achievements

- Runner up for the College of Mental Health Pharmacy Practice Oral Presentation Prize at the 11th Annual International Psychiatric Pharmacy Conference of College of Mental Health Pharmacy that was held on 8-9 October 2021.
- Second place Award for Poster Presentation at the Division of Pharmacy and Optometry Postgraduate Research Showcase that was held on 22 January 2020.

Chapter 1 : Introduction

This chapter provides an introduction to the programme of research and outlines the thesis structure.

1.1 Overview

Mental disorders are one of the largest contributors toward the global burden of disease,[1] and affect approximately 1 in 5 adults within a given 12 month period and about 1 in 3 at some point in their lives.[2] However, the quality of care provided to some patients with mental illness compared to those with physical health illnesses has been found to be inferior, and their care needs may often remain unmet [3], including the management of comorbid physical conditions.[4] In addition, evidence has consistently indicated that patients with mental illness have increased prevalence of physical illness and reduced life expectancy compared to the general population.[5-11] This led the United Kingdom (UK) government in 2011 to publish a mental health strategy to improve the overall mental health of these individuals and the wider population.[12] One of the main objectives of this policy was that fewer people suffer from avoidable harm originating from their care. This strategy also highlighted the importance of developing quality indicators to measure progress and improvement for mental health patients, including those relating to treatment such as prescribed medications.[12]

Medications are the most frequently used type of treatment for mental disorders [13] and there has been substantial growth in the proportion of individuals worldwide using medications for mental illness.[14-17] In view of the considerable impact of mental disorders on the affected individuals,[18] their families, the community and the economy,[12] encouraging rational and safe prescribing of psychotropic medications is of major significance to support optimal treatment outcomes. However, there are various challenges when prescribing for patients with mental disorders.[19] Examples of these challenges include the risk of adverse reactions associated with psychotropic medications,[20] a high prevalence of psychotropic polypharmacy,[21,22] unlicensed psychotropic prescribing [23,24] and the use of high-risk psychotropic medication,[20] coupled with the high prevalence of physical co-morbidity and associated polypharmacy in people with mental disorders which increases the risk of drug interactions with non-psychotropic medications.[7] Consequently, research

evidence suggests that prescribing errors, inappropriate prescribing and preventable medication-related harm are common in this population.[25-27]

Effective measurement is vital to facilitate improvements in the quality and safety of healthcare services provided to those with mental disorders. Indicators have been used widely to assess the quality of healthcare services, including prescribing. However, many prescribing indicators focus on the effectiveness of prescribing and not safety, which is important to address given the known risks prescribing can pose to patient safety.[28] Indicators that measure unsafe prescribing are known as prescribing safety indicators; these are statements describing potentially hazardous prescribing and inadequate medication monitoring practices that may put the patient at increased risk of harm.[29] Even though these prescribing practices are not considered good practice and should generally be avoided, not all of them may necessarily be errors, and they may require judgement from the patient and clinical team.[30] Prescribing safety indicators offer an opportunity to assess and improve prescribing safety by identifying patients at risk of adverse drug reactions to prompt further investigations before actual harm occurs.[31] Prescribing safety indicators have been used to estimate the level of variation in prescribing safety between practices [32], to observe change after interventions [33], and to develop clinical decision support (CDS) alerts in computerized provider order entry (CPOE).[34,35] Prescribing safety indicators are also being used for benchmarking at practice level as with the National Therapeutic Indicators in Scotland, the National Prescribing Indicators in Wales, and the Quality and Outcomes Framework (QOF) in all UK nations.[36-38]

In 2017, the World Health Organisation (WHO) launched their third Global Patient Safety Challenge "*Medication Without Harm"*, which aims to reduce the global burden of severe and avoidable medication-related harm by 50% over five years.[39] The potential for prescribing safety indicators to be used as part of different approaches designed to reduce medication related harm has led to growing interest in their use. In the UK and the United States (US), suites of prescribing safety indicators are being used as part of several multi-faceted interventions allowing for real time feedback on prescribing safety in primary care to identify patients who are currently at risk of preventable drug related harm.[33,39-46] Prescribing safety indicators have also been used for the development of pharmacist-led information technology intervention for medication errors (PINCER) [47] which is currently being rolled out nationally across England to electronically search clinical records to identify patients at risk of hazardous prescribing and to act accordingly.[48] This programme is projected to reduce medication-related harm, hospital admissions and associated costs to the National Health Service (NHS).[49] Accordingly, the UK Department of Health and

Social Care highlighted the need to develop comprehensive suites of indicators that involve other types of medicines associated with high risk of harm.[50,51]

However, whilst numerous sets of prescribing safety indicators have been developed for different populations and settings, mental health illnesses and the medications used to treat them have received little attention in this regard, with a limited number of mental health specific indicators and a limited coverage of breadth of psychotropic medications and their risks in existing suites applied currently in practice.[52,53] Without such indicators, it would be difficult to truly assess and improve the safety of prescribing for people with mental illness.

1.2 Thesis structure

The **first chapter** presents an introduction and an overview of the thesis layout.

The **second chapter** reviews the nature and impact of mental illness in healthcare and society, and explores the current issues relating to the use of medications to treat mental illness and the organisation and delivery of mental health services. It also reviews the quality and safety of healthcare and the broader differences between them, with a focus on medication safety. The argument is made for the need to focus on prescribing safety for those with mental disorders. The chapter also reviews the measurement of health care quality and safety by exploring quality and safety indicators, their significance, development and use in mental health with a focus on prescribing safety indicators.

The **third chapter** describes the rationale and the overall aim and objectives of this programme of work.

The **fourth chapter** presents the first study, which describes a systematic review that was conducted to identify potential mental health related prescribing safety indicators from existing prescribing assessment tools.

The **fifth chapter** presents the second study, which was a consensus-based study with experts using the e-Delphi method to develop a suite of prescribing safety indicators related to mental illness and medications and also to assess the risk of harm associated with each of the developed indicators.

The **sixth chapter** presents the third and final study, which was a retrospective population-based cross-sectional and longitudinal study using the Clinical Practice Research Datalink (CPRD). This study explored the prevalence, variation between practices, change over time

and risk factors for triggering specific mental health related prescribing safety indicators identified in Chapter 5.

The **seventh and final chapter** concludes the thesis by discussing the findings from the overall programme of research in relation to the aims of the thesis and in the context of the wider literature. This chapter summarises the key findings and highlights the strengths and limitations of the programme. This chapter also discusses the implications of the thesis findings for policy and practice and recommends areas for further research to improve prescribing safety.

Chapter 2 : Background

This chapter reviews the nature and impact of mental disorders in healthcare and society, and explores the current issues relating to the use of medications in the treatment of mental disorders and the structure of mental health services. The chapter also provides an overview of the quality and safety of healthcare with a focus on medication safety in mental health, and discusses the measurement of health care quality and safety by reviewing quality and safety indicators, their significance, development and use in mental health with a focus on prescribing safety indicators.

2.1 Mental disorders

Mental disorders, i.e. mental illnesses, include different conditions, with different characteristics. They are usually characterised by abnormal thoughts, perceptions, emotions and behaviours, which can have a major impact on the patients' life and make it difficult for some to cope with work, relationships and other daily activities.[54] There are two major classification systems for mental disorders, the WHO's International Classification of Diseases (ICD-11) Chapter 6: Mental, behavioural or neurodevelopmental disorders and the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-5).[55,56] Mental disorders include: [54-56]

- Anxiety disorders, such as generalised anxiety disorder (GAD),
- Mood disorders, such as depression and bipolar disorder,
- Psychotic disorders, such as schizophrenia and other psychoses,
- Personality disorders, such as borderline personality disorder (BPD),
- Sleep disorders, such as insomnia,
- Cognitive disorders, such as dementia and delirium, and
- Neurodevelopmental disorders, such as attention-deficit hyperactivity disorder, autism spectrum disorders, learning disabilities, and intellectual disability.

2.1.1 Significance

Mental illness is a major concern worldwide, and one of the main causes of overall mortality and disability. A review identified mental illness as one of the largest contributors toward the global burden of disease (GBD), being responsible for 21% of years lived with

disability (YLDs).[1] Furthermore, it has been argued that this is an underestimation, and the actual burden is estimated to be 32.4% YLDs.[18] In the UK, 23% of the total burden of disease is caused by mental illness and is considered the largest single cause of disability.[12,57] The GBD Collaborative Network data showed that in 2016, the prevalence of mental illness and YLDs caused by them were more than two and four times higher than cardiovascular disease (CVD), respectively.[58] Depression alone is the leading cause of YLDs in 56 countries, and the second in another 56 countries.[1] It is also estimated that over a third of the population in Europe suffers at least one mental health condition each year.[59] Unsurprisingly, with the high prevalence of mental disorders there is an enormous associated financial burden. It is reported that mental health disorders are the leading source of world economic burden, with an estimated global cost of £1.6 trillion, which is more than CVD, chronic respiratory disease, cancer, or diabetes.[60] It is also estimated that in England alone mental disorders costs £105.2 billion every year.[61] The cost of mental illness can be attributed to health and social care costs, lost productivity, and quality of life.[60]

2.1.2 Health concerns in those with mental illness

2.1.2.1 Inequalities and disparities

Mental illness is associated with many forms of inequalities. A report published by the Mental Health Task force to NHS England in 2016 indicated that 75% of patients with mental illness did not receive any form of care.[62] The report also found that of the few patients who received help, many did not receive the recommended care, including appropriately prescribed medications. As half of all mental health disorders are recognised by the age of 14, and 75% by the age of 24, this results in approximately 1 in 10 children having diagnosable mental disorders and yet the majority do not receive treatment or support for their conditions.[62] Concerns with the quality of mental health care are global and not limited to the UK, with the WHO in its 2013-2020 action plan stating that up to 85% of people with severe mental disorders received no treatment for their conditions in low and middle-income countries, with a figure of up to 50% in high-income countries. The quality of care was also found to be poor for patients who did receive treatment.[63]

People who suffer with mental illnesses can also experience a negative effect on their physical health, which may in part be caused by the care inequalities that they encounter, along with medications and health behaviours. It is reported that around 46% of people with mental illness have a long-term physical health condition. Similarly, physical health

disorders may lead to an increased risk of developing mental illness. About 30% of patients with a long-term physical condition have a mental illness.[7]

People with mental illness could also have shorter life expectancy; it is reported that patients who have visited specialist mental health services have a mortality rate 3.6 times higher than the general population,[5] and patients with severe mental illnesses (SMI) have a reduction in life expectancy of 10 to 20 years.[6] The majority of premature deaths in the SMI population are reported to be caused by physical diseases and suicide, and in particular CVD, which is shown to be linked with the use of antipsychotic medications.[8] Patients with SMI, compared to the general population, tend to have poorer physical health and higher rates of CVD, diabetes, infectious diseases, respiratory disease and cancer.[9,10] More common mental disorders such as depression have also been associated with 67% and 50% increased risk of death from heart disease and cancer, respectively.[11]

One of the factors that may contribute to these physical problems are health behaviours.[10,64] Patients with mental disorders have a significantly higher prevalence of smoking [65], heavy alcohol use [66], poor dietary intake and lack of physical activity compared to the general population.[64] Another factor that may contribute to poor physical health is that these patients tend to receive poorer quality physical health services and access the required physical health assessments less frequently,[62,64] as will be discussed in section 2.1.2.2. An example of these inequalities is monitoring physical health of patients prescribed antipsychotic medications, where a review stated that none of the UK and US recommendations were adequately implemented.[67] Indeed, a US based study published in 2009 reported that lipid and glucose monitoring was still low in those prescribed second-generation antipsychotics, 12-week monitoring rates were only 9.0% for lipids and 17.9% for glucose, despite nationally recognised guidelines being in place.[68]

Patients with mental illness also suffer from strong social stigma, which can have an adverse effect on several aspects of their daily lives [69], as well as on their clinical outcomes [70] by delaying seeking healthcare and reducing adherence to medications. A survey of 3,038 patients with mental illness and 661 carers in the UK published in 2008 showed that 87% of respondents experienced some form of stigma which had a negative effect on their lives.[69]

There has also been association between poverty and mental health, where it has been reported that people living in poverty are significantly more likely to develop mental illness.[71] In addition, a UK based observational cohort study in 2015, described that in

England, those from more deprived areas are less likely to be prescribed anti-dementia medications.[72]

2.1.2.2 The use of mental health services

The structure of mental health services in the UK is complex, with services categorised into three broad categories, primary care, specialist community-based mental health services, and inpatient mental health. Primary care which includes general practices is the first point of contact in the healthcare structure. Patients are expected to use primary care services if they experience mild or moderate illness.[73,74] Specialist community-based mental health services may then be for some the next level of care in the health system (though some may be admitted directly to hospital). These community services cover adult and older adult community mental health teams, mental health crisis services, and specialist children and young people's mental health services (CYPMHS) community teams, among others.[75-77] Inpatient mental health includes mental health hospitals, inpatient psychiatric wards in general hospitals and inpatient CYPMHS.[77]

Against a background of significant health challenges and inequalities for those with mental illness, the use of specialist mental health services by the UK population has been increasing steadily over time.[77] In 2016/2017, more than 2.6 million people, an estimated increase of 10% from the previous year, contacted secondary mental health, learning disability and autism services in England.[78] In addition, the number of detentions per annum under the Mental Health Act increased by 26% from 2012/13 to 2015/16.[77] This increase in demand coupled with efficiency savings, bed shortages and staff shortages has put mental health services under pressure.[79,80]

This pressure can affect the safety and quality of the provided care.[79] Findings from England's Care Quality Commission (CQC) indicated in 2017 that approximately 40% of mental health services in England were rated as inadequate or required improvement in terms of safety.[77] In addition, surveys have indicated that the number of patients reporting a poor experience of community mental health services in England has increased from 2% in 2013 to 3.3% in 2017.[81] There has also been media coverage in recent years about the poor quality of care provided to patients with mental illness and its impact, including bed shortages, waiting for months or years to receive treatment for mental and physical health care, and the deficiencies in mental health services compared to other sectors.[82-87]

Mental health in primary care

Primary care for mental health was defined by the WHO as:

> *"first line interventions that are provided as an integral part of general health care and are provided by primary care workers who are skilled, able and supported to provide mental health care services".*[88]

Pressure on specialised mental health services has placed emphasis on the support for mental illness within primary care. Consequently, 90% of adults with mental illness are managed entirely in primary care, including people with high levels of need and complexity, including patients with psychosis, bipolar disorder and personality disorders.[62,89,90] In addition, most patients with mental illness in England do not have contact with specialist mental health services.[91] General practitioners (GPs) report that around 40% of their consultations are related to mental health[92] and local areas have introduced a wide range of initiatives in primary care to meeting patient's needs, in part due to pressures on specialist services. As a consequence, mental health care provided in primary care might be influenced by the local area and the services they provide.[89,91]

However, there has been some concern about whether GPs are adequately equipped with the capabilities to support the increasing demand of people with mental illness.[93] There is evidence that patients who need mental health support in primary care may experience poor quality of care affecting both their physical and mental health care needs.[62,89] Evidence suggests GPs may not always feel capable of managing patients with mental illness and making alterations to an established treatment.[89] A research study showed that less than half of GP trainees in England and Wales undertook a training placement in a mental health setting between 2013 and 2015.[94] In addition, the increasing demand for primary care services in the UK, which is expected to grow, can have impact on the quality of care provided including mental health care.[62,73]

Mental health care and the COVID-19 pandemic

The COVID-19 pandemic has had great impact for population mental health globally.[95,96] In England, it is estimated that up to 10 million people will require new or additional mental health support as a result of the pandemic, which is equivalent to 20% of the population.[97] It has also been suggested that even after the pandemic begins to fade, the subsequent economic crisis will have an effect on the mental health of the general population.[98]

COVID-19 has also affected children's mental health and increased the burden on mental health services. It has been estimated that 1.5 million children will require new or additional support for mental disorders, which is about 15% of children aged 5-19.[97] A report from the UK Children's Commissioner also indicated that there is robust evidence that COVID-19 has had a major implication on children's mental health. It has been shown that children's referrals to mental health services were 72% higher in September 2020 than September 2019, but the access to those services was inadequate.[99] Another report by NHS England also stated that the rate of children with mental disorders has risen from 10.8% in 2017 to 16.0% during the first lockdown in 2020.[100,101]

However, despite the evidence of increased mental health burden due to the COVID-19 pandemic, several studies reported substantial reductions in accessing primary care mental health services in the UK since the start of the pandemic.[102-104] A rapid assessment by the WHO reported that mental health services have been substantially disrupted in 93% of countries across the globe.[105] These disruptions could potentially lead to increases in severity of mental illness, and rises in demand, which may lead to increased pressure and potentially reduced quality of care. Primary care is now at the forefront of the expected increase in mental health presentations.[106]

2.1.2.3 The use of mental health medication

Medications are a vital tool used in the treatment of mental illness and can be otherwise known as 'psychotropics'. Perhaps reflecting the increase in service access by patients described earlier, the proportion of individuals worldwide using medications for mental illness has also grown.[14-17] In England between 2006 to 2016 the number of dispensed psychiatric medication items in the community almost doubled, with nearly 100 million items dispensed in 2016.[17] This group includes antidepressants, antipsychotics, sedative, hypnotics and anxiolytics, mood stabilisers, anti-dementia medications and ADHD medications.[107] Table 2.1 summarises the major classes of psychotropic medications that were used throughout the thesis. As with all licenced medications, psychotropics have numerous adverse effects and there are some considered to be 'high risk' medicines with narrow therapeutic indexes, which means there is a small margin between the therapeutic and toxic dose. The nature of psychotropic medications, coupled with the complexity of healthcare (i.e. ageing population with comorbidities, more treatment options and more patients), places them at an increased risk of being associated with deficiencies in their use, in terms of both quality and safety.

Table 2.1: Classes of psychotropic medications

Class	Sub-class
Antidepressants	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), norepinephrine reuptake inhibitors (NRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs) and atypical antidepressants.
Antipsychotics	Typical and atypical antipsychotics
Sedative, Hypnotics and Anxiolytics	Benzodiazepines, Z-drug hypnotics, barbiturates, 1st generation antihistamines, and Others such as melatonin.
Mood stabilisers	Lithium and anticonvulsants such as valproate, carbamazepine and lamotrigine.
Dementia medications	Memantine and acetylcholinesterase inhibitors such as donepezil, rivastigmine and galantamine.
ADHD medications	Stimulants such as methylphenidate, dexamfetamine and lisdexamfetamine, and non-stimulants such as atomoxetine, clonidine and guanfacine.

Antidepressants

The prescribing of antidepressants has increased dramatically in the last decade. In 2016, there were more than 64 million antidepressant items dispensed in England, more than double the figure from 2006.[108] In the US, between 2009/2010 and 2017/2018, antidepressant use among adults aged 18 and over increased from 10.6% to 13.8%.[109]

A systematic review and network meta-analysis of 522 trials including 116,477 patients reported that all antidepressants were more effective than placebo in adults with major depressive disorder.[110] The use of antidepressants for adults is recommended in the National Institute for Health and Care Excellence (NICE) depression guideline for moderate and severe depression, and to be considered for mild depression if the patient has a history of moderate or severe depression, the symptoms have been present for more than 2 years, or if there is an inadequate response to other interventions.[111] For children aged 12-18 the use of antidepressants should be considered only for moderate to severe depression.[112] They are also used for generalised anxiety disorder.[113] Antidepressants include selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs).

With regards to the safety of antidepressants, these medications are linked with suicidal behaviour in younger populations,[114] serotonin syndrome,[113] hip fracture in the elderly,[115,116]

hyponatraemia,[117] sexual dysfunction,[118] and bleeding.[119] In addition, the Medicines and Healthcare products Regulatory Agency (MHRA) [120] published an alert concerning the use of the SSRIs citalopram and escitalopram and the risk of QT prolongation of the heart's electrical conductivity cycle, which has been associated with a high risk of sudden cardiac death.[121] In 1999, researchers from the US have also found a significant association between antidepressant use and preventable adverse events among hospitalised patients when they performed a cohort study to identify potential risk factors for adverse drug events.[122]

Antipsychotics

These agents include typical (i.e. first generation) and atypical (i.e. second generation) antipsychotics. Antipsychotics are mainly used for psychosis, schizophrenia and bipolar disorder.[113] According to the Maudsley prescribing guidelines antipsychotics are effective in acute and maintenance treatment of schizophrenia and other psychotic illnesses.[20] Two network meta-analyses reported that all antipsychotics were more effective than placebo in schizophrenia.[123,124]

However, these medications are associated with several physical health problems, such as obesity, QT prolongation, impaired glucose tolerance and dyslipidaemia. These adverse effects are thought to be responsible for links between the use of antipsychotics and CVD, diabetes [125], venous thromboembolism [126] and sudden cardiac death.[125] Additionally, as mentioned earlier, the use of antipsychotics was associated with premature death and shortened life expectancy in those with SMI as a result of CVD.[8] Therefore, physical health monitoring is vital for patients taking antipsychotics.[20,127]

It has also been reported that using higher doses of antipsychotics is associated with a higher risk of mortality from coronary heart disease and stroke [128] and that the majority of antipsychotic adverse effects are dose related.[129] High dose antipsychotic can be described as using a dose higher than recommended in manufacturer/national specifications, either for a single medication or for a cumulative high dose of more than one.[130] The use of high dose antipsychotics is also associated with the use of antipsychotic depots/long-acting injections in addition to oral antipsychotics and the use of regular antipsychotics along with as required (PRN) antipsychotics.[20] Despite prevalent use of high dose/combination antipsychotics as reported by one UK study in 2012 where 28% of 5079 hospitalised patients were affected,[129] this practice is not currently recommended in relevant guidelines.[20,127]

Another issue regarding antipsychotics is the use of clozapine. While effective in reducing mortality in schizophrenia it is a 'high risk' medication, which can cause serious, life-threatening adverse effects, such as agranulocytosis, thromboembolism myocarditis, cardiomyopathy, intestinal obstruction, faecal impaction, and paralytic ileus. Consequently, careful monitoring is fundamental during clozapine treatment.[20,131,132] In addition, clozapine was found to metabolise faster with smoking, and therefore, smoking cessation can cause a rise in clozapine blood levels.[133]

The use of antipsychotics is not recommended for people with dementia because of the serious adverse effects that may occur. Yet, it is estimated that around 180,000 people with dementia are treated with antipsychotics per year in England. As a result of this use, it is estimated that 1,800 people die and another 1,620 suffer from cerebrovascular adverse events every year.[134] Similarly, another study showed that in the UK, a large proportion of antipsychotics prescriptions in primary care were prescribed for conditions not routinely recommended to be treated with these medications.[135]

Sedative, Hypnotics and Anxiolytics

This group includes benzodiazepines and the 'Z–drugs', zaleplon, zolpidem, and zopiclone. These medications are used as short-term measure for anxiety and insomnia, and they can also be used as adjuncts, in the treatment of depression and schizophrenia.[20] These medication are commonly prescribed, a study in Europe reported that around 10% of adults had taken a benzodiazepine in 12 months period.[136] It has been reported that 15–20% of the population in France are prescribed one of these medications, making them the most commonly used medications there.[137,138]

Hypnotics and anxiolytics can cause drowsiness, ataxia and confusion. Therefore, this group of medications may cause falls and/or injury especially in the elderly.[113] In addition, these medications can cause physical and psychological dependence.[139] Physical dependence occurs when the user experiences withdrawal symptoms such as confusion, psychosis and convulsions after stopping the medication. However, psychological dependence describes the users craving and emotional behaviour.[140] Hence, this group of medications is not recommended for long term use, particularly in the elderly, and must be withdrawn gradually to prevent withdrawal symptoms.[113] Despite these risks, a recent study showed that 12.1% of older people in Scotland were prescribed benzodiazepines and/or Z–drugs, and in care homes the percentage increases to 28.4% of residents.[141] In addition, a

study published in 2020 in Spain found 36% of patient over 65 years old were on benzodiazepines long-term.[142]

Mood stabilisers

This group includes several medications such as lithium, valproate, lamotrigine and carbamazepine. Lithium is a common treatment for bipolar disorder.[143] However, it has a narrow therapeutic index.[144] Consequently, many adverse effects of lithium can be minimised by monitoring lithium plasma levels and maintaining them within the recommended range.[145] An audit conducted in the UK in 2013 showed an improvement in lithium monitoring over time following a quality improvement programme. Yet, gaps still remained between the recommendations and current practice, even in those patients who were prescribed another medication (angiotensin-converting enzyme (ACE) inhibitors, diuretics, non-steroidal anti-inflammatory drugs (NSAIDs)) that increased the risk of lithium toxicity.[146] Adverse effects of lithium include hypothyroidism, weight gain, prolonged QT interval and renal failure.[144]

In regards to valproate, an alert was produced by the MHRA in 2015 which indicated that children exposed to valproate in utero are at high risk of serious developmental disorders and congenital malformations.[147] Therefore, valproate is now contraindicated in women or girls of childbearing potential unless they meet the conditions of a pregnancy prevention programme.[148]

Dementia medications

Dementia medications include memantine and acetylcholinesterase inhibitors, such as donepezil, rivastigmine and galantamine.[20,113] Acetylcholinesterase inhibitors are recommended for the treatment of mild to moderate severity dementia in Alzheimer's disease, memantine is recommended for moderate to severe dementia in Alzheimer's disease.[149] Rivastigmine is also used in the treatment of mild to moderate severity dementia associated with Parkinson's disease.[20] There are other medications such as statins and gingko biloba that have been used for dementia, but they are not recommended by the British Association for Psychopharmacology for lack of evidence of effectiveness.[150]

Memantine and acetylcholinesterase inhibitors are associated with potentially fatal cardiovascular adverse reactions such as bradycardia and syncope.[20] Due to cardiovascular adverse reactions the US Food and Drug Administration (FDA) issued a warning restricting galantamine use in patients with mild cognitive impairment.[151] In addition, electrocardiogram (ECG) monitoring is advised for patient at higher-risk of experiencing

the cardiovascular adverse reactions.[20] Memantine and acetylcholinesterase inhibitors can also cause neuropsychiatric adverse effects such as dizziness, insomnia and convulsions, and gastrointestinal adverse effects such as nausea, vomiting, and diarrhoea. The gastrointestinal symptoms are more common with the use of rivastigmine. However, slow titration can help reduce the symptoms.[20]

ADHD medications

ADHD medications are not recommended for children aged under 5 without specialist opinion from an ADHD service, and should only be offered for adults and children aged 5 and over if their symptoms are still causing a persistent significant impairment after non-pharmacological (psychological) interventions.[152] Methylphenidate is usually the first line when a medication is offered. Other ADHD medications include dexamfetamine, lisdexamfetamine, atomoxetine, clonidine and guanfacine.[20] These medications can cause hypertension, palpitation, weight loss and growth retardation in children. Therefore, children on these medications require their height, weight, blood pressure and heart rate to be carefully monitored. For adults, monitoring should include measurement of weight, blood pressure and heart rate.[20,113]

Overall psychotropic use

Overall, it is important to remark that each psychotropic medication in each class described above might have different adverse effects and safety profile than the others. Besides, some of the medications that treat the side effects of these psychotropics can in themselves cause serious side effects, such as the use of anticholinergic medications for treatment of extra-pyramidal side effects caused by antipsychotics which may be associated with constipation and cognitive impairment.[153] Thus, providing health care to patients with mental illness is a complex process and it is essential to tailor treatment to individual patients.

Another significant global issue with all types of psychotropic medications is nonadherence.[154] A recent systematic review and meta-analysis of 35 studies on psychotropic medication non-adherence, reported that 49% of patients with major psychiatric disorder were non-adherent to their psychotropic medication.[155] Moreover, it has been reported in the US that half of the outpatients who are prescribed an antidepressant for the first time stop their treatment within the first month.[156] Although nonadherence is a major problem throughout healthcare, there are potential aspects that make it particularly challenging in mental health care. These include a lack of insight into illness, the nature of the illness such as cognitive impairment, social isolation, substance

misuse, stigma, and the complexity of mental health services in many countries.[157] In addition, the consequences of non-adherence for patients with mental illness can be devastating and could result in violence, hospitalisation, suicide and premature mortality.[154] A study showed that adverse effects may be one of the main reasons for medication non-adherence in patients with mental illness.[158]

One of the factors that increases the risk of adverse effects in patients with mental illness is polypharmacy. A review article in 2013 reported that the prevalence of polypharmacy in mental health populations ranges from 13% to 90%, and is defined as using more than one psychiatric medication concurrently.[159] In the US, a study analysed office-based psychiatry practice data from 1996-2006, and reported that polypharmacy prescribing trends are increasing with antidepressant and antipsychotic medications.[160]

2.1.3 Mental health policy

The importance of mental health is reflected in the Constitution of the WHO, where health was defined as *"a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity"*.[161] However, people with mental illness are susceptible to several safety risks, such as self-harm, violence and aggression, falls and other risks from their care and treatment and as a result they are considered more vulnerable than the general population. Despite this, evidence indicates that mental health and physical health may not be valued equally, demonstrated by unequal treatment access, premature mortality and significant underfunding of mental healthcare and mental health research.[162] However, in recent years mental health has moved up the policy agenda in the UK and in many countries and it started to be given an equal priority in healthcare, which consequently strengthened the efforts to improve the quality and safety in mental health.[12,62,163,164] In 2008, UK guidance called "Seven steps to patient safety in mental health" was published to improve patient safety and quality of care in mental health settings. This report stressed the importance of monitoring progress toward safer care using safety indicators.[163]

The burden and impact of mental disorders on health care and society as a whole led the Department of Health in England in 2011 to publish a mental health strategy entitled "No Health without Mental Health", which was designed to improve the overall mental health of the individuals and the wider population.[12] The report set six objectives including improvement in the outcomes, physical health and experience of care of people with mental illness, and a reduction in avoidable harm and stigma. This strategy also highlighted

the importance of developing quality indicators to measure progress and improvement for mental health patients, including those relating to treatment such as prescribed medications.[12] As a results of this strategy, in 2012, the Health and Social Care Act created a new legal responsibility for the NHS to deliver 'parity of esteem' between physical and mental health, which means valuing them equally, such as equal access to effective and safe treatment and equal efforts to improve the quality of care.[162]

In 2016, The Five Year Forward View for Mental Health, a report from the independent Mental Health Taskforce to NHS England, was published. The report included multiple recommendations for improving outcomes for those with mental health illness.[62]

For over a decade, the WHO has called for the integration of mental health services into primary care.[88] In the UK, building on the Five Year Forward View for Mental Health, the NHS Long Term Plan in 2019 set out plans to create a new and integrated model of primary and community mental health care.[165] The new models will be built around Primary Care Networks, which were established in the Long Term Plan. The Primary Care Networks allows groups of practices in their local areas to work together with community, mental health, social care, pharmacy, hospital and voluntary services.[166] Subsequently, it is essential to assess the impact of these changes on the quality and safety of care provided to people with mental disorders. Indeed, a new mental health dashboard has been developed to measure the performance of mental health services across the NHS in delivering the Long Term Plan for mental health.[167] Figure 2.1 illustrates the more recent UK mental health policy timeline.

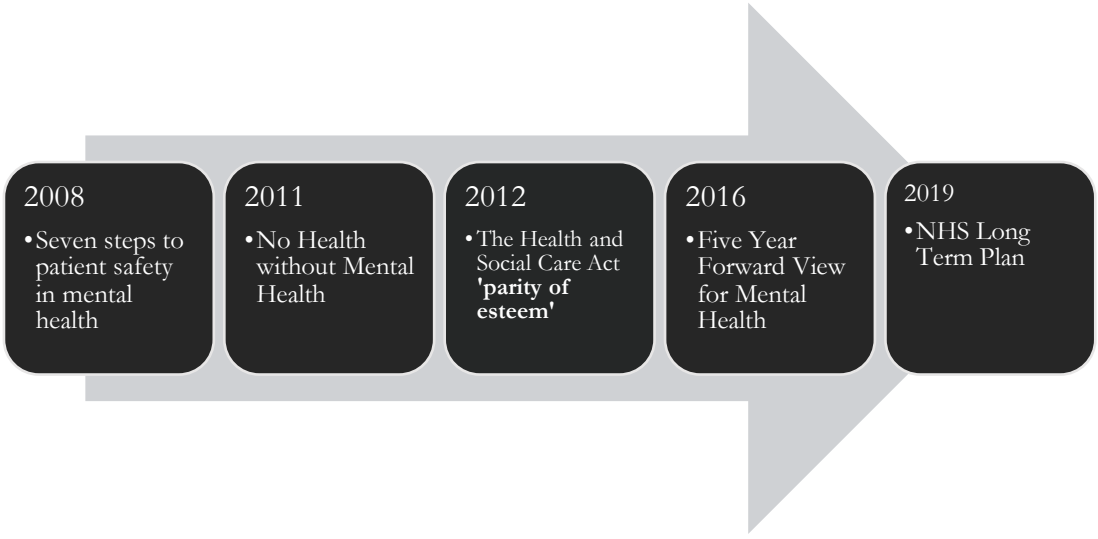

Figure 2.1: UK mental health policy timeline

2.2 Quality of care and patient safety

Section 2.1 reviewed the challenges that face mental health care and highlighted the importance of monitoring and assessing the quality and safety of healthcare services provided to patients with mental illness in order to ensure optimum care is delivered. However, before examining the measurement, this section will first provide an insight into the concepts of quality and safety of the health care in general, with a focus on medication safety in mental health.

Quality of care can be defined as:

> *"The degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge".*[168]

The UK Department of Health in 2008 indicated that quality in the NHS [169] should cover three main areas; patient safety, patient experience and clinical effectiveness.[170] In addition, the US Institute of Medicine stressed that quality of care must be safe, effective, patient centred, timely, efficient and equitable.[171] Therefore, quality can be described by many organisations as an umbrella term which contains different elements, and patient safety is one of them. Patient safety is concerned with the avoidance and minimisation of harm, which is defined as: *"The avoidance, prevention and amelioration of adverse outcomes or injuries stemming from the process of healthcare".*[172]

Patient safety is a crucial component of quality of care. However, sometimes, quality and safety are separated to highlight the difference between benefits and risk (e.g. harm).[173] An example of safety issue would be prescribing a potentially hazardous medication such as antipsychotics for elderly patients with dementia.[113] However, an example of quality issue that is not necessarily safety-related would be prescribing without following guideline recommendations, such as prescribing venlafaxine first-line for depression which is not recommended in current NICE guidelines.[174]

Healthcare advances have created more effective, yet more complex systems and mental health care is no differently affected than other care models. With the use of new technologies, a growing number of medicines and treatment options, along with an ageing population who often have multiple co-morbidities, more difficult and complex decisions may often need to be made about therapy.[175] Despite the Hippocratic Oath stating that physicians should '*do no harm*'; the complicated nature of healthcare indicates that harm

might occur. [176,177] Harm caused by health care is known as "*iatrogenic harm*". The publication of the 'To Err is Human' report in 1999 by the US Institute of Medicine showed the significance of patient safety and iatrogenic harm in the US where it was reported that between 44,000 and 98,000 patients died every year due to medical errors.[178] This publication was a catalyst for the evolution of patient safety movements worldwide and made patient safety a cornerstone of quality in healthcare. Similarly, in the UK the Department of Health published 'An Organisation with a Memory' in 2000 which estimated that more than 850,000 adverse events occurred in NHS hospitals each year, which is around 10% of admissions.[179]

A national patient safety incident report by NHS England [180] indicated that in 2019, more than 2.2 million patient safety incidents have been reported, and that medication incidents were the fourth most common type of reported incident with 228,083 events. This report also highlighted that in one year; more than 10,000 patient safety incidents caused severe harm or death. The report has also identified that more than 296,375 patient safety incidents originated from mental health services, with more than 3100 events causing severe harm or death and 21,571 medication incidents.[180]

A systematic review and meta-analysis of 149 studies of preventable harm across healthcare services published in 2019, showed that the most common type of preventable harm was medication-related.[181] Likewise in mental health, a US based study in 2018 analysed 9,780 safety reports in mental health units indicated that falls were the most commonly reported event, followed by medication events. One of the main factors contributing to patients' falls has been found to be medications.[182]

2.2.1 Medication safety

Medication is the most commonly used intervention in healthcare.[183] In England, it is reported that more than one billion prescription items are dispensed annually in primary care [184], and half a million inpatient prescriptions every year in an average hospital.[169] In addition, in 2015/2016, 48% of adults in England were in receipt of at least one prescribed medicine in the last week with 24% taking three or more.[185] Likewise, in the US, over 4 billion prescriptions had been dispensed in a year.[186] Medications are generally safe. However, they have the potential to cause harm, and with the large number of medicines prescribed by health services each year, even a small risk of harm could result in a large number of adverse events. Indeed, the use of medication is one of the most common causes of patient harm in healthcare internationally.[39]

2.2.1.1 Terminology

Several terms are defined in the literature to describe medication safety issues. 'Medication- or drug- related problems' is an umbrella term, which can be defined as an *"event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes"*.[187] Medication-related problems include medication errors, adverse drug events (ADEs) and adverse drug reactions (ADRs).[188]

Medication errors can be defined as

> *"any preventable event that may cause or lead to inappropriate medication use or patient harm, while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing, order communication, product labelling, packaging, and nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use".*[189]

Adverse drug events (ADEs), can be defined as "*an injury due to a medication*".[190] An ADE is not always preventable; if it was preventable then it would be considered a medication error.[190] If an ADE is non-preventable it can be called an adverse drug reaction (ADR), which can be defined as *"An injury due to a medication where there is no error in the medication process".*[190] Medication errors also include potential ADEs, which are errors that have high probability to cause harm, yet they did not. This could be because they are either intercepted "near misses", or they reached the patient but did not cause any harm.[191] Figure 2.2 shows the relationship between drug related problems, medication errors, potential, preventable and non-preventable ADEs, and ADRs.[192]

Medication-related problems could also include other terms such as inappropriate prescribing, potentially inappropriate prescribing and potentially hazardous prescribing, which describe prescriptions that significantly increases the risk of adverse drug reactions and therefore lead to medication-related problems.[193-195] These terms will be discussed in more details in section 2.2.1.4 and section 2.3.1 . Table 2.2 summaries the main medication safety terms and their definitions.

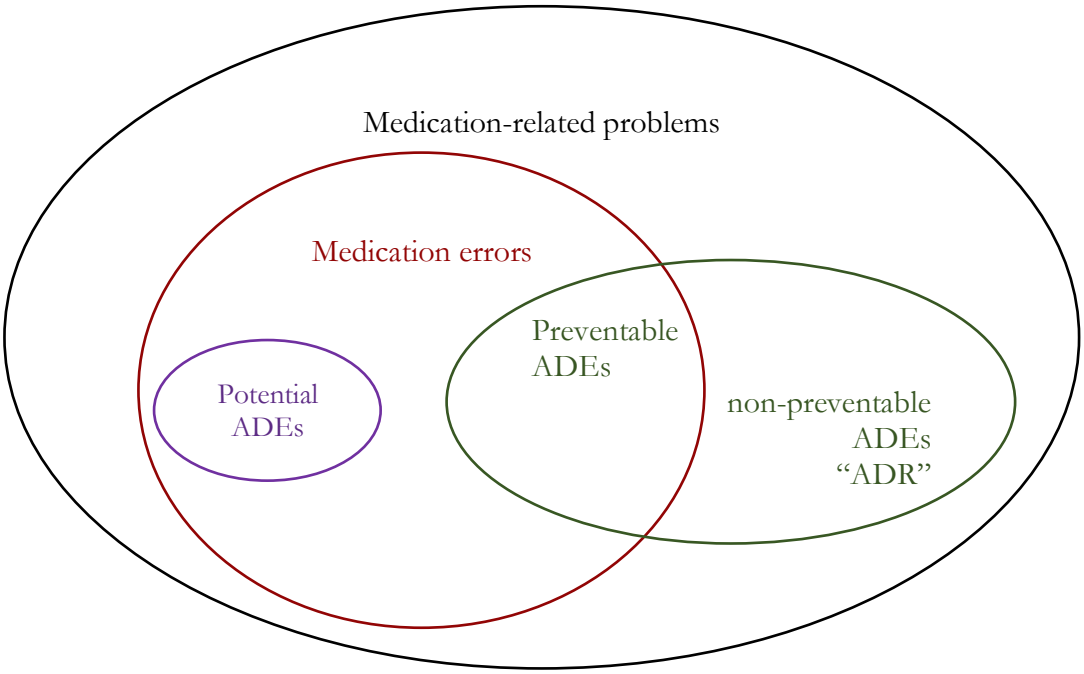

Figure 2.2: The relationship between drug related problems, medication errors, potential, preventable and non-preventable ADEs, and ADRs[192]

Adapted from Gandhi TK, Seder DL, Bates DW. Methodology matters. Identifying drug safety issues: from research to practice. *International Journal for Quality in Health Care.* 2000;12(1):69-76 with permission from Oxford University Press.

Table 2.2: Summary of the main medication safety terms and their definitions

Term	Definition
Medication-related problems	Any event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes.[187]
Medication Errors	Any preventable event that may cause or lead to inappropriate medication use or patient harm, while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing, order communication, product labelling, packaging, and nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use.[189]
Adverse drug events (ADEs)	Any injury due to a medication.[190]
Preventable adverse drug event	An injury due to a medication error.
Adverse drug reaction (ADRs) **Non-preventable adverse drug event**	An injury due to a medication where there is no error in the medication process.[190]
Inappropriate prescribing	Inappropriate prescribing includes:

	misprescribing, when the risk of adverse drug events outweighs the clinical benefits; **overprescribing**, when a medication is prescribed for no clear indication; and **underprescribing**, when potentially beneficial medications are not prescribed.[196] [197]

2.2.1.2 Impact of medication-related problems

Medication-related problems are associated with increased hospitalisation [198], significantly prolonged length of hospital stay, increased healthcare cost [199], and increased risk of death.[199,200] In the US in 2013/2014 it was found that 1 out of every 250 Americans went to an emergency department because of an ADE, and more than 25% of them required hospitalisation.[201] In addition, a systematic review of 25 prospective observational studies reported that 5.3% of hospital admissions were associated with ADRs.[202]

It is estimated that 237 million medication errors occur every year in the NHS in England. Of these, 68.3 million errors (28%) cause moderate or serious harm. Moreover, the estimated burden of definitely preventable ADEs was £98.5 million per year, causing 712 deaths and contributing as one of the factors to 1708 deaths.[203] The same report also estimated that 54.4% of medication errors occur at the administration stage, 28.2% at the prescribing and monitoring stage, 15.9% at the dispensing and 1.4% at the transition.[203] However, a systematic review of 29 studies stated that medication errors resulting in preventable ADEs occurred mostly in the prescribing and monitoring stages.[204] More recently, it was also found in a large scale meta-analysis of preventable patient harm across medical care settings that the highest proportion (60%) of preventable medication-related harm was caused in the prescribing and monitoring stages.[181,205]

2.2.1.3 Detection of medication-related problems

There are different approaches to detect medication errors, such as voluntary reports, incident reports, chart review, claims data and direct observation. Rates of errors may vary depending on the method used to detect them. Each method has its own advantages and disadvantages, and there is no ideal method to detect all types of medication errors. For instance, voluntary reports and incident reports underestimate the rates of errors. However, chart review and observations are time consuming and costly.[206] Additionally, one of the disadvantages of all of these methods is that they identify many errors that did not cause any harm.[35] Therefore, it is important to find ways to identify situations where

the risk of harm is more likely. Accordingly, other methods are used to detect ADEs as an alternative to traditional medical record review approaches, such as trigger tools. These tools include triggers such as the use of specific antidotes (e.g. the use of vitamin K or naloxone), the presence of critical laboratory values (e.g. high INR or digoxin level) or abrupt medication discontinuation.[207] However, this method requires retrospective analysis of medical charts after the triggers have occurred to confirm the presence of harm and if it is preventable (i.e. error).[206] Recently, safety indicators have been increasingly used to measure prescribing safety and examine the variation between health institutions using routinely collected data, such as the CPRD.[208-210] They are valuable and offer a convenient way in routinely identifying areas for improvement, provide feedback to health care professionals and monitor change over time, particularly with the expansion of e-prescribing system in mental health trsusts.[138,165] These indicators also offer an opportunity to improve prescribing safety by identifying patients at risk of adverse drug reactions to prompt further investigations before actual harm occurs.[31] In England, they are being rolled out nationally to electronically search primary care clinical records to identify patients at risk of hazardous prescribing.[48] Prescribing safety indicators will be discussed in more detail in section 2.3.1 .

2.2.1.4 The safe prescribing and monitoring of medicines

Prescribing is not an easy process; it is complex and challenging. Indeed, the preceding sections of this chapter highlighted it as one of the most high-risk stages in the medication use process.[211-213] Many factors need to be taken into consideration before prescribing. Therefore, achieving balanced prescribing, which was defined by Aronson as *"a process that recommends a medicine appropriate to the patient's condition and, within the limits created by the uncertainty that attends therapeutic decisions, a dosage regimen that optimizes the balance of benefit to harm"*[214] could be challenging.

In a retrospective case-note review of prescribing over a period of 12 months in 15 general practices in England, 4.9% of the reviewed prescriptions were found to contain prescribing and/or monitoring errors.[215] In addition, the previous section has identified prescribing as a stage associated with a high prevalence of errors and preventable ADEs. In addition, as emphasised by the 3rd WHO Global Patient Safety Challenge "Medication without harm", the safe prescribing and monitoring of medicines is a substantial component of healthcare.[39]

Prescribing errors definition state that:

> *"A clinically meaningful prescribing error occurs when, as a result of a prescribing decision or prescription writing process, there is an unintentional significant (1) reduction in the probability of treatment being timely and effective or (2) increase in the risk of harm when compared with generally accepted practice".*[216]

Therefore, prescribing errors might occur in each of the two main stages of prescribing: the decision making stage and the writing stage.[216] Errors at the writing stage can be known as prescription errors.[217] However, errors at the decision making stage can be known as inappropriate prescribing, irrational prescribing, prescribing faults and hazardous prescribing.[218] Figure 2.3 illustrate the stages of prescribing errors.

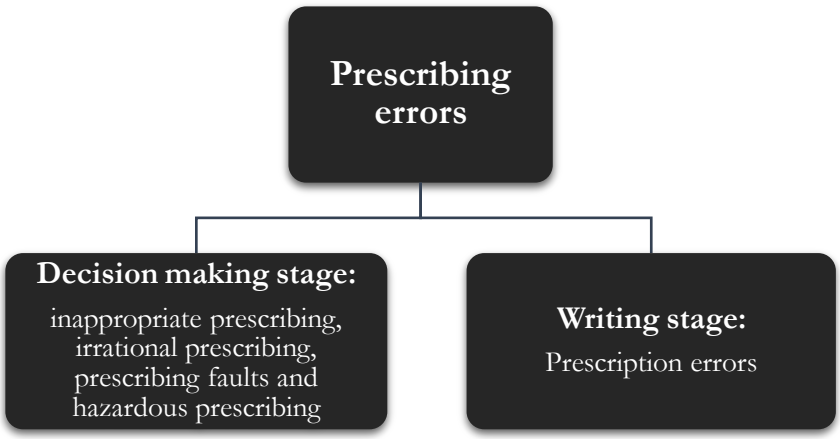

Figure 2.3: Stages of prescribing errors

Medication monitoring is an essential part of the prescribing process.[217,219,220] Therefore, monitoring errors or inadequate medication monitoring are sometimes examined with prescribing. In the UK, a study investigating prescribing safety in primary care using prescribing safety indicators found that 5.26% of patients received potentially hazardous prescriptions and 11.8% did not receive adequate medication monitoring in a cohort of 526 general practices. The authors also found high variation between practices which suggest potential for improvement.[32]

2.2.2 Medication safety in mental health care

As described in 2.1.2.3 the use of mental health medications can be associated with ADEs. Increasing evidence is available concerning ADEs and medication errors occurring in mental health hospitals but little relates to the primary care setting.[25,221-224] This is despite GPs being responsible for most of psychotropic prescribing in many countries.[225] For

example in Sweden around 95% of all psychotropic medications for the elderly are prescribed in primary care.[226].

A systematic review of 20 studies published between 1999 to 2016 reported that ADEs and medication errors were common in psychiatric hospitals, and that between 13-17.3% of ADEs may be preventable. This review also indicated that most errors and preventable harm were associated with psychotropic medications, and in particular atypical antipsychotics. In addition, it was reported that errors were most common in the prescribing and administration stage.[25] Recently, a study analysed medication safety incidents reported by inpatient mental health settings across England and Wales, finding that more than 10% of the incidents have resulted in harm.[227]

2.2.2.1 Prescribing safety in mental health

In patients with mental illness unique challenges in prescribing include the growing number of medication options which have the potential to increase the risk of irrational prescribing. Some of these patients have comorbidities and substance misuse problems which can cause drug–disease and drug-illicit drug interactions, polypharmacy which may lead to pharmacodynamics and pharmacokinetic drug-drug interactions.[19] Taking all these factors into account, it is difficult to achieve balanced prescribing in mental health.[27] Consequently, prescribing errors may be common in populations with mental illness.

In 2014, a prospective multicentre study of prescribing errors in mental health hospitals in England reported that more than half of errors had the potential to cause significant patient harm, with 7% of these errors being potentially serious or life threatening.[26] In 2016, another study in Denmark found that 59% of patients admitted to a psychiatric hospital had at least one potentially inappropriate prescription, with 45% being potentially serious or fatal.[27] In addition, a systematic review of medication errors in mental health hospitals reported that between 52.2–82.1% of inpatients are affected by prescribing errors based on two studies.[25] Hence, there should be a focus of attention on prescribing safety in this population, particularly as errors and substandard prescribing are common. However, although 9 out of 10 people with mental illness are managed completely in primary care as discussed in section2.1.2.2,[62,89,90] little data is available on the safety of prescribing in primary care specifically for this population.[224]

A pilot study in primary care in England for patients with SMI reported that only 67% of patients on the SMI register were on antipsychotics or mood stabilisers. In those who were on antipsychotics, 3.5% were on high dose, 6% were on combination antipsychotics, and

5% had an overdue physical health monitoring.[228] Another study, investigating the prevalence of overall prescribing errors in 15 general practices in England, reported that 13.4% of the identified prescribing errors were associated with CNS medications, which they are mostly psychotropic medications.[229] In addition, a cohort study in UK primary care examining antipsychotic prescribing, reported that more than half of the patients prescribed antipsychotics did not have a diagnosis of psychosis or bipolar disorder.[135] Therefore, there are some evidence of inappropriate mental health prescribing in primary care. However, most of these studies were either from a small number of practices, or were limited to a specific therapeutic group or a specific illness.

2.2.3 Patient and medication safety policy

Improving the safety of patients is a priority for health policy and health services. In 2000 and 2001 the 'An Organisation with a Memory' and 'Building a Safer NHS for Patients' reports focused on the importance of adopting an open culture of reporting and learning from adverse events and failures in healthcare.[179,230] As a result of these publications, the National Patient Safety Agency (NPSA) was established in 2001 to improve the safety of patient care, before having its functions taken over by NHS England in 2012, then transferred to NHS Improvement in 2016, and lastly merged with NHS England again in 2019.[180]

In order to improve the safety of medications in the UK, the Department of Health published a report titled: "Building a Safer NHS for Patients: Improving Medication Safety" in 2004.[219] This report explored the causes and rates of medication errors and identified specific recommendations to improve medication safety in high risk areas.

In 2004, the Quality and Outcomes Framework (QOF) was introduced as part of a new national General Medical Services contract for primary care practices in the UK. The scheme is voluntary and aims to reward higher-quality general practices by offering financial incentives. It contains a number of quality indicators against which clinical practice is measured, including prescribing and monitoring indicators.[231]

Safe prescribing was also the subject of key organisational reports in mental health settings. In 2005, the Royal College of Psychiatrists' established the Prescribing Observatory for Mental Health (POMH-UK) within the College Centre for Quality Improvement which aims to support rational, effective and safe prescribing in mental health services. The POMH-UK conduct audit-based Quality Improvement Programmes (QIPs) using

indicators that focus on particular important topics within mental health prescribing.[232] The QOF and POMH-UK mental health related indicators will be examined in more details in section 2.3.3

In 2017, the WHO launched its third Global Patient Safety Challenge: Medication Without Harm, which aims to "*reduce severe avoidable medication related harm globally by 50% in the next 5 years*".[39] In order to achieve the goal, the Department of Health and Social Care established the Short Life Working Group (SLWG).[50] This group produced several recommendations in line with the WHO goal. One of the recommendations was to develop a comprehensive suite of indicators on medication errors, focused on prescribing that has a high or higher risk of harm, to better understand and monitor high risk prescribing.[50] As a result of this report, a national medication safety dashboard has been developed by the Department of Health and Social Care to monitor a limited set of prescribing safety indicators to inform safer prescribing, which needs to be expanded in the future to monitor prescribing safety of several fields including mental health.[233]

In 2019, NHS Improvement published their Patient Safety Strategy.[234] It introduced the Medicines Safety Improvement Programme (MSIP) which aims to reduce medication-related harm in the NHS by focusing on high risk drugs, situations and vulnerable patients. The programme aims to deliver system enablers to identify cases in primary care to reduce clinically important errors in general practice prescribing using safety indicators.[234] In addition, NHS England in 2019 set out in its long-term plan a pledge for pharmacists to undertake an expanded role at the local Primary Care Networks, which would ensure that an adequate workforce was in place capable of delivering the MSIP aim.[48,165]As part of the of the Primary Care Networks, a new Structured Medication Review (SMR) and Medicines Optimisation service was developed. The new service requires each network to use appropriate tools to identify and prioritise patients at risk of harm or medicines-related problems because of their current medicine regimen and who therefore would benefit from the review. This also included reviewing psychotropics and supporting patients with severe mental illness.[89,165] Figure 2.4 illustrates the more recent UK patient and medication safety policy timeline.

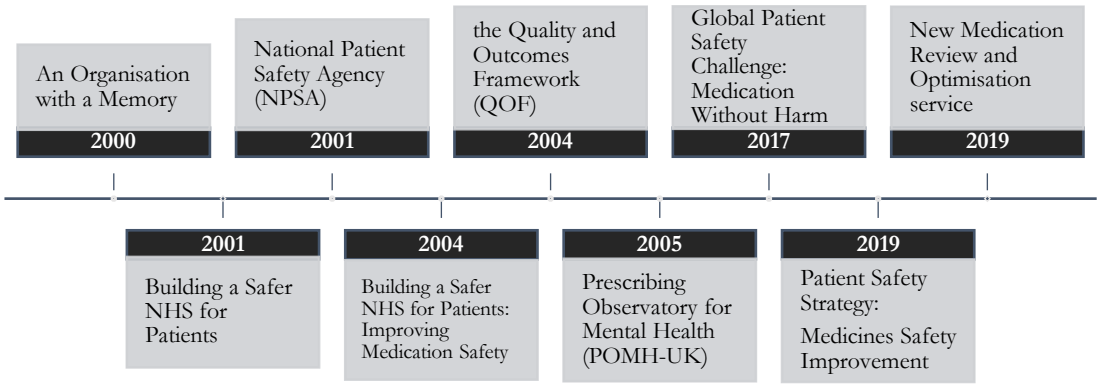

Figure 2.4: UK patient and medication safety policy timeline

2.3 The measurement of health care quality and safety

The measurement of health care quality and safety is fundamental to identifying areas for improvement and monitoring improvement initiatives. This is emphasised by the internationally-known author on performance and quality improvement H. James Harrington's well-known quote:

> *''Measurement is the first step that leads to control and eventually to improvement. If you can't measure something, you can't understand it. If you can't understand it, you can't control it. If you can't control it, you can't improve it''.*[235]

However, measuring quality of care is not straightforward, because it is theoretical multi-dimensional concept, with subjective and intangible elements.[236,237] Donabedian argues that it is essential to have a definition of quality before measuring it:

> *"We cannot assess quality until we have decided with what meanings to invest the concept. A clear definition of quality is the foundation upon which everything is built".*[238]

In the 'Dictionary of the Social Sciences', an indicator is defined as a *"quantitative measure that provides information about a variable that is difficult to measure directly",* such as quality of care.[237,239] Therefore, quality indicators are commonly used to measure the quality and/or safety of healthcare.

Quality indicators can be defined as:

> *"A measurable element of practice performance for which there is evidence or consensus that it can be used to assess quality, and hence in changing the quality of care provided".*[138]

In healthcare, quality indicators can be classified according to Donabedian's conceptual framework as structure, process or outcome indicators.[240] Structure indicators cover the infrastructure of institutions and providers, for example the use of electronic medical records or medication order entry systems. Process indicators comprise the care provided to patients such as prescribing, for example the percentage of patients who have been prescribed appropriate treatment, or who have been monitored appropriately. Outcome indicators describe the consequences of that care; for example, the rate of mortality, complications or hospital-acquired infections.[138,241]

Quality indicators can be used to monitor quality at the national, regional or local level[138] and for benchmarking and providing feedback. They are also used to observe the changes in quality over time [242], between places [32] or to evaluate interventions.[47] In addition, indicators can be used for accreditation [138], financial incentives "pay for performance" [243] and doctors' revalidation.[209] With the advances of information technology infrastructure and electronic medical records, indicators are now also used for improvement by searching clinical records electronically to identify patients at risk of hazardous prescribing, allowing for real time feedback on prescribing safety.[41,42,48] Indicators can also be used to develop CDS warnings with computerised physician order entry, in order to alert prescribers to prescribing practices that have the greatest potential to cause harm[35,210] rather than using untargeted alerts which can cause irrelevant information overload to prescribers and lead them to override important alerts.[244]

2.3.1 Overview of prescribing indicators

Indicators have been used to assess the overall quality of healthcare and in particular prescribing quality for decades. Prescribing indicators can be classified based on the information they incorporate.[138] This can be demonstrated by the step model presented in Figure 2.5. Higher steps necessitate more clinical information and may therefore be more relevant to quality and safety. For instance, indicators on volume and expenditure are mainly used for comparisons between health care providers but mostly they do not have any attribute with quality. On the other hand, disease-oriented indicators include information on the prescribed medications and the diagnosis on a patient level, and

therefore can be easily linked to safety and quality.[138] Table 2.3 shows an example for each type of prescribing indicator.

It is preferably that the quality and safety indicators information to be derived from routinely available data, to minimise subjective judgment in data collection.[138] However, historically, prescribing data are typically only available in administrative databases, such as reimbursement data.[138] Though, due to the lack of clinical information available in these databases, they mostly cannot be used to assess quality and safety and therefore were limited to volume & expenditure indicators and aggregate drug-oriented indicators.[138,245,246] However, the evolution in information technology infrastructure allowed for a growth in the availability of Electronic Health Record (EHR) databases and also allowed for record-linkage between databases,[138,246,247] such as the CPRD. This offered an opportunity to assess prescribing safety using readily available data and without subjective judgment.[138]As a result, more sophisticated indicators have been developed that are linked to electronic clinical records to be used specifically to assess the safety of care.[246]

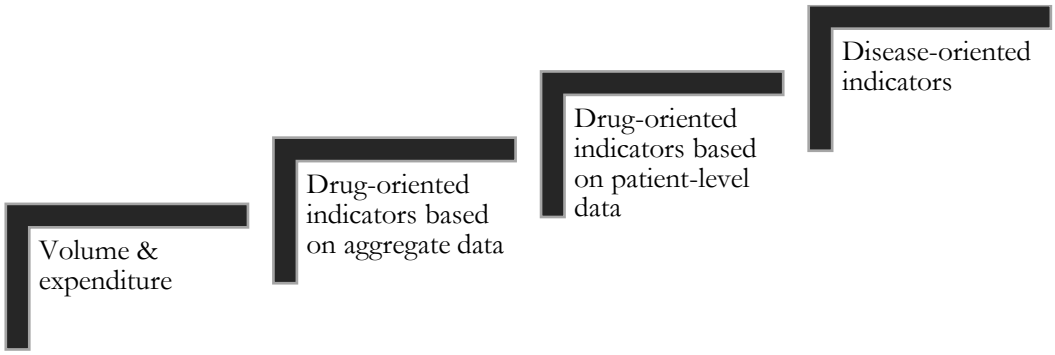

Figure 2.5: Different types of prescribing indicators

Adapted from Elseviers M, Wettermark B, Almarsdóttir AB, et al. Drug utilization research: methods and applications. John Wiley & Sons, Ltd; 2016 with permission from Wiley.[138]

Table 2.3: An example for each type of prescribing indicators

Type	Example
Volume & expenditure	Tramadol DDDs per 1,000 patients.[37]
Drug-oriented indicators based on aggregate data	Ratio of bendrofluazide 2.5 mg items to all bendrofluazide items.[248]
Drug-oriented indicators based on patient-level data	Co-prescription of lithium with thiazide diuretic.[29]
Disease-oriented indicators	Bupropion prescribed to a patient with epilepsy.[29]

Measuring the safety of prescribing is vital to improving patient safety and quality of care. As a result, several sets of prescribing safety indicators and inappropriate prescribing criteria and have been developed. These usually aim to detect prescribing patterns that should generally be avoided or appropriate prescribing that had been omitted. Spencer et al. defined prescribing safety indicators as *"statements describing prescribing events that put the patient at risk of harm"*.[29]

Prescribing safety and quality indicators can be divided into implicit or explicit indicators. Implicit indicators are usually not specific to a drug or to a disease, they can be applied to any prescription, but they are subjective and may be influenced by the reviewer's knowledge, meticulousness, consistency and judgement.[197,249,250] An example of an implicit indicator is "*Is there an indication for the drug?"*.[251] Donabedian claims:

> *"When a reviewer of the quality of care begins by using implicit criteria, we must depend entirely on his judgement and integrity, unless he reveals, in detail, the reasons for his judgements"*[250]

On the other hand, explicit indicators are clearly defined, are mostly drug or disease oriented, and can be used for objective and reproducible measurement. An example of an explicit indicator is "*Prescription of diltiazem or verapamil in a patient with heart failure"*.[29] However, explicit indicators can oversimplify clinical issues and cannot take into account patient individual needs and circumstances.[250] Therefore, explicit prescribing safety indicators that detect potentially hazardous prescribing and potentially inappropriate prescribing criteria are not always definite errors. Thus, in practice they are used as a trigger to alert health care professionals to any potential inappropriate prescribing.[252] For that reason, they cannot substitute prescriber's careful clinical decision-making.[253] For instance, *"Prescription of aspirin to a child aged ≤16 years*" is one of the indicators from Spencer et al.[29] - this prescribing can be justified for the treatment of Kawasaki disease. Nevertheless, some indicators are usually absolute errors and cannot be justified, such as "*Weekly dose of an oral bisphosphonate prescribed daily*".[35] Figure 2.6 shows the relationship between prescribing errors and potentially inappropriate prescribing, potentially hazardous prescribing and high-risk prescribing.

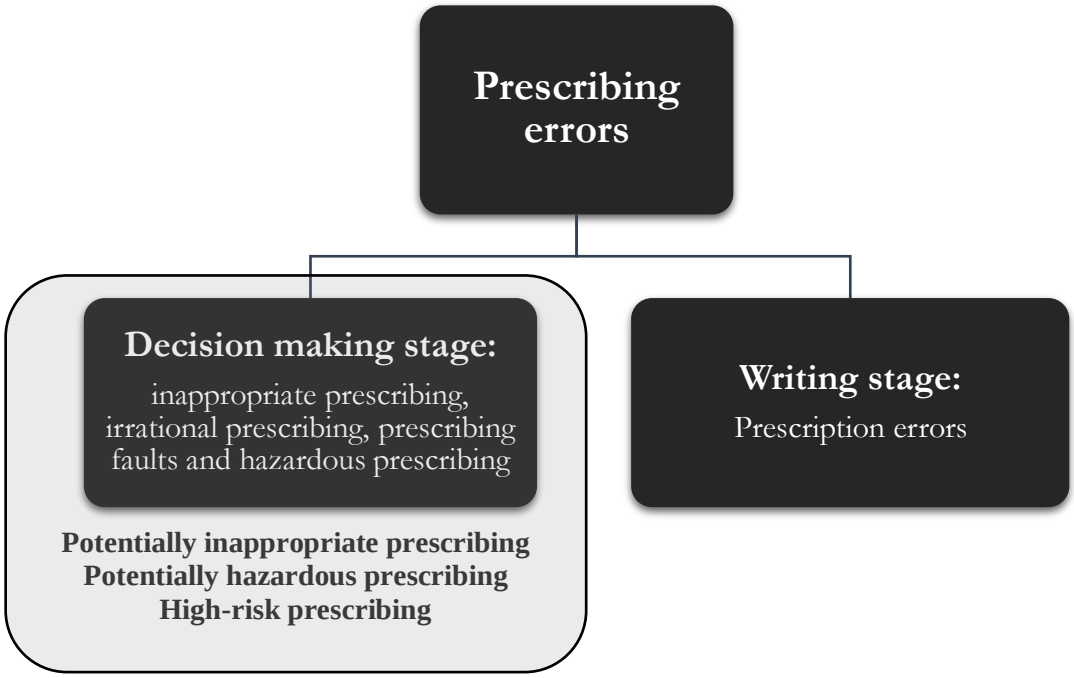

Figure 2.6: The relationship between prescribing errors and potentially inappropriate prescribing, potentially hazardous prescribing and high-risk prescribing

The first known explicit tool that has been used to identify potentially inappropriate medications was developed by Beers in 1991 for nursing home residents.[254] Afterwards, numerous different suites have been developed for use in different settings and different populations. Some of these were developed to be used specifically for primary care [29,255] or inpatient settings [35,210], while others are specific for elderly patients [256,257] or paediatrics.[210,255] However, mental health settings and populations have not received much attention in this regard, as well be discussed further in section 2.3.3

2.3.2 The development of prescribing indicators

In order to develop prescribing indicators it is essential to consider which aspect of prescribing will be assessed; process or outcome.[138] Most tools use process indicators [35,209,210] since prescribing is a healthcare process, and because outcome indicators are more difficult to measure. Nevertheless, process indicators must be related to outcomes [258] as the aim of medication prescribing is to improve patients' outcomes.[138]

Ideally, indicators need to be based on strong scientific/clinical evidence. [259] However, strong evidence-based information is often scarce.[258-260] Therefore, combining expert opinions and scientific evidence using formal consensus methods is common in developing quality and safety indicators in prescribing [29,35,209,210,261] and in other healthcare areas.[262-264] Consensus techniques work by synthesising and clarifying expert opinions so that

consensus amongst a group of experts can be reached. The three most commonly used formal methods to gather consensus include: the Delphi technique[265,266], the RAND/UCLA appropriateness method (RAM) [267], and the Nominal Group Technique (NGT).[268] These formal methods of consensus development are used because of the assumption that several people are less likely to arrive at the wrong decision than one individual and they are more likely to lend some authority to the produced decisions. In addition, by using a structured process, formal methods can minimise negative characteristics of group decision-making and can have more scientific credibility. Furthermore, decisions are improved by reasoned argument in which assumptions are challenged and members forced to justify their views.[269]

The Delphi technique was developed by the RAND Corporation in 1953 [265,266], and comprises of several rounds of anonymous questionnaires, usually two to three, between an expert panel. In the Delphi method, typically there is no face-to face discussion, and originally a potential list of statements would be generated during the first Delphi round. However, usually the research team would generate a list beforehand from multiple resources. This is a common modification from the general Delphi method.[270] Afterwards, the expert panel members are chosen based on certain factors, such as their profession, experience and geographical location, dependent upon the research aims and objectives. After that, the list of statements is distributed to the panellist for rating.[29,35,209,210,261] Between rounds, the participants are usually provided with feedback of the results from the previous round. The Delphi method allows a large number of statements to be rated at the same time and it also may support recruiting a large number of panellists from different geographical regions.[259] The Delphi process is a flexible research method, different rating scales and different consensus criteria are described in the literature, and there appears to be no standardised approach.[271,272]

The RAND/UCLA appropriateness method (which is a modified-Delphi process) usually involves a detailed literature review sent to the panel, followed by a two round traditional Delphi questionnaire.[267] However, before the second round, a face-to-face meeting between the panel members is required which provides the panel with the opportunity to discuss their opinions.[267] However, the face-to-face meeting may make some members uncomfortable or intimidated to discuss their opinions.[259,273] In addition, the RAND/UCLA appropriateness method can be more costly and difficult to organise as it includes other considerations such as travel and availability of panel members (particularly if panel members are recruited from wide geographical areas). It usually involves 7 to 15 members and it uses 1-9 Likert scale to the statements.[267]

There is also the NGT, which is a highly structured interaction between a group of experts and is mainly used for generating ideas or statements.[274] It usually involves silent generation of ideas by each individual, sharing of ideas in a round-robin format, discussing the ideas, and finally ranking or voting on the ideas.[275] Table 2.4 illustrates the characteristics, advantages and disadvantages of the three methods.

Table 2.4: Characteristics, advantages and disadvantages of the nominal group technique, the Delphi method and the RAND/UCLA appropriateness method.

	NGT	Delphi	RAND/UCLA
Mailed questionnaire	No	Yes	Yes
Face to face meeting	Yes	No	Yes
Private decisions elicited	Yes	Yes	Yes
Formal feedback of group ratings	Yes	Yes	Yes
Structured Interaction	Yes	Yes	Yes
Advantages	- Allows for discussion and debate - Single face to face meeting	- Larger number of participants - Geographically dispersed participants - Avoids dominance by particular participants - Participant able express their opinions freely - More time to express ideas, reflect upon answers and make changes - Convenient - Relatively inexpensive	- Allows for discussion and debate - Systematic method of combining expert opinion and evidence
Disadvantages	- Smaller number of participants - Potential for dominant participants to influence the group - Costs associated with face-to- face meeting	- Limited opportunity for discussion and debate to resolve differences of opinion - Time consuming (each round may take several weeks or months).	- Smaller number of participants - Potential for dominant participants to influence the group - Time consuming (gathering of the evidence to multiple rounds of consensus). - 9-point Likert scale can be cumbersome - Costs associated with face-to- face meeting

* Based on Campbell et al.,[273] Murphy et al.,[269] Nair et al.,[276] and Humphrey-Murto et al.[277]

Indicators developed using consensus methods have high face validity, and those based on evidence in accordance with updated recommendations and current guidelines may also possess high content validity. Indicators could also be further tested for acceptability, feasibility, reliability, sensitivity to change, and predictive validity.[138,259]

2.3.3 Prescribing safety indicators in mental health

As mentioned in section 2.3.1 mental health disorders and/or settings have not received much attention in published literature with regards to prescribing indicators. The only

study found that developed prescribing quality indicators for patients with mental illness was limited to inpatient settings and some of the presented indicators did not include enough clinical information to be attributed as safety indicators.[278] Furthermore, the indicators from this study did not address many potential hazardous prescribing in mental health (Table 2.5) and the study was published in 2004 and has since not been updated.[278] This is important as prescribing indicators need to be reviewed and updated continuously to check their relevance - as new medications are approved, and the use of older ones might decline and subsequently their importance might change.[35]

Table 2.5: Psychiatric inpatient prescribing quality indicators

(1) "High dose antipsychotics": percentage of patients prescribed any antipsychotic whose total daily dose of antipsychotic drugs is above the maximum recommended by the British National Formulary (BNF).
(2) "Antipsychotic polypharmacy": percentage of patients prescribed any antipsychotic drug in whom more than one antipsychotic drug is being prescribed concurrently. (3) "Atypical polypharmacy": percentage of patients prescribed any atypical antipsychotic in whom another antipsychotic drug is being concurrently prescribed.
(4) "Multiple PRN": proportion of all patients being prescribed three or more psychotropic drugs on an as required (PRN) basis.
(5) "Subtherapeutic doses of mood stabilisers": percentage of patients prescribed either valproate or carbamazepine for whom the dose prescribed is below the therapeutic level.
(6) "Hypnotic prescribing": percentage of all patients prescribed a hypnotic drug.
(7) "Benzodiazepines: antidepressants": ratio of total number of prescriptions for benzodiazepines to total number of prescriptions for antidepressants.

In 2016, a study in the Netherlands aimed to assess the applicability of using the Beers criteria 2012 and the screening tool of older person's potentially inappropriate prescriptions (STOPP) and screening tool of alert doctors to the right treatment (START) criteria,[257,279] which both were created for the elderly population, to detect inappropriate prescribing in patients admitted to mental health hospitals. The identified prevalence of potentially inappropriate medications in this study ranged between 47%-79% of the patients, depending on the used tool. It was concluded that inappropriate prescribing was common in this population. However, the authors argued that there is a need to develop a new specific tool for patients with mental disorders to assess prescribing more accurately.[280]

The POMH-UK indicators, which were discussed in section 2.2.3 , do not take into account multiple risks associated with mental health prescribing practices, such as the risk of QT prolongation and torsade de pointes, the risk of falls and the risk of bleeding. [232] [20,281-298] Furthermore, the program is focused on NHS mental health trusts and

organisations that provide specialist mental health services and does not cover routine primary health care where most patients with (particularly less severe) mental illness are managed.[232]

The QOF indicators which were discussed in section 2.2.3 in general cover only some aspects of quality and may disregard other important unmeasured dimensions.[299] In the 2020/2021 QOF indicators in England 8 prescribing indicators were included, none of which were mental health related. Two mental health medication monitoring indicators were included for the monitoring of blood pressure and weight for people with schizophrenia, bipolar affective disorder and other psychoses. Indicators related to the monitoring of lipid and glucose for the same population were retired and indicators related to lithium monitoring were also retired.[300,301]

Whilst there are a number of informative academic papers describing the development of broad suites of prescribing safety indicators across primary and secondary care in the UK that include some mental health related indicators, these were not developed to be used specifically for populations with mental illness and were not reviewed with experts in mental health.[29,30,35,209,210] Therefore, they may not reflect all prescribing risks in the mental health context, such as the known risk of foetal congenital malformations due to exposing the mother to valproate.[148] For instance, the current PINCER suite of indicators that is being rolled out across practices in England include only one mental health related prescribing safety indicator, which is "Prescription of antipsychotics for >6weeks in a patient aged ≥65 years with dementia but not psychosis".[48] Therefore, there is evidence of some isolated mental health related prescribing indicators present in studies of risk in broader patient groups that could be valuable for the development of prescribing safety indicators specifically for people with mental illness. However, there is no systematic reviews available that bring together the disparate literature on this topic. For example, a systematic review was conducted to identify prescribing safety indicators relevant to primary care, and another systematic review was conducted to identify prescribing safety indicators relevant to people with chronic kidney disease.[302]

2.4 Conclusion

The concerns raised in this chapter with the growing burden and evidence of poor quality and safety of mental health care highlight the importance of monitoring and assessing the quality and safety of health care services provided to mental health patients in order to ensure optimum care is delivered, as carried out by the CQC, POMH-UK and the QOF. In addition, this chapter illustrated the significance of prescribing safety for people with mental disorders and the importance of assessing and improving prescribing safety for this population. Furthermore, it has been indicated that none of the recently published sets of prescribing safety indicators were developed to be used specifically for patients with mental disorders. However, there is mental health related prescribing indicators available in studies of risk in other patient groups. Therefore, there may be a need to develop a new set of prescribing safety indicators for mental health conditions and medications based in part on indicators extracted from existing sets that do not focus on mental health, which can be validated with experts within mental health and medication safety from the UK. Finally, the chapter also highlights the lack of medication safety data for this population is primary care.

Chapter 3 : Research aims and objectives

This chapter describes the rationale and the overall aim and objectives of this programme of work.

The previous chapter presented a rich body of literature focusing on prescribing assessment tools designed to detect potentially inappropriate and hazardous prescribing, such as the Beers and STOPP/START criteria for elderly, and the PINCER indicators for primary care.[33,303,304] The chapter also explained the advantages of using these safety indicators such as the ability to identify patients at risk of adverse drug reactions to prompt further investigations before actual harm occurs, and the ability to use routinely collected data to identify identifying areas for improvement, provide feedback to health care professionals and monitor change over time.[31,138,165] However, a specific suite of prescribing safety indicators tailored to mental health illness and medications remains absent, which is important to better understand, routinely monitor and improve medication related harm in this population across health settings, as well as address national and international safety goals. Especially since there are unique challenges when prescribing for people with mental illness. Including the risk of adverse reactions associated with psychotropic medications,[20] the high prevalence of psychotropic polypharmacy,[21,22] the use of high-risk psychotropic medication,[20] the high prevalence of physical co-morbidity and associated polypharmacy in people with mental illness,[7] the enduring problem of high dose and combination antipsychotic prescribing.[19] Consequently, research evidence suggests that prescribing errors, inappropriate prescribing and preventable medication-related harm are common in this population.[25-27] Furthermore, the previous chapter has shown that there is evidence of different types of mental health related indicators reported in studies of risk in broader populations that needs to be put together to form a foundation for the development of a specific suite prescribing safety indicators for people with mental illness.

In addition, while there is emerging evidence concerning medication and prescribing safety in mental health hospitals,[25,223] it has been shown that little data were available on the safety of prescribing in primary care specifically for people with mental disorders. Future work is therefore needed since most patients with mental disorders are managed in primary care, and particularly given that there have been concerns about the quality of care provided to those people in this setting.[25,223,224] Therefore, the work conducted in this thesis aimed to address these gaps in the literature.

This programme of research will describe details of the first two stages of the Medical Research Council (MRC) framework, namely, the development and feasibility/piloting of the prescribing safety indicators.[305] The initial development stage is fundamental in identifying potential mental health related prescribing safety indicators and achieving consensus on the final suite of indicators with experts in mental health. The next stage involves feasibility and pilot testing of the indicators in a large primary care database.

3.1 Aim

The overall aim of this programme of research was to assess the safety of prescribing for people with mental illness through the development and implementation of a suite of prescribing safety indicators related to mental health conditions and medications, and to use the findings to set an agenda for future research, policy and practice to support prescribing safety improvement efforts.

3.2 Objectives

In order to achieve this aim, the following objectives were set:

Objective 1: Identify comprehensively from the existing published literature potential prescribing safety indicators related to mental health disorders and medications,

Objective 2: Achieve consensus on a suite of prescribing safety indicators specific for populations with mental disorders,

Objective 3: Estimate the risk of harm associated with each prescribing safety indicator identified in objective 2,

Objective 4: Operationalise and apply prescribing safety indicators specific for populations with mental disorders in primary care health records,

Objective 5: Examine the prevalence and patterns of different mental health related prescribing safety indicators in primary care in the UK.

Objective 6: Generate recommendations to inform clinical practice, policy makers and future research to support prescribing safety improvement efforts.

Chapter 4 : Identifying potential prescribing safety indicators related to mental health disorders and medications: a systematic review

The purpose of this chapter is to describe the aims, method, results and discussion of a systematic review designed to identify potential prescribing safety indicators related to mental health. This is the first study in this research programme and was published in 2019 in PLOS ONE.[306]

4.1 Introduction

The literature review presented in Chapter 2 indicated that none of the recently published sets of prescribing safety indicators were developed to be used specifically for patients with mental illness. This is significant as there are unique challenges when prescribing for this population. Against the background of underlying complexity there is evidence that prescribing errors and substandard prescribing might be common in this patient group.[25-27] Therefore, the creation of a tailored suite of prescribing safety indicators for this vulnerable patient group is warranted in order to assess prescribing more comprehensively and guide much needed improvement efforts.

Chapter 2 has shown that there is evidence of different types of mental health related indicators reported in some studies of risk in broader populations. Therefore, in order to develop a new suite of prescribing safety indicators, there is a need to identify all studies that developed indicators or criteria that assessed prescribing in terms of safety or quality, and to extract from those studies any explicit mental health related prescribing indicators to form a foundation for the development of a specific suite prescribing safety indicators for people with mental illness. However, previous systematic reviews of prescribing indicators did not include all known types of prescribing assessment tools[52,53] For instance, an earlier systematic review [53] published in 2014 was limited to inappropriate prescribing, and did not search for other types of indicators,[53] such as prescribing errors, hazardous prescribing indicators and high risk prescribing. Another review by Song et al. [52] published in 2017 did not include several prescribing safety indicators sets. Therefore, both reviews missed several studies which contain potential mental health related prescribing safety indicators, such as Gurerriro et al. in 2007 [307], Dreischulte et al. in 2012 [173] and Wessell et al. in 2010.[308]

Accordingly, there is a need to complete a systematic review to ensure (a) all previously published prescribing indicators are included, and (b) to identify both quality and safety indicators because of the overlap between the terms. Once this list of indicators is gathered, it can then be used as a starting point to identify the most comprehensive list of potential mental health illness/medication related prescribing safety indicators in order to develop a new tailored suite of safety indicators.

4.2 Aim and objectives

This chapter aimed to systematically and comprehensively identify from the existing literature prescribing indicators and suites of all kinds from across all settings, and to extract from these any individual potential prescribing safety indicators related to mental illness and medications

The objectives of this systematic review were:

- To search relevant electronic literature databases to identify studies that developed indicators or criteria that assessed prescribing in terms of safety or quality,
- To extract from these studies any mental health related prescribing indicators,
- To select from the extracted mental health related prescribing indicators potential mental health related prescribing safety indicators.

4.3 Methods

4.3.1 Rationale

In order to achieve the study aim, a literature review was needed. For this study, a systematic review was chosen instead of a narrative review. Systematic review is considered the gold standard to search, evaluate and summarise the best available evidence regarding a question.[309] Systematic reviews allow comprehensive and systematic literature searches, which minimise selection bias.[310]

4.3.2 Study design

In order to achieve the aim of this systematic review and the three objectives, we followed three stages (Figure 4.1); (1) identifying studies that reported prescribing indicators of any kind; (2) identifying and extracting mental health related prescribing indicators; and (3) selecting potential prescribing safety indicators related to mental health disorders and medications.

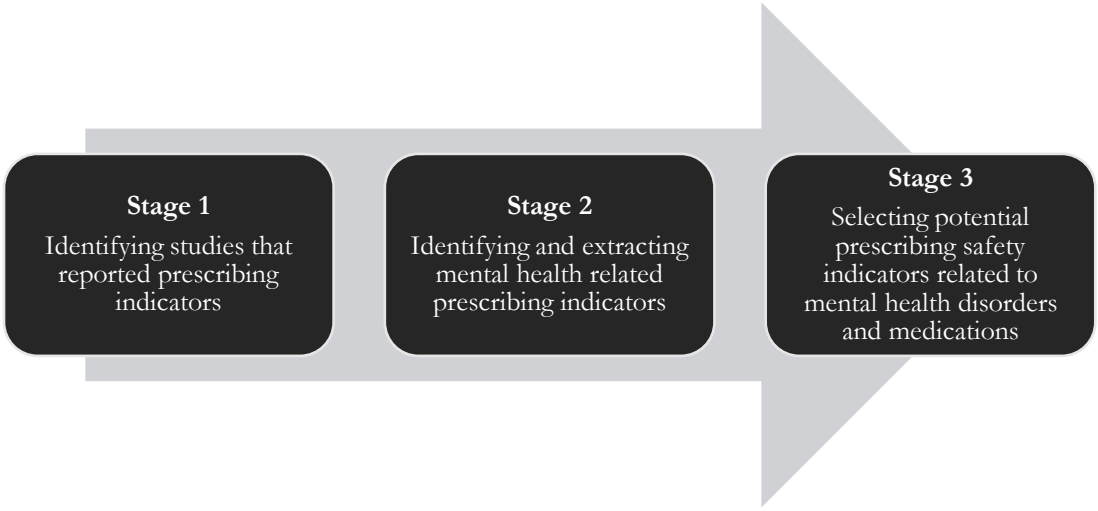

Figure 4.1: Systematic review stage

4.3.3 Stage 1: Identifying studies that reported prescribing indicators of any kind

4.3.3.1 Database search strategy

A systematic search was conducted using the following electronic databases: Embase, MEDLINE, PsycINFO, Web of Science, Health Management Information Consortium

(HMIC), International Pharmaceutical Abstracts (IPA) and Cumulative Index to Nursing and Allied Health Literature (CINAHL). The search strategy was designed using Medical Subject Headings (MeSH) and free text words tailored to each database (Appendix (1)). Three sets of search terms were combined; medication safety terms, quality measure terms and indicators development/validation terms. The search timeframe was limited from January 1990 to February 2019, since one of the earliest examples of inappropriate prescribing explicit criteria was published in 1991 by Beers.[311,312] The bibliographies of included studies and of relevant review articles were reviewed manually to identify additional citations.

The search results were assessed for eligibility by screening the title and abstract by one reviewer (WK). Afterwards, the full-texts of potentially relevant articles were each reviewed for inclusion by WK. Any uncertainty regarding the eligibility of an article was discussed by the research team (WK, DS and RNK) until consensus was reached.

4.3.3.2 Definitions

The term 'indicator' was used to describe all the different types of prescribing indicator/criteria. Explicit indicators were included in the study and can be described as drug- or disease-oriented indicators that can be applied as firm standards (e.g. prescribing Benzodiazepines for ≥ 4 weeks for elderly patients [304]). Implicit indicators are person-specific, and their use requires professional skills (e.g. is there an indication for the drug? [251]) and were not included in this review.

The definition of 'Mental disorders' has been defined in Chapter 2 in section 2.1 and the definition of 'Psychotropics' has also been defined in Chapter 2 in section 2.1.2.3.

4.3.3.3 Inclusion criteria

Articles were eligible for inclusion if they developed, validated or updated a set of explicit indicators or criteria that measured prescribing in terms of safety or quality, including inappropriate prescribing, prescribing errors, hazardous prescribing, prescribing faults, monitoring errors or any other term that might be used to describe prescribing safety or quality. As the initial aim was to capture all relevant materials so that mental health indicators could be identified, there were no restrictions on the type of study design, targeted setting, the age group the indicators were intended for use in, publication language and intended country for deployment. All relevant articles were included whether they featured any mental health related indicators or not.

4.3.3.4 Exclusion criteria

We excluded articles that developed implicit indicators only (e.g. is there an indication for the drug? [251]), because they were not drug- or disease-oriented. We also excluded articles that developed indicators based on aggregate data and did not have any relation to patient level data (e.g. Ratio of co-trimoxazole items to trimethoprim items [248]). Studies that developed indicators non-specific to a medication or therapeutic class were also excluded (e.g. If the duration of a drug is outside the range stated in the British National Formulary (BNF) [313]), as were conference abstracts unless we were able to obtain the full indicator list. Studies that measured the prevalence of prescribing quality or safety, using a previously published prescribing indicator suite/tool without further development were considered duplicates and were not included, as were those involving adaptation/translation of single published prescribing indicator suite/tool to be used in another country without further development. Studies describing sets of indicators exclusively limited to a specific disease or specific therapeutic drug class that were not related to mental health medications and/or illnesses were also excluded (e.g. prescribing quality indicators for patients with type 2 diabetes [314]), as were those studies whose main focus was not prescribing (e.g. assessing care of vulnerable elders (ACOVE) quality indicators [315]).

4.3.3.5 Data Extraction

The data extraction process for each study was conducted independently by two authors (WK and DS, or WK and RNK) into a standardised and piloted electronic data extraction sheet (Appendix (2)). Discrepancies were discussed by the research team until agreement was reached. The following data were extracted from each included study where presented: **Study information:** Study title, main author, country, aim of the study. **Study design:** Setting, targeted population, indicators sources, validation methods. **Results**: Total number and type of indicators.

4.3.3.6 Quality assessment

Due to the heterogeneity of the included studies objectives and methods, we did not formally assess the methodological quality of the included studies. In addition, even though most studies used a consensus approach to develop their indicators, to our knowledge, there are no formal tools to assess the quality of consensus-based studies. However, certain aspects of the quality of the included studies are discussed later in this chapter, such as the methods used to select indicators and the process to validate the indicators.

4.3.4 Stage 2: Identifying and extracting mental health related prescribing indicators

All included studies from the first stage were screened to identify and extract all mental health related indicators based on the definition in Box 4.1.

Box 4.1: mental health related indicators definition

Indicators were defined as mental health related if they included:

- A medication that can be used to treat or prevent any mental health condition (e.g. prescribing atypical antipsychotic for elderly [316,317]), unless the indicator was specific for a non-mental health indication (e.g. clonidine for the treatment of arterial hypertension in the elderly [318]),
- A medication that can be used to treat or prevent side effects of any of the medications that can be used to treat or prevent any mental health condition (e.g. Trihexyphenidyl for treatment of extrapyramidal symptoms caused by antipsychotics for elderly [303]), unless the indicator were specific for a non-mental related health indication, or
- A drug-disease interaction of any medication with any mental health condition (e.g. H2 receptors antagonist [303] or antimuscarinic drugs [304] with dementia, or chronic cognitive impairment in elderly).

The following information sources were used to determine the uses of each medication when screening for mental health related indicators: BNF, Martindale, AHFS Drug Information (all accessed via Medicines complete[319]). In addition, ICD-10 Chapter 5: Mental and behavioural disorders [320] and DSM-5 [55] were used to determine mental health conditions.

Some indicators were considered mental health related because they included medication within a wider therapeutic class that could be used to treat mental health conditions, such as first-generation antihistamines. It was not always clear whether all medication within certain classes may be used to treat mental health disorders, however the class was included due to variation between clinical practice in different countries but only if more than one medication within that class was identified as being used in the treatment of mental illness. Conversely, some other classes were not included entirely as mental health related, because only one of the medications within that class could be used in the treatment of mental illness (e.g. clonidine).

After identifying all mental health related indicators, duplicates were removed, and if an indicator included more than one medication, class or condition it was split into more than one. For example, "*Benzodiazepine or benzodiazepine-like drug prescribed to a patient with chronic obstructive pulmonary disease [35] ",* was split into two indicators, one for benzodiazepine and another for benzodiazepine-like drug. In addition, in regards to the

identified outcome indicators, these included an adverse outcome that was caused by a pattern of care (for example: Outcome: Fall and/or hip fracture and/or other bone fracture and/or bone break, Process of care: Use of a long-half-life hypnotic-anxiolytic [321]). For such indicators, we only extracted the process of care that leads to the outcome in the list of potential indicators.

The identified mental health related indicators were categorised according to the type of prescribing problem (potentially inappropriate medication (PIM): independent of diagnoses or conditions, PIM: considering diagnoses or conditions, drug-drug interaction (DDI), inappropriate dosing, inappropriate duration, inadequate monitoring and omission) (Table 4.1), these categories were adapted from previous studies. [308,322,323] Identified indicators were also categorised to their therapeutic class (Antipsychotics, Antidepressants, Sedatives, hypnotics and anxiolytics, ADHD medications, Anti-dementia, Mood stabilisers, Non-specific anticholinergics and Non-specific psychotropics). The numbers and percentages of the indicators in each category were calculated.

Table 4.1: Descriptions and examples of the types of prescribing problems

Type of prescribing problem	Description	Example
PIM: independent of diagnoses or conditions	Medication/class that is potentially prescribed inappropriately to a specific population	Prescribing antipsychotics to patients aged ≥65 [303,304,321,324,325]
PIM: considering diagnoses or conditions	Medication/classes that is potentially prescribed inappropriately with a specific diagnose or condition.	Prescribing antipsychotics for patients with dementia and aged ≥65 [303]
DDI	Medication/classes that is potentially interacts with another medication/class	Prescribing antipsychotics with antiparkinsonian for patients aged ≥65 [326]
Inappropriate dosing	Medication that was prescribed in inappropriate dose	Prescribing Haloperidol at a dose >2 mg for patients aged ≥65 [327-329]
Inappropriate duration	Medication/class that was prescribed in inappropriate duration	Prescribing antipsychotics for >1 month to patients aged ≥65 [330]
Inadequate monitoring	Medications/class that was not monitored adequately	Prescribing lithium without monitoring lithium level every 6 months [29,307,331]
Omission	Medication/class that should be prescribed with a specific diagnose or condition.	Patients diagnosed with mild-moderate Alzheimer's dementia and aged ≥65 and were not prescribed acetylcholinesterase inhibitor [304]

DDI= drug-drug interaction. PIM= Potentially inappropriate medication.

4.3.5 Stage 3: Selecting potential prescribing safety indicators related to mental health disorders and medications

Following the identification and extraction of all mental health related indicators as described in the second stage, two experienced mental health pharmacists (RNK and JN) together reviewed the identified list and used respected recourses, such as NICE guidelines [332], the Maudsley Prescribing Guidelines in Psychiatry [20], Psychotropic Drug Directory [333],

Stockley's Drug Interactions [319] and the resources described in stage two along with their clinical knowledge to select potential prescribing safety indicators that met our adapted [29] definition: statements that described a pattern of potentially hazardous prescribing or drug monitoring that could cause significant risk of harm. The definition differed to the original in that we did not focus on prescribing specific to the UK and we did not consider data extraction feasibility due to the likelihood of different health care record/prescribing systems being used across the globe. This process is an initial stage of selecting potential prescribing safety indicators before validation in the next chapter using the Delphi method. This method is similar to a previous work that developed prescribing safety indicators for primary care were two experts identified potential indicators that described a pattern of prescribing that could be hazardous and may put patients at risk of harm.[29] This approach allow excluding indicators that focus on prescribing effectiveness rather than safety or indicators describe prescribing practices that do not cause potential significant risk of harm.

When selecting prescribing safety indicators, if more than one indicator shared similar characteristics, the broader indicator was selected. For example, if an indicator was found for a class of medication but other indicators for specific medications existed within that class, only the former was selected as prescribing safety indicator. Another example, an indicator for elderly versus an indicator for all ages. If the risk of harm was relevant for all populations, then the latter was selected. This step was performed to reduce the large number of identified prescribing safety indicators by removing similar indicators with slight variations. Prescribing safety indicators were also categorised according to the type of prescribing problem and to their therapeutic class as described for general mental health related indicators in stage two.

4.3.6 Data analysis

A descriptive analysis was performed on textual data to identify potential mental health related prescribing indicator statements, to extract their key word content and to categorise them. In depth thematic analysis was therefore not applicable for the purpose of the study. This approach is consistent with two previously conducted systematic reviews on medicine related quality indicators.[52,334] The extracted information was presented in tabular form. Numbers and percentages were calculated when appropriate. In addition, the average number of reported indicators and standard deviation were provided. Data were summarised as a list of prescribing safety indicators.

4.4 Results

4.4.1 Stage 1: Identifying studies that reported prescribing indicators of any kind

The database search process identified 22,773 citations. Of these, 9,715 studies were removed because of duplication. The remaining 13,058 citations were screened for eligibility, where 12,842 were subsequently excluded. Hence, 216 full texts were retrieved for in-depth review. Of these, 129 were excluded leaving 87 studies for inclusion. After reviewing the reference lists of included studies and relevant reviews a further 3 studies were included, bringing the final number of the eligible studies to 90. However, 11 studies [209,254,257,279,311,318,322,335-338] were older versions of new articles, and only their most recent versions were included. Therefore, 79 unique studies were included in the analysis. A summary of the review process is shown in Figure 4.2. Table 4.2 summarises the information extracted from each included study. Table 4.3 summarises the characteristics of the 79 unique studies.

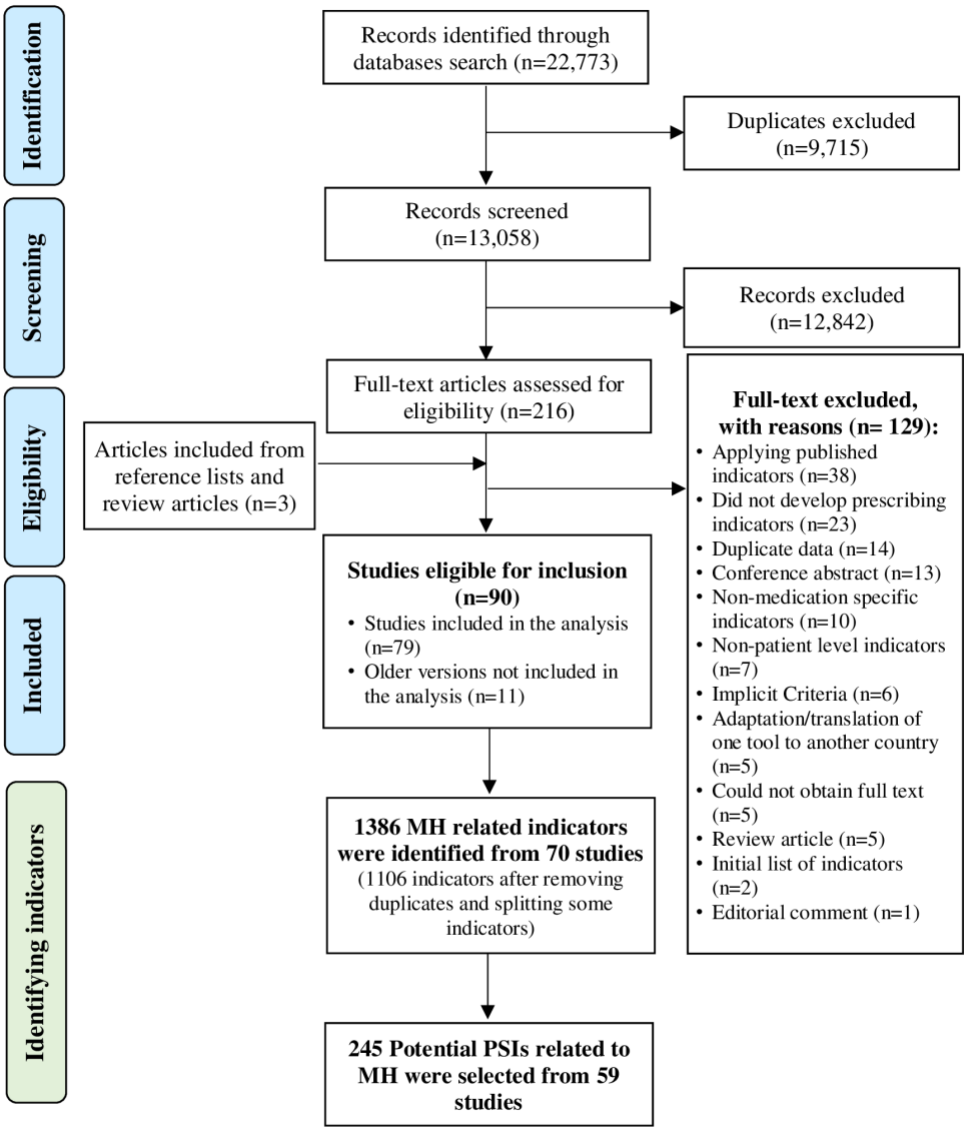

Figure 4.2: Flow diagram of the review process.
MH= Mental health. PSI= Prescribing Safety Indicators

Table 4.2: Summary of each included study

Author Year	Targeted Country(s)	Targeted Setting	Targeted Population	Indicators Source	Validation Method	Type of Criteria/Indicators		No. of indicators	No. of MH indicators
						P/O	The used term		
AGS 2015 [303] **Older versions** **Beers** 1991 [254] **Beers** 1997 [335] **Fick** 2003 [322] **AGS** 2012 [279]	US	MS	Elderly	Literature review + older version [279]	Delphi[M]	P	PIM, DDI, DSI	231	125
Al-Taweel 2017 [331]	International	MS	Adults with Bipolar disorder	Guidelines	NS consensus	P	Adherence to management guidelines	26	26
Alldred 2008 [339]	UK	LTC	Elderly	Guidelines + experience	NS consensus	P	Medication monitoring errors	25	3
Avery 2009 [47]	UK	Community	NS	NR	NR	P	Hazardous prescribing and inadequate monitoring	10	1
Barnett 2014 [43]	UK	Community	NS	Selected previously published studies	NS consensus	P	High risk prescribing	6	1
Barry 2016 [255]	UK and Ireland	Community	Paediatric	Literature review	Delphi[M]	P	PIP	12	0
Basger 2012 [340] **Older version** **Basger** 2008 [311]	Australia	MS	Elderly	Older version [311]	RAM	P	DRPs (Prescribing appropriateness)	41	6
Castillo-Páramo 2013 [325]	Spain	Community	Elderly	STOPP / START 2008 [257]	RAM	P	PIM, PPO	86	21
Caughey 2014 [341]	Australia	Hospitals	NS	Literature review	RAM[M]		Preventable medication-related hospitalisations	29	1
Chang 2012 [342]	Taiwan	MS	Elderly	Selected previously published studies	Delphi[M]	P	PIM, DSI	182	68
Chen 2005 [343]	UK	Community	NS	Textbooks	NR	P	DDI, DSI	213	NR
Clyne 2013 [344]	Ireland	Community	Elderly	Selected previously published studies	NS consensus	P	PIP	39	14
Constantine 2013 [345]	US	NS	All ages	Guidelines	Expert Panel	P	Unusual prescribing	12	10
Cooper 2014 [346]	UK and Ireland	NS	Middle aged	Selected previously published studies + Experience	Delphi	P	PIP	22	7

Desnoyer 2017 [347]	International	Hospitals	Adults	Literature review + Experience	Delphi	P	PIM	160	22
Desrochers 2011 [348]	Canada	Pharmacies	CKD patients	Literature review + Experience	RAM	P	DRPs	50	2
Dreischulte 2012 [173]	UK	Community	NS	Literature review	RAM[M]	P	High risk and suboptimal prescribing and monitoring	176	16
Elliott 2001 [349]	Australia	Hospitals	Elderly	Selected Previously published studies + Experience	Expert panel	P	PQ (Prescribing appropriateness)	19	3
Fernández Urrusuno 2013 [350]	Spain	Community	NS	Guidelines	NGT	P	PQ	14	1
Fialová 2013 [329]	Czech	NS	Elderly	Literature review	Delphi[M]	P	PIM, DSI	121	48
Fox 2016 [210]	UK	Hospitals	Paediatric	Thomas study [35] + Literature review + Local and national incidents + NPSA alerts	Delphi	P	PE (high risk prescribing)	41	0
Galán Retamal 2014 [351]	Spain	Hospitals	Elderly	Selected previously published studies	Delphi	P	PIM	50	15
Guerreiro 2007 [307]	Portugal	Community	NS	Selected previously published studies	Delphi	P	PDRM	35	4
Guthrie 2011 [30]	UK	Community	NS	Literature review	RAM[M]	P	High risk (Hazardous) prescribing	9	2
Hanora Lavan 2017 [352]	Ireland	MS	Elderly with Limited life expectancy	Literature review + Experience	Delphi	P	PIP or PIM	27	2
Harper 2014 [353]	US	Hospitals	Paediatric	NR	NS consensus	P	DDI	19	7
Holmes 2008 [354]	US	LTC	Palliative with advanced dementia	Textbooks	Delphi[M]	P	Medication appropriateness categories	54	54
Holt 2010 [327]	Germany	NS	Elderly	Literature review + selected previously published studies	Delphi[M]	P	PIM	83	51
Hurley 2005 [355]	US	Community	Adults	Textbooks + FDA black box warnings + Guidelines	NR	P	Medication monitoring	24	11
Khodyakov 2017 [317]	US	LTC	Elderly	STOPP/START 2015 [304]	Delphi[M]	P	PIM, PPO	24	9
Kim 2015 [356]	Korea	Community	NS	WHO-ATC classification + the Korean National Health Insurance criteria for pharmacy benefits + guidelines	Delphi	P	Duplication	33	0

Kim 2015 [357]	Korea	NS	Elderly	Selected previously published studies	Delphi	P	PIM (DSI)	26	18
Kim 2018 [358] **Older version** **Kim** 2010 [338]	Korea	MS	Elderly	Selected previously published studies + Older version	Delphi[M]	P	PIM	110	54
Kojima 2016 [359]	Japan	NS	Elderly	Literature review	NS consensus	P	PIM, PPO	37	9
Kroger 2015 [360]	Canada	LTC	Patients with severe dementia	Literature Review	RAM[M]	P	Medication appropriateness categories	49	49
Laroche 2007 [361]	France	NS	Elderly	Literature review	Delphi	P	PIM	34	19
Lindblad 2006 [362]	US	Community	Elderly	Literature Review	Delphi	P	DSI	28	19
Mackinnon 2002 [321]	US and Canada	NS	Elderly	Literature Review	Delphi	O	PDRM	52	17
Maio 2010 [316]	Italy	Community	Elderly	Beers 2003 [322]	NGT	P	PIP	23	5
Malone 2004 [363]	US	Pharmacies	NS	Literature Review + DDI resources	Delphi[M]	P	DDI	25	11
Mann 2012 [364]	Austria	MS	Elderly	PRISCUS preliminary list	Delphi[M]	P	PIM	73	37
Marzi 2018 [365]	Argentina	NS	Elderly	Literature review + selected previously published studies	Delphi	P	PIM	128	63
Mast 2015 [366]	Netherlands	Community	Elderly	Literature review + guidelines + experience	Delphi	P	DRPs	124	16
McLeod 1997 [367]	Canada	NS	Elderly	Textbooks + Beers 1991 [254]	Delphi[M]	P	PIP	38	14
Morris 2003 [368] **Older version** **Morris** 2002 [336]	UK	Community	NS	Older version + Selected previously published studies	Delphi	O	PDRM	24	0
Nyborg 2015 [369]	Norway	LTC	Elderly	NORGEP criteria [370] + Literature review + Experience.	Delphi	P	PIM	34	17
O'Mahony 2015 [304] **Older version** **Gallagher** 2008 [257]	Europe	MS	Elderly	Older version [257] + Literature review + Experience.	Delphi	P	PIM, PPO	114	25

Oborne 1997 [371]	UK	Hospitals	Elderly	Literature Review	Expert panel	P	Harmful and appropriate Prescribing	14	0
Oborne 2003 [372]	UK	LTC	Elderly	Selected previously published studies	NR	P	Harmful and Appropriate Prescribing	13	0
Okechukwu 2006 [373]	Ireland	Community	NS	Literature Review	NS consensus	P	PQ	11	1
Onder 2014 [326]	Italy	NS	Elderly	Literature Review	Delphi[M]	P	Poor Prescribing Quality	13	1
Onder 2014 [374]	International	MS	Complex Elderly	Literature review + Guidelines	NS consensus	P	Recommendations to Prescribe	19	0
Paton 2004 [278]	UK	Hospitals	Psychiatric patients	NR	NR	P	PQ	7	5
Pazan 2018 [375] **<u>Older version</u>** **Kuhn-Thiel** 2014 [337] **Pazan** 2016 [318]	Europe	NS	Elderly	Older version [337]	Delphi	P	Medication appropriateness categories	264	63
Phansalkar 2011 [376]	US	Pharmacies	NS	Selected previously published studies + Medications databases	NS consensus	P	DDI	15	7
Prot-labarthe 2014 [377]	France	NS	Paediatric	Literature Review	Delphi	P	PIM, PPO	102	9
Quintense 2019 [378]	Belgium	Hospitals	NS	Literature review + Guidelines	Expert panel	P	Clinical rules	78	8
Rancourt 2004 [323]	Canada	LTC	Elderly	Literature Review	Delphi[M]	P	PIP	111	53
Raebel 2006 [379]	US	Community	NS	FDA black-box warnings + Guidelines + Experience	NR	P	Medication monitoring	12	2
Reabel 2007 [380]	US	Community	Elderly	Selected previously published studies	Expert panel	P	PIM	11	5
Renom-Guiteras 2015 [328]	Europe	NS	Elderly	Selected previously published studies	Delphi	P	PIM	282	127
Robertson 2002 [381]	Canada	NS	Elderly	Mackinnon study [321] + Experience	Delphi and NGT	O	PDRM	52	15
Rognstad 2009 [370]	Norway	Community	Elderly	Literature Review + Experience	Delphi[M]	P	PIP (PIM, DDI)	36	22
Ruths 2003 [382]	Norway	LTC	Elderly	Literature Review + Guidelines + Experience	Expert panel	P	DRPs	17	7
Saverno 2011 [383]	US	Pharmacies	NS	Literature Review + DDI references	Consensus among the researchers	P	DDI	13	1

Smits 2016 [261]	Netherlands	MS	CKD patients	Guidelines + Literature review	RAM	P	Optimal and unsafe prescribing	16	0
Solberg 2004 [384]	US	Community	Adults	3 key DDI references	Expert panel	P	DDI	44	17
Spencer 2014 [29] **Older version** **Avery** 2011 [209]	UK	Community	NS	Literature review + older version [209] + Textbooks	RAM	P	Hazardous prescribing and inadequate monitoring.	56	7
Tamblyn 1994 [385]	Canada	MS	Elderly	Literature Review + Experience + Textbooks	Expert panel	P	High risk prescribing and DDI	32	17
Thomas 2013 [35]	UK	Hospitals	NS	literature review + Experience	Delphi	P	PE (high risk prescribing)	80	18
Tjia 2010 [386]	US	Community	Adults	Literature Review + FDA black-box warnings + Guidelines	Delphi[M]	P	Medication monitoring	61	13
Tommelein 2015 [330]	Belgium	Pharmacies	Elderly	Literature Review	RAM	P	PIP	83	18
Van der Linden 2014 [324]	Belgium	NS	Elderly	STOPP 2008 [257]	NS consensus	P	PIP	76	11
Van Dijk 2003 [387]	Netherlands	LTC	Elderly	NR	NR	P	Suboptimal prescribing	17	1
Wessell 2010 [308]	US	Community	Adults	Literature Review	NS consensus	P	Prescribing and Monitoring errors	30	8
Williams 2005 [388]	Ireland	Community	NS	Literature Review	NS consensus	P	Harmful and Appropriate Prescribing	16	1
Winit Watjana 2008 [389]	Thailand	NS	Elderly	Literature Review + Textbooks	Delphi	P	High-risk medications, DDI and DSI	77	28
Yu 2011 [390]	US	Hospitals	NS	Literature Review + Experience	Delphi[M]	P	Medication monitoring	24	1
Zhan 2001 [391]	US	Community	Elderly	Beers 1997 [335]	Delphi[M]	P	PIM	33	17

ATC: The Anatomical, Therapeutic and Chemical. CKD: Chronic kidney disease. DDI: drug-drug interaction. DRPs: Drug related problems. DSI: drug-disease interaction. FDA: Food and Drug Administration. LTC: Long-term care. [M]: Modified. MH: Mental Health. NGT: Nominal group technique. NORGEP: The Norwegian General Practice. NPSA: National Patient Safety Agency. NR= not reported. NS= not specified. O=Outcome (outcome indicator is the consequences of provided healthcare). P=Process (process indicators comprises the care provided to the patients). P/O= Process/Outcome. PDRM: preventable drug related morbidity. PE: prescribing errors. PIM: potentially inappropriate medication. PIP: potentially inappropriate prescribing. PPO: potentially prescribing omission. PQ: prescribing quality. RAM: RAND/UCLA Appropriateness Method. STOPP/START: Screening tool of older people's prescriptions and screening tool to alert to right treatment. UK: United Kingdom. US: United States. WHO: World Health Organization.

Table 4.3: Summary of included study characteristics

Characteristics	All unique studies (79 studies) N (%)	Studies included MH-related indicators (70 studies) N (%)	Studies MH-related potential PSIs were selected from (59studies) N (%)
Continent			
Europe	42 (53.2%)	35 (50.0%)	27 (47.5 %)
North America	24 (30.4%)	24 (34.3%)	22 (37.3%)
Asia	6 (67.7%)	5 (7.1%)	5 (8.5%)
International	3 (3.8%)	2 (2.9%)	2 (3.4%)
Australia	3 (3.8%)	3 (4.3%)	1 (1.7%)
South America	1 (1.3%)	1 (1.4%)	1 (1.7%)
Publication Year			
1990-1999	3 (3.8%)	2 (2.9%)	2 (3.4%)
2000-2009	26 (32.9%)	23 (32.9%)	18 (30.5%)
2010-2019	47 (63.3%)	45 (64.3%)	39 (66.1%)
Targeted population			
Elderly	40 (50.6%)	38 (54.3%)	31 (52.5%)
Not specified	20 (25.3%)	17 (24.3%)	15 (25.4%)
Adults	5 (6.3%)	5 (7.1%)	5 (8.5%)
Paediatric	4 (5.1%)	2 (2.9%)	2 (3.4%)
CKD	2 (2.5%)	1 (1.4%)	1 (1.7%)
All ages	1 (1.3%)	1 (1.4%)	1 (1.7%)
Middle aged	1 (1.3%)	1 (1.4%)	1 (1.7%)
Psychiatric	1 (1.3%)	1 (1.4%)	1 (1.7%)
Adults with bipolar disorder	1 (1.3%)	1 (1.4%)	1 (1.7%)
Severe dementia	1 (1.3%)	1 (1.4%)	1 (1.7%)
Elderly with Limited life expectancy	1 (1.3%)	1 (1.4%)	-
Palliative with advanced dementia	1 (1.3%)	1 (1.4%)	-
Complex elderly	1 (1.3%)	-	-
Targeted setting			
Community	26 (32.9%)	22 (31.4%)	19 (32.2%)
Not specified	17 (21.5%)	17 (24.3%)	16 (27.1%)
Hospitals	11 (13.9%)	9 (12.9%)	8 (13.6%)
Multiple settings	11 (13.9%)	9 (12.9%)	6 (10.2%)
Long-term care	9 (11.4%)	8 (11.4%)	5 (8.5%)
Pharmacies	5 (6.3%)	5 (7.1%)	5 (8.5%)
Methods to identify indicators [a]	**Reported 75 (94.9%)**	**Reported 66 (94.3%)**	**Reported 56 (94.9%)**
Literature review	41 (51.9%)	36 (51.4%)	33 (55.9%)
Experience	16 (20.3%)	16 (22.9%)	13 (22.0%)
Multiple selected tools [b]	16 (20.3%)	14 (20.0%)	11 (18.6%)
Guidelines	12 (15.2%)	9 (12.9%)	8 (13.6%)
Single selected tool [c]	9 (11.4%)	7 (10.0%)	6 (10.2%)
Textbooks [d]	7 (8.9%)	6 (8.6%)	5 (8.5%)
Older versions	7 (8.9%)	6 (8.6%)	5 (8.5%)
FDA black box warnings	3 (3.8%)	3 (4.3%)	3 (5.1%)
DDI references	3 (3.8%)	3 (4.3%)	3 (5.1%)
medication databases	1 (1.3%)	1 (1.4%)	1 (1.7%)
preliminary list	1 (1.3%)	1 (1.4%)	-
Safety incidents	1 (1.3%)	-	-
Validation method	**Reported 72 (91.1%)**	**Reported 65 (92.9%)**	**Reported 55 (93.2%)**
Delphi	38 (48.1%)	34 (48.6%)	29 (49.2%)
NS consensus	12 (15.2%)	11 (15.7%)	10 (16.9%)
RAM	10 (12.7%)	9 (12.9%)	8 (13.6%)
Expert panel	8 (10.1%)	7 (10.0%)	5 (8.5%)
NGT	2 (2.6%)	2 (2.9%)	1 (1.7%)
Consensus among research group	1 (1.3%)	1 (1.4%)	1 (1.7%)

Delphi and NGT	1 (1.3%)	1 (1.4%)	1 (1.7%)
Type of prescribing indicators			
Process	75 (94.9%)	67 (95.7%)	56 (94.9%)
Outcome	4 (5.1%)	3 (4.3%)	3 (5.1%)
Number of indicators	**4507 reported indicators**	**1386 MH related indicators (1106 after removing duplicates and splitting indicators)**	**245 MH related PSIs [c]**
Average (SD)	57 (SD=59.8)	20 (SD=25.1)	-
Range	6-282	1-127	-

CKD: Chronic kidney disease. DDI: Drug-drug interactions. FDA: Food and Drug Administration. MH: Mental health. NGT: nominal group technique. NS: not specified. PSIs: Prescribing safety indicators. RAM: RAND/UCLA Appropriateness Method. SD: Standard deviation

[a]. The total percentage exceed 100% because most studies used more than one method.

[b]. These studies selected multiple previously published tools.

[c]. These studies selected one specific tool

[d]. These studies used selected textbooks.

[c]. The average, SD and range were not calculated for the potential PSIs because they were selected after removing duplicates and splitting indicators.

4.4.2 Stage 2: Identifying and extracting mental health related prescribing indicators

From the 79 included unique studies, a total of 4507 individual prescribing indicators were reported containing an average of 57 (SD=59.8) indicators per study, ranging from 6 [43] to 282 [328] indicators.

Seventy studies (88.6% of unique studies) contained at least one mental health related indicator. Following data extraction and review, a total of 1386 (30.8% of total) indicators were deemed to be mental health related based on the operational definition (Box 4.1). There was an average of 20 (SD=25.1) mental health related indicators per study, and ranging from 1 [43,47,326,341,350,373,383,387,388,390] to 127 [328] indicators. Five studies were concerned exclusively with prescribing indicators in the mental health population/setting,[278,331,345,354,360] two of these studies [354,360] were exclusively for patients with dementia and one was for patients suffering with bipolar disorder.[331] Nine studies did not report any mental health prescribing indicators.[210,255,261,343,356,368,371,372,374] Table 4.3 summarises the characteristics of the studies that included mental health related prescribing indicators (n=70).

The following subsections from 4.4.2.1 to 4.4.2.8 will examine the characteristics of the 70 studies that contained at least one mental health related indicator.

4.4.2.1 Countries

Most studies developed prescribing indicator tools to be used in the US [303,308,317,345,353-355,362,363,376,379,380,383,384,386,390,391] (n=17/70, 24.3%), followed by the UK [29,30,35,43,47,173,278,339] (n=8, 11.4%) and Canada [323,348,360,367,381,385] (n=6, 8.6%). The remaining studies described tools developed for Ireland [344,352,373,388] (n=4, 5.7%), Spain [325,350,351] (n=3, 4.3%), Australia [340,341,349] (n=3, 4.3%), Norway [369,370,382] (n=3, 4.3%), Belgium [324,330,378] (n=3, 4.3%), The Netherlands [366,387] (n=2, 2.9%), Italy [316,326] (n=2, 2.9%), France [361,377] (n=2, 2.9%), Korea [357,358] (n=2, 2.9%), Germany [327] (n=1, 1.4%), Taiwan [342] (n=1, 1.4%), Austria [364] (n=1, 1.4%), the Czech Republic [329] (n=1, 1.4%), Portugal [307] (n=1, 1.4%), Japan [359] (n=1, 1.4%), Argentina [365] (n=1, 1.4%) and Thailand [389] (n=1, 1.5%). Another 7 studies developed tools to be used in more than one country; 3 (4.3%) [304,328,375] were for European countries, 2 (2.9%) [331,347] were for international use, 1 (1.4%) [346] were for the UK and Ireland, and 1 (1.4%) [321] was for Canada and the US.

4.4.2.2 Publication year

Only 2 studies (2.9%) [367,385] were published prior to the year 2000. A total of 23 (32.9%) studies were published between 2000-2009, and 45 (64.3%) from 2010 onwards.

4.4.2.3 Targeted population

The elderly population was the most common patient group specifically targeted by the indicator tools (n=38/70, 54.3%). Of these, 26/38 (68.4%) [303,304,316,317,323,325-329,339,340,342,349,351,357,358,362,364,366,375,380-382,385,391] studies defined their elderly population as ≥65 years old, 3 (7.9%) [344,369,370] as ≥70 years old, 2 (5.3%) [359,361] as ≥75 years old, and the remaining 7 (18.4%) [321,324,330,365,367,387,389] tools did not define a specific age. Of the remaining studies, 5/70 (7.1%) [308,347,355,384,386] described tools specifically for adults, 2 (2.9%) [353,377] for paediatric patients, 4 (5.7%) for psychiatric patients (including bipolar disorder (n=1),[331] general psychiatric patients (n=1)[278] and severe/advanced dementia (n=2)[354,360]), and 1 (1.4%) [348] for patients with chronic kidney disease. Another 3 indicator tools specifically targeted either middle age (45-46 years old) patients [346], patients of all ages [345] and patients with limited life expectancy [352]. A total of 17 (24.3%) [29,35,43,47,173,307,341,350,363,373,376,378,379,383,388,390,392] of the 70 studies did not identify a population that their indicators were meant to be applied to.

4.4.2.4 Setting

A total of 22 (31.4%) studies developed tools that were specific to patients in the community, including primary care (n=14, 20.0%)[29,30,43,47,173,307,308,325,344,350,366,370,373,388], ambulatory care (n=5, 7.1%) [355,379,380,384,386] and 3 studies (4.2%) [316,362,391] targeted any patients in the community.

Seventeen (24.3%) studies did not specify a setting for their developed tools. The remaining tools targeted hospitals (n=9/70, 12.9%) [35,278,341,347,349,351,353,378,390], multiple settings (n=9, 12.9%) [303,304,331,340,342,352,358,364,385], long-term care settings (n=8, 11.8%) [317,323,339,354,360,369,382,387] and pharmacies (n=5, 7.1%).[330,348,363,376,383]

4.4.2.5 Method to identify prescribing indicators

Methods used to identify indicators were reported in 66 (94.3%) of the studies. A total of 38 (54.3%) studies used one method to identify their prescribing indicators, with 28 (40.0%) using more than one method. Another 4 (5.7%) [47,278,353,387] studies did not report a source of their indicators. Literature review was the most commonly method used, being used in 36 (51.4%) studies. Authors who provided additional detail described literature review processes as including searching for indicators from previously published tools and/or searching to identify new indicators from randomised controlled trials and observational studies.

Other reported sources of prescribing indicators included clinical experience (n=16, 22.9%), selecting multiple previously published tools (n=14, 20.0%) or a single tool (n=7, 10.0%) (without mentioning literature review), guidelines (n=9, 12.9%), textbooks (n=6, 8.6%), older versions to be updated (n=6, 8.6%), FDA black box warnings (n=3, 4.3%), DDI references (n=3, 4.3%), preliminary list of previous tool (n=1, 1.4%) and medication databases (n=1, 1.4%).

4.4.2.6 Validation method

The most commonly used method for validation of prescribing indicators was the Delphi method, [266] which was used during development of 34 (48.6%) tools (of these, 16/34 (47.1%) used a modified Delphi). The RAND/UCLA appropriateness method (RAM) [267] was used in development of 9 tools (12.9%) [29,30,173,325,330,340,341,348,360] (of these, 4/9 (44.4%) [30,173,341,360] used a modified RAM). Of the remaining studies, 7 (10.0%) [345,349,378,380,382,384,385] used an expert panel, 2 (2.9%) [316,350] used the Nominal Group Technique (NGT), 1 (1.4%)

[383] used consensus among the research group without further description and 1 (1.4%) [381] used both Delphi and NGT. A total of 11 (15.7%) [43,308,324,331,339,344,353,359,373,376,388] studies used a non-specific consensus building approach, and 5 (7.1%) [47,278,355,379,387] did not report any validation of their prescribing indicators.

4.4.2.7 Type of prescribing indicators

A total of 67 (95.7%) studies developed prescribing process indicators. Numerous terms describing the prescribing processes of interest were used in the included studies. These included: hazardous, suboptimal, optimal, inappropriate, unsafe, high risk, omitted and unusual prescribing, prescribing appropriateness, drug-related problems (DRPs), adherence to management guidelines, PIM, high risk medication, DDI, drug disease interaction, inadequate monitoring and monitoring errors. The remaining 3 (4.3%) [307,321,381] studies developed prescribing outcome indicators to identify preventable drug related morbidity (PDRM) and preventable medication-related hospitalisations.

4.4.2.8 Categorising mental health related prescribing indicators

From the 1386 extracted mental health related indicators, duplicates were removed and some indicators were split and re-categorised by the research team, which reduced the final number of the included indicators to 1106. These indicators were categorised into eight types of prescribing problems and into nine medication categories. The full list of mental health related indicators can be found in Appendix (3).

For prescribing problems, the highest number of indicators were categorised under 'PIM: Considering Diagnoses or Conditions' which contained 447 (40.4%) indicators. This was followed by 'PIM: Independent of Diagnoses or Conditions' (n=269, 24.3%), 'DDI' (n=153, 13.8%), 'inappropriate duration' and 'inappropriate dose' (n=74 each, 6.7%). The categories containing the fewest number of indicators were 'omission' with only 8 (0.7%) indicators, along with 'others' (n=28, 2.5%) and 'monitoring' indicators (n=53, 4.8%).

Medications classed under the sedative, hypnotic and anxiolytics group were the most commonly reported in the developed tools with 317 indicators (28.7%). This was followed by antidepressants (n=241, 21.8%), antipsychotics (n=191, 17.3%) and mood stabilisers (n=88, 8.0%). The remaining categories were anticholinergics (n=56, 5.1%), anti-dementia (n=49, 4.4%) and ADHD medications (n=24, 2.2%). Fifteen indicators (1.4%) included psychotropics without specifying a class. Furthermore, 125 (11.3%) indicators included non-mental health medications with mental health conditions. These conditions included

delirium, insomnia, depression, dementia, advanced dementia, palliative advanced dementia and non-palliative dementia. Table 4.4 summarises the number of prescribing indicators in each category.

Table 4.4: Numbers of prescribing indicators related to mental health in each prescribing problem and medication category

Prescribing Problem	PIM Independent of Diagnoses or Conditions	PIM Considering Diagnoses or Conditions	DDI	Inappropriate Duration	Inappropriate Dose	Monitoring	Omission	Others	Total: n (%)
Medication Category									
Antipsychotics	45	85	13	19	18	7	0	4	**191 (17.3%)**
Antidepressants	42	102	67	9	9	0	4	8	**241 (21.8%)**
Sedative, hypnotics and anxiolytics	119	75	36	40	44	3	0	0	**317 (28.7%)**
Mood stabilisers	2	10	22	0	2	42	2	8	**88 (8.0%)**
Anti-dementia	27	13	7	0	0	0	2	0	**49 (4.4%)**
ADHD medications	8	13	1	0	1	1	0	0	**24 (2.2%)**
Anticholinergics	26	24	2	4	0	0	0	0	**56 (5.1%)**
Non-Specific Psychotropics	0	1	5	1	0	0	0	8	**15 (1.4%)**
Non-MH medication with MH condition	0	124	0	1	0	0	0	0	**125 (11.3%)**
Total: n (%)	**269 (24.3%)**	**447 (40.4%)**	**153 (13.8%)**	**74 (6.7%)**	**74 (6.7%)**	**53 (4.8%)**	**8 (0.7%)**	**28 (2.5%)**	**1106 (100%)**

ADHD: Attention deficit hyperactivity disorder. DDI: drug-drug interaction. MH: Mental Health. PIM: potentially inappropriate medication

4.4.3 Stage 3: Selecting potential prescribing safety indicators related to mental health disorders and medications.

From the 1106 identified mental health related indicators, 245 were considered to meet the prescribing safety indicator definition following review as they described prescribing or drug monitoring practices that could be hazardous and may put patients at significant risk of harm. These potential prescribing safety indicators were selected from 59 studies out of the 70 that included mental health related indicators. Table 4.3 summarises the characteristics of the studies that potential prescribing safety indicators related to mental health were selected from (n=59).

4.4.3.1 Categorising potential prescribing safety indicators related to mental health disorders and medications

Potential prescribing safety indicators were categorised into eight types of prescribing problems. The highest number of indicators were categorised under 'PIM: Considering Diagnoses or Conditions' which contained 91 (37.1%) indicators. This was followed by

'DDI' (n=66, 26.9%), 'inappropriate dose' (n=24, 9.8%), 'PIM: Independent of Diagnoses or Conditions' (n=20, 8.2%), 'monitoring' (n=17, 6.9%), 'inappropriate duration' (n=12, 4.9%), 'Other' (n=10, 4.1%) and 'Omission' with only 5 (2.0%) indicators.

Potential prescribing safety indicators were also categorised into nine medication categories. Antidepressants were the most commonly selected with 85 (34.7%) potential prescribing safety indicators. This was followed by sedative, hypnotic and anxiolytics (n=50, 20.4%), antipsychotics (n=38, 15.5%) and mood stabilisers (n=33, 13.5%). The remaining were ADHD medications (n=12, 4.9%), non-mental health medications with mental health conditions (n=11, 4.5%), anticholinergics and anti-dementia (n=7 each, 2.9%), and 2 indicators (0.8%) included psychotropics in general.

Table 4.5 summarises the number of potential prescribing safety indicators in each category. Table 4.6 provides some examples of the selected potential prescribing safety indicators. The full list can be found in Table 4.7

Table 4.5: Numbers of potential prescribing safety indicators related to mental health in each prescribing problem and medication category

Prescribing Problem	PIM Independent of Diagnoses or Conditions	PIM Considering Diagnoses or Conditions	DDI	Inappropriate Duration	Inappropriate Dose	Monitoring	Omission	Others	Total: n (%)
Medication Category									
Antipsychotics	2	19	4	3	3	6	0	1	38 (15.5%)
Antidepressants	7	37	31	3	3	0	2	2	85 (34.7%)
Sedative, hypnotics and anxiolytics	6	9	14	4	17	0	0	0	50 (20.4%)
Mood stabilisers	0	3	13	0	0	10	1	6	33 (13.5%)
Anti-dementia	0	3	2	0	0	0	2	0	7 (2.9%)
ADHD medications	4	5	1	0	1	1	0	0	12 (4.9%)
Anticholinergics	1	5	1	0	0	0	0	0	7 (2.9%)
Non-Specific Psychotropics	0	0	0	1	0	0	0	1	2 (0.8%)
Non-MH medication with MH condition	0	10	0	1	0	0	0	0	11 (4.5%)
Total: n (%)	20 (8.2%)	91 (37.1%)	66 (26.9%)	12 (4.9%)	24 (9.8%)	17 (6.9%)	5 (2.0%)	10 (4.1%)	245 (100%)

ADHD: Attention deficit hyperactivity disorder. DDI: drug-drug interaction. MH: Mental Health. PIM: potentially inappropriate medication

Table 4.6: Examples of the selected potential prescribing safety indicators

Prescribing problem	Medication category	Example	Sources
PIM: Independent of Diagnoses or Conditions	***Antidepressants***	Prescribing tricyclic antidepressant to a patient aged ≥ 65 years	303,317,321,341
PIM: Considering diagnoses or conditions	***Antipsychotics***	Prescribing antipsychotics other than quetiapine or clozapine to a patient aged ≥ 65 years with Parkinson's disease	173,304,317,330,366
DDI	***Anticholinergics***	Prescribing two anticholinergics to a patient aged ≥ 65 years	303,304,317,330
Inappropriate Duration	***Sedative, hypnotics and anxiolytics***	Prescribing Benzodiazepine for more than 1 month	35,373

Inappropriate dose	***Antipsychotics***	Prescribing high dose antipsychotics (*total daily dose is above the maximum recommended by the British National Formulary)*	278
Monitoring	***Mood stabilisers***	Prescribing lithium without monitoring lithium plasma level every 3 months	47,339
Omission	***Antidepressants***	Patients diagnosed with moderate/severe depressive symptoms lasting at least three months without prescribing antidepressant	304

DDI: drug-drug interaction. MH: Mental Health. PIM: potentially inappropriate medication.

Table 4.7: List of potential Prescribing Safety Indicators related to mental health medications and conditions

PIM: Independent of Diagnoses or Conditions				
Therapeutic Category	Medication/Class		Age	References
Antipsychotics	Antipsychotics		≥ 65	303,304,321,324,325
			0–5	345
Antidepressants	Antidepressants		0–5	345
	TCA		≥ 65	303,317,321,341
			≤ 18	377
	SSRI other than fluoxetine		≤ 18	173,377
	NDRI (Bupropion)		≥ 65	328
	NRI (Reboxetine)		≥ 65	328
	MAOi (Tranylcypromine)		≥ 65	327,328,351
Sedative, hypnotics and anxiolytics	Benzodiazepine		≥ 65	304,324,325,344
	Z-drugs		≥ 65	304,324
	Barbiturates		≥ 65	308,391
	Meprobamate		≥ 65	303,308,323,328,342,391
	Sedating antihistamine		≥ 65	330
	Promethazine		≥ 65	303,328,329,342,365,382,391
ADHD medications	All ADHD Medications		< 6	377
	Clonidine		≥ 65	303,316,328,330,342,365,389
	Guanfacine		≥ 65	303,328
	Methylphenidate		≥ 65	328,365
Anticholinergics	Anticholinergics		≥ 65	321
PIM: considering diagnoses or conditions				
Therapeutic Category	Condition	Medication/Class	Age	References
Antipsychotics	Dementia but Not Psychosis	Antipsychotics	≥ 65	173
	BPSD	Antipsychotics	≥ 65	303,304
	Seizures or Epilepsy	Antipsychotics	≥ 65	389
	Parkinson's Disease	Antipsychotics other than quetiapine or clozapine	≥ 65	173,304,317,330,366
	History of prostatism or previous urinary retention of BPH	Antipsychotics	-	347
	Glaucoma	Fluphenazine	-	347
		Perphenazine		347
		Trifluoperazine		347
	Syncope	Antipsychotics	≥ 65	358
	Postural Hypotension	Antipsychotics	≥ 65	358
	History of Falls	Antipsychotics	≥ 65	303,329,358
	Delirium	Antipsychotics	≥ 65	303,358
	ADHD without Hyperactivity	Antipsychotics	Children	377
	Arrhythmia	Antipsychotics	≥ 65	389
	Lewy Body Disease	Antipsychotics other than quetiapine or clozapine	≥ 65	304,317
	Chronic constipation	Perphenazine	≥ 65	357
		Clozapine		357
		Haloperidol		357
		Olanzapine		357
Antidepressants	Heart block	TCA	≥ 65	362,367,389
	Cardiac conduction abnormalities	TCA	≥ 65	304,325,344
	Cardiovascular risk factors or CVD	TCA	≥ 65	366
	Heart failure	TCA	-	30,173,347

	Arrhythmia	Amitriptyline at dose >75mg	-	29
	HTN	Venlafaxine	-	347
		Duloxetine		347
		MAOIs		347
	Postural hypotension	TCA	≥ 65	362,366,367
	Syncope	TCA	≥ 65	329,389
	History of falls	Amitriptyline	≥ 65	357
		Clomipramine		357
		Imipramine		357
	Seizures or epilepsy	SSRI	-	35,347
		TCA	-	347
	Dementia or cognitive impairment	TCA	-	35
	Glaucoma	TCA	-	347
		Mianserin	-	347
		MAOI	-	347
		Citalopram	-	347
		Escitalopram	-	347
		Fluoxetine	-	347
		Fluvoxamine	-	347
		Paroxetine	-	347
	Prostatism or history of urinary retention or BPH	TCA	-	347
	Constipation	TCA	≥ 65	325,329,344,362,389
	Current or recent significant hyponatraemia	SSRI	-	35
	Hepatic impairment or cirrhosis	TCA	-	347
	Gastrointestinal haemorrhage	Paroxetine	≥ 75	359
		Sertraline		359
		Fluvoxamine		359
		Escitalopram		359
	Peptic ulcer disease	SSRI	-	347
	Delirium	Amitriptyline	≥ 65	357
		Clomipramine		357
		Imipramine		357
	Acute bipolar depression	TCA	Adults	331
Sedative, hypnotics and anxiolytics	Dementia or cognitive impairment	Benzodiazepines	≥ 65	303,342,358,362
	History of falls or fractures	Sedative-hypnotics	≥ 65	362
	Acute or chronic respiratory failure	Benzodiazepines	≥ 65	304
	Sleep apnoea syndrome	Benzodiazepines	≥ 65	342,389
	Delirium	Benzodiazepines	≥ 65	303,358
	BPH	Antihistamine	≥ 65	389
	Advanced dementia	Antihistamine 1st generation	-	360
	Hepatic impairment or cirrhosis	Benzodiazepines	-	347
	Chronic constipation	antihistamines	≥ 65	389
Mood stabilisers	Renal failure	Lithium	-	347
	Thyroid disorders	Lithium	-	347
	Epilepsy	Lithium	-	347
Anti-dementia	Persistent bradycardia	Acetylcholinesterase inhibitors	≥ 65	304,324
	Heart block	Acetylcholinesterase inhibitors	≥ 65	304
	Recurrent unexplained syncope	Acetylcholinesterase inhibitors	≥ 65	303
Anticholinergics	Dementia or cognitive impairment	Anticholinergics	-	308
	Delirium	Anticholinergics	≥ 65	303,304,317,324
	Chronic constipation	Anticholinergics	-	347
	Glaucoma	Anticholinergics	≥ 65	304,324,329,342,362
	History of urinary retention of BPH	Anticholinergics	-	307
ADHD medications	HTN	Atomoxetine	-	347
	Anorexia and malnutrition	Methylphenidate	≥ 65	329
	Epilepsy	Methylphenidate	-	347
	Insomnia	Amphetamine	≥ 65	303
		Methylphenidate		303,329,358
	Delirium	H2-receptor antagonists		358
		Corticosteroids	≥ 65	303

Non-MH medication with MH condition		Meperidine (Pethidine)		303,358
	Insomnia	Pseudoephedrine	≥ 65	303,329,358
		Phenylephrine		303,329,358
		Armodafinil		303
		Modafinil		303
		Theophylline		303,358
	Depression	Methyldopa	≥ 65	389
	Dementia or cognitive impairment	Selegiline	≥ 65	375

Drug-drug interactions

Therapeutic Category	Medication/Class	Medication/Class	Age	References
Antipsychotics	Antipsychotics	Antipsychotic	-	278,347
		Antiparkinsonian agents	≥ 65	326
	Pimozide	Macrolides antibiotics	-	363
		Azole antifungal		363
Antidepressants	TCA	MAO	-	35
		TCA	≥ 65	323,385
		Cimetidine	-	384
		Fluoxetine	-	384
		Fluvoxamine	≥ 70	370
		Paroxetine	-	384
		Selegiline	-	376
	SSRI	Tramadol	-	35
		Aspirin (no protection)	-	35
		MAOI	-	363
		SSRI's	≥ 65	304,325,344
		NSAID (no protection)	≥ 45	346
		Venlafaxine	≥ 45	346
		Vitamin K antagonists	-	347
		Selegiline	-	384
	MAO	Tramadol	-	35
		Dextromethorphan	-	363
		Amphetamine and derivatives	-	376
		Narcotic analgesics	-	376
		Triptans	-	376
		Levodopa	-	378
		MAOI	≥ 65	323,385
	Amitriptyline	Sertraline	children	353
		Trazodone		353
	Citalopram	QT-prolonging drugs	-	35
	Citalopram	Linezolid	children	353
	Sertraline			353
	Fluvoxamine	Theophylline	-	363
		Ramelteon		376
	Trazodone	anti-HCV antivirals	-	347
	Escitalopram			347
Sedative, hypnotics and anxiolytics	Hypnotic or sedative	Hypnotic or sedative	≥ 65	317,323,385
	Benzodiazepine	Azole antifungal agents	-	363
		Cimetidine	≥ 65	389
		Benzodiazepines	-	347
	Alprazolam	Strong CYP3A4 inhibitor	≥ 65	330
	Midazolam			330
	Triazolam			330
	Flurazepam	Anti-HCV antivirals	-	347
	Guazepam			347
	Triazolam			347
	Alprazolam			347
	Zolpidem	Strong CYP3A4 inhibitor	≥ 65	330
	Zopiclone			330
	Zolpidem	Anti-HCV antivirals	-	347
Mood stabilisers	Valproic acid	Carbapenems	-	378
		Lamotrigine	Children	353
	Carbamazepine	Clarithromycin	-	383
		Erythromycin	≥ 45	346
		Cimetidine	≥ 65	389
		oral or intravaginal contraceptives, patches	-	347

		or pure progestogen pills			
		Warfarin	-		[384]
		Propoxyphene	-		[363,384]
		Rivaroxaban	-		[347]
	Lithium	ACEi	≥ 65		[303]
		NSAID	≥ 65		[330]
		Diuretics	-		[331]
	Lamotrigine	Hormonal contraceptive or combination pills	-		[347]
Anti-dementia	Anticholinesterase drugs	Anticholinergic	≥ 65		[351]
		Anticholinesterase drugs	-		[347]
Anticholinergic	Anticholinergic	Anticholinergic	≥ 65		[303,304,317,330]
ADHD medications	Clonidine	Propranolol	-		[384]
Inappropriate Duration					
Therapeutic Category	Class/Medication	Condition	Duration	Age	References
Antipsychotics	Antipsychotics	Dementia but not psychosis	>6 weeks	≥ 65	[29]
		as long-term hypnotics	>1 month	≥ 65	[325,329,351]
	More than one Antipsychotics	-	>2 month	Adults	[345]
Antidepressants	Three or more Antidepressants	-	>3 month	adults	[345]
	More than one SSRI	-	>2 month	adults	[345]
	SSRI and SNRI combination	-	>2 month	adults	[345]
Sedative, hypnotics and anxiolytics	Hypnotics	-	>1 month	-	[388]
	Benzodiazepine	-	>1 month	-	[35,373]
	Z-drugs	-	>1 month	-	[35]
	First-generation antihistamine	-	> 1 week	≥ 65	[325,329]
Non-Specific Psychotropics	Four or more Psychotropics	-	>3 months	6–17	[345]
Non-MH medication with MH condition	Opioids	Dementia (unless palliative)	long term	≥ 65	[325]
Inappropriate dose					
Therapeutic Category	Medication	Dose	Condition	Age	References
Antipsychotics	Haloperidol	>2 mg/day		≥ 65	[327-329]
	Risperidone	3 mg/day	BPSD: restlessness, agitation	≥ 65	[375]
	Antipsychotics	High dose Total daily dose is above the maximum recommended by the British National Formulary (BNF)		-	[278]
Antidepressants	Fluoxetine	>40 mg/day		≥ 65	[323]
	Imipramine	>100 mg/day		≥ 65	[323]
	Trimipramine	>100 mg/day		≥ 65	[323]
ADHD medications	SR Methylphenidate	two doses per day, rather than one dose		Children	[377]
Sedative, hypnotics and anxiolytics	Alprazolam	>2 mg/day		≥ 65	[308,329,344]
	Brotizolam	>0.125 mg/day		≥ 65	[327,328]
	Gabapentin	>1400mg/day	CrCl 30-59 mL/min	-	[348]
	Gabapentin	>700mg/day	CrCl 15-29 mL/min	-	[348]
	Gabapentin	>300mg/day	CrCl 10-14 mL/min	-	[348]
	Gabapentin	>150mg/day	CrCl < 10 mL/min	-	[348]

	Lorazepam	> 2 mg/day			≥ 65	[327]
	Lormetazepam	>0.5 mg/day			≥ 65	[327,328]
	Oxazepam	>60 mg/day			≥ 65	[308,327,328,344]
	Pregabalin	>300mg/day		CrCl 30-59 mL/min	-	[348]
	Pregabalin	>150mg/day		CrCl 15-29 mL/min	-	[348]
	Pregabalin	>75mg/day		CrCl < 15 mL/min	-	[348]
	Temazepam	>15 mg/day			≥ 65	[308,344]
	Triazolam	>0.25 mg/day			≥ 65	[308,342,344]
	Zaleplon	>5 mg/day			≥ 65	[327,328]
	Zolpidem	>5 mg/day			≥ 65	[327-329]
	Zopiclone	>7.5mg/day			≥ 70	[370]
Monitoring						
Therapeutic Category	Medication/Class	Test	Age	Frequency		References
Antipsychotics	Antipsychotics	Glucose	-	Annually		[308]
				3-4 months after starting therapy		[331]
		Weight	-	Annually		[308]
				3-4 months after starting therapy		[331]
		Lipid profile	-	3 months after starting therapy		[331]
	Clozapine	WBC	-	NR		[390]
Mood stabilisers	Carbamazepine	LFT	-	Annually		[355]
		FBC	-	Annually		[355,379]
		Carbamazepine level	-	Every 6 months		[307]
	Valproate	LFT	-	Annually		[355]
				first 6 months of therapy		[331]
		FBC	-	Annually		[355,386]
				First 6 months of therapy		[331]
	Lithium	lithium level	-	every 3 months		[47,339]
		TFT	-	every 6 months		[331]
		Creatinine	-	annually		[355,379]
ADHD medications	Methylphenidate	Growth chart (height and weight)	Children	NR		[377]
Omission						
Therapeutic Category	Medication/Class	Condition			Age	References
Anti-dementia	Acetylcholinesterase inhibitor	Mild- moderate Alzheimer's dementia			≥ 65	[304]
		Lewy Body dementia				[304]
Antidepressants	Antidepressants	moderate/severe depressive symptoms lasting at least three months			≥ 65	[325]
	SSRI	Persistent severe anxiety that interferes with independent functioning.			≥ 65	[304]
Mood stabilisers	Mood stabilisers	on antidepressants for acute bipolar depression			Adult	[331]
Other						
Therapeutic Category	Indicator				Age	References
Antidepressants	TCA except in case of severe depression or in low dose for neuropathic pain				≥ 65	[324]
	Patient diagnosed with acute bipolar depression is prescribed antidepressant monotherapy				Adult	[331]
Antipsychotics	Risperidone continued following discharge without follow-up to a patient with dementia				≥ 75	[381]
Mood stabilisers	Lithium dose not adjusted or omitted in a patient with a lithium concentration above the therapeutic range (>1. - mmol l-1)				-	[35]
	Lithium prescribed in conjunction with newly prescribed nonsteroidal anti-inflammatory drugs without dose adjustment or increased monitoring				-	[35]

	Lithium therapy prescribed in conjunction with newly prescribed loop or thiazide diuretics without dose adjustment or increased monitoring	-	[35]
	Patient treated with lithium in bipolar disorder does NOT have a serum level 0.8–1.1 mmol/L	Adult	[331]
	Patient on lithium in bipolar disorder and with lithium serum level [1.5 mmol/L) has lithium not discontinued	Adult	[331]
	In bipolar disorder, Patient who has discontinued lithium, does NOT have a recorded gradual reduction of lithium dose over at least 4 weeks	Adult	[331]
Non-Specific Psychotropics	Three or more psychotropic drugs on an as required (PRN) basis.	-	[278]

ADHD: Attention deficit hyperactivity disorder. ACEi: Angiotensin-converting-enzyme inhibitor. BPH: Benign prostatic hyperplasia. BPSD: Behavioural and Psychological Symptoms of Dementia. CrCl: Creatinine clearance. CVD: Cardiovascular disease. CYP: Cytochrome P450. FBC: Full blood count. HCV: Hepatitis C virus. HTN: Hypertension. LFT: Liver function test. MAOi: Monoamine oxidase inhibitor. MH: Mental health. NDRI: Norepinephrine–dopamine reuptake inhibitor. NR: Not reported. NRI: Norepinephrine reuptake inhibitor. NSAID: Nonsteroidal anti-inflammatory drugs. SNRI: Serotonin and norepinephrine reuptake inhibitors. SSRI: Selective serotonin reuptake inhibitor. TCA: Tricyclic antidepressants. TFT: Thyroid function test. WBC: White blood count.

4.5 Discussion

To our knowledge, this is the first systemic review conducted to identify and screen all known published prescribing quality and safety indicators in order to extract potential prescribing safety indicators related to populations with mental illness, and indeed any broader type of mental health related prescribing quality indicators.

Five studies specifically focused on developing/reporting prescribing indicators for populations with mental illness have been found.[278,331,345,354,360] However, two of these studies [354,360] were exclusively for patients with dementia and one was for patients suffering with bipolar disorder.[331] Although 2 studies were found that involved development of prescribing indicators for a range of mental disorders and which contained some prescribing safety indicators [278,345], their main focus was not on safety and therefore they did not capture many hazardous prescribing issues, such as medication monitoring and omissions.[278,345]

The methods used to identify indicators were reported in 94.3% of the studies reporting mental health related indicators, which is consistent with another systematic review that examined the development of general health care quality indicators using the Delphi method.[393] However, these methods varied significantly between the included studies, with some not reporting any sources for their indicators [47,353,354,387], or using a single previously published study. In contrast, others conducted comprehensive systematic reviews of the relevant literature to identify previously published indicators or new potential indicators. Even though there is no agreed optimum method to identify/develop potential indicators reported in the literature, literature review was found to be the most commonly used method in this review and in a previous publication.[393] In addition, this method was also used by the Agency for Healthcare Research and Quality (AHRQ) to identify potential indicators.[394]

Most studies reported a validation process with differences in approach and the depth of detail provided. The majority of studies used a consensus approach to validate their indicators. Each consensus method has its own advantages and disadvantages. However, there is a lack of standardisation in defining, using and reporting of consensus methods.[277] For example, some studies used modified Delphi and other used the RAM. However, the RAM can also be known as modified Delphi.[267] Therefore, it is important that studies report how the original method has been modified. Moreover, some studies did not specify which consensus method they used. In future it would be worthwhile to develop a method

to assess the quality of implementation and reporting of consensus-based studies. A small number of studies did not report any process of validation for their indicators.[47,278,343,355,373,379,382,384,385,387,388] However, some of these studies did not aim to report the development of indicators such as the PINCER trial [47] which instead aimed to compare the effectiveness of an intervention and prescribing indicators were used as the outcome measure. Therefore, potential indicators retrieved from these studies require further validation.

Given that most prescribing assessment tool were developed for application to elderly populations, the majority of the identified mental health related indicators targeted elderly, with a limited number of indicators designed for other populations. In addition, no indicators have been reported for pregnant or breastfeeding women, despite the risk of some psychotropics in this group such as prescribing valproate in women of child bearing potential.[148] Consequently, it is important that future work takes the into consideration the unique characteristics of populations with mental illness and different prescribing problems when developing new suites of indicators.

Based on the findings, none of the recently published sets of prescribing safety indicators were developed to be used specifically for mental health disorders and medications. While we have identified expansive lists of different mental health related indicators, these lists have been identified from different types of studies with different purposes, settings and populations. In addition, the majority of these studies did not focus on patients with mental illness or clinical practice within specialist mental health settings. Therefore, these indicators may not reflect all potential prescribing safety indicators in the mental health context.

In addition, the identified potential indicators are not prioritised. It can be unwieldy to assess all indicators of the current list in clinical practice, otherwise health care staff might be overburdened.[395] Therefore, there is a need to focus on indicators with the greatest risk. Hence, we have labelled these indicators as 'potential' and further development and validation may be recommended before they are applied into clinical practice locally.

There is therefore a need to develop a new set of prescribing safety indicators specifically for application to patients with mental illness that takes into consideration the unique characteristics of the patient population, the different therapeutic classes of psychotropics, the broad areas of potentially hazardous prescribing and drug monitoring in this population. This prescribing safety indicators set should then undergo consensus-based

validation with experts in mental health and medication management in order to be further developed and prioritised.

4.6 Conclusion

This chapter present the first systematic review to identify a list of potential prescribing safety indicators related to mental illness and medications that may be used to assess the safety of prescribing. Examination of the included studies and the types of the identified potential prescribing safety indicators extracted highlights the need for development of a suite of prescribing safety indicators specific to patients with mental illness. The next chapter will present the findings of a consensus-based study with experts that was conducted to address this need by developing a suite of prescribing safety indicators specific for populations with mental disorders in the UK.

Chapter 5 : Development of prescribing safety indicators related to mental health disorders and medications: modified e-Delphi study

The purpose of this chapter is to describe the aims, method, results and discussion of the Delphi study, which was designed to develop a suite of prescribing safety indicators specific for populations with mental illness. This is the second study in this research programme and it was published in 2021 in the British Journal of Clinical Pharmacology.[396]

5.1 Introduction

As Chapter 2 indicated, there are various challenges when prescribing for patients with mental disorders. Consequently, research evidence suggests that prescribing errors, inappropriate prescribing and preventable medication-related harm are common in this population.[25-27] Accordingly, developing a suite of prescribing safety indicators specific for populations with mental disorders to assess and improve prescribing safety is fundamental, as recommended by the Department of Health and Social Care to develop prioritised and comprehensive suites of indicators to help reduce medication related harm. However, as described in Chapter 4, the systematic review findings showed that whilst there are a number of prescribing safety indicator sets that have been developed for different populations and settings, such as primary [29,30,173,209,308] and secondary care,[35,210] a suite specific to psychotropic medications and populations with mental illness has not been developed, with only one set with broad indicators relating to quality of prescribing.[278,306]

Chapter 4 has also identified a large list of potential mental health related prescribing safety indicators. However, these indicators were not specifically validated or prioritised by experts to reflect prescribing within the UK context to facilitate improvement in line with the national policy. In addition, it was reported that the list might not fully represent wider areas of risk in psychiatry. Therefore, there is a need to refine the indicators to UK practice context, prioritise the indicators needing more attention from clinicians, and to identify areas that has not yet been covered.

5.2 Aim

The chapter aimed to develop a suite of prescribing safety indicators specific for populations with mental disorders.

The objectives of this chapter were:

- To select a refined list of potential mental health prescribing safety indicators based on the findings of Chapter 4,
- To select and recruit an appropriate expert panel to rate the indicators,
- To design an efficient online Delphi questionnaire to distribute the list of indicators to the expert panel,
- To achieve consensus from the expert panel on a set of mental health indicators to assess the safety of prescribing,
- To estimate the risk of harm associated with each indicator to prioritise them.

5.3 Methods

5.3.1 Rationale

The Delphi technique is a structured consensus method that uses a series of questionnaires or rounds "*to obtain the most reliable consensus of opinion of a group of experts*".[265] The decision to use the Delphi method was driven by the nature of the study. Ideally, indicators of health care quality need to be based on strong scientific/clinical evidence.[259] However, robust supporting data is often scarce.[258-260] Therefore, combining expert opinion and scientific evidence using consensus methods, such as with the Delphi method, is a common approach to developing prescribing quality and safety indicators.[29,35,209,210,261]

The NGT was excluded as it is usually used to generating new ideas and statements. However, there was no need as the systematic review presented in Chapter 4 already identified a large list of potential prescribing safety indicators. Moreover, the Delphi technique would allow additional indicators to be included if panellists felt any were missing.

The RAND/UCLA appropriateness method was also excluded, because it requires that panellists meet face-to-face to discuss and then rate the indicators. It was difficult to convene a meeting for a group of mental health experts from across the country, in terms of cost and time. However, the Delphi would allow this, as no face-to-face contact is required. Finally, since the panellists would have different backgrounds and expertise, the anonymous nature of the Delphi would help to minimise peer pressure while encouraging the panellists' freedom in expressing their ratings.

5.3.2 Study design

A modified electronic Delphi (e-Delphi) technique was used to develop the prescribing safety indicators. The e-Delphi process in this study involved two stages adapted from similar work to develop prescribing safety indicators in primary care.[29] The *first stage* consisted of two rounds to develop and agree on a set of prescribing safety indicators related to mental health disorders and medications. The *second stage* included a single round which aimed to identify the most clinically significant indicators based on the severity of harm and likelihood of them occurring in clinical practice. The main modification from the original Delphi approach was not limiting data collection to open questions in the first round as potential indicators were already identified from the literature. However,

participants were allowed to suggest new indicators in the first round, as well as comment on those presented. In addition, the questionnaires were distributed through email using an online survey portal as opposed to post in the original Delphi. Using an online questionnaire reduces the required time for postal communications and helps with recruitment. [397,398]

5.3.3 Identifying potential indicators

In the previous chapter we identified a list of 245 potential mental health-related prescribing safety indicators.[306] This list was used as the major source of indicators to propose to participants in this study. Indicators from this review were combined with other new potential prescribing safety indicators identified after reviewing several resources such as the BNF, Martindale, AHFS Drug Information, Stockley's Drug Interactions (all accessed via Medicines Complete[319]), relevant NICE guidelines,[332] the Maudsley Prescribing Guidelines in Psychiatry,[20] the Psychotropic Drug Directory [333] and searching safety alerts produced by national agencies such the MHRA [399] and the FDA.[400] Further potential indicators were identified from the clinical experience of two mental health clinical pharmacists within the research team (RNK and JN).

Indicators were defined as mental health related if they included (a) mental disorders according to the ICD-10 [320] and the DSM–5;[55] (b) medications that could be used to treat or prevent mental disorder (i.e. psychotropics) ; or (c) medication that can be used to treat or prevent side effects of the psychotropics (e.g. anticholinergic medications for the treatment of sialorrhoea and extrapyramidal symptoms caused by antipsychotics).[401]

A refined list of potential indicators was then constructed using the lists identified from the above sources by applying predefined inclusion and exclusion criteria,[209] (Box 5.1) to restrict the indicators to UK practice and to select only potentially hazardous prescribing practices that could cause significant risk of harm. Two mental health clinical pharmacists (JN and RNK) applied the criteria, using existing guidelines/literature and professional opinion. The refined list was then circulated between the research team to recommend any necessary modifications.

Box 5.1: Inclusion and exclusion criteria

Inclusion criterion:

- **The indicator describes a pattern of prescribing that is potentially hazardous and may put patients at risk of harm.**

Exclusion criterion:

- **The indicator describes a pattern of prescribing that is unusual in the UK**

The final list of indicators that were included in the first round of stage 1, contained 101 potential prescribing safety indicators. The indicators were not specific for a patient age group unless specified within the indicator. Most of these potential indicators (n=61/101, 60.4%) were identified from existing sets of indicators from Chapter 4. However, 55.7% (n=34/61) of these indicators identified from existing indicator sets were slightly modified by the research team. Most of these modifications were undertaken to broaden the age group when the risk covers a wider population, to change monitoring frequency according to UK recommendations, or to restrict the indicator to specific medications within a therapeutic class when the risk has a stronger association with these medications. The remaining 40/101 (39.6%) indicators were newly identified from the previously stated resources such as the BNF,[319] Maudsley prescribing guidelines [20] and the clinical experience of the research team.

5.3.4 Questionnaire design

Each indicator included in the initial list was presented in a structured fashion similar to a set of prescribing indicators developed in the UK for hospital settings,[35] as a medication/class, process, and rationale. For example: benzodiazepine [class] prescribed to a patient >65-years-old [process] (risk of fall and fracture [rationale]). The web-based online questionnaire was designed using SelectSurvey.Net (V4.075.003, ClassApps).

The first-round questionnaire of the e-Delphi was piloted with two consultant psychiatrists in order to improve clarity and to identify any ambiguities with the questions and the instructions. Feedback from the pilot was incorporated into the final version of the questionnaire.

5.3.5 Expert panel selection and recruitment

Given that indicators were designed to assess prescribing safety for people with mental disorders, it was agreed that panellists for the e-Delphi would be qualified health care

professionals with experience and interest in prescribing and/or medicines management and safety for patients with mental disorders, including psychiatrists, mental health pharmacists, mental health nurses and GPs, each with a minimum of five years post qualification experience.

Potential experts were identified through professional and social networks by distributing flyers (Appendix (4)) and introductory emails (Appendix (5)) to gather expressions of interest. Participants were invited via email (Appendix (6)), and were provided with a participant information leaflet (Appendix (7)) to ensure they were fully informed prior to accepting.

A total of 48 experts were invited to participate in the study, of whom 32 agreed. A target of a minimum of 20 experts participating was set prior to the study. Although the optimal size of a Delphi panel is not a subject of consensus in the published literature,[260,393] previous studies in the UK utilised approximately 20 experts to successfully develop prescribing indicators using the e-Delphi method.[35,210]

5.3.6 Ethical Considerations

Even though the research participants might be NHS staff, NHS Research Ethics Committees (RECs) approval was not required, as the research dose not included sensitive questions about their personal role. In addition, Health Research Authority (HRA) study-wide assessment is not required since the research involves participants solely by virtue of their qualifications, experience or professional capacity rather than in relation to their employment by a specific NHS organization. Ethical approval for this study was obtained following proportionate review by the University of Manchester Research Ethics Committee (UREC), Reference 2019-4632-9361 and 2019-4632-11444 (Appendix (8)).

5.3.6.1 Consent

Participants were asked to provide consent before starting the questionnaire. Consent questions were embedded into the first page of the questionnaire. Participants were given four weeks to decide whether or not to take part in the research. Participants were able to withdraw without giving a reason. However, it was not possible to remove their data from the project once it has been anonymised and forms part of the data set, which was 1 week after the survey is submitted.

5.3.6.2 Anonymity, Confidentiality and Data Protection

The following personal data of participants were collected: name, telephone number, email address, job title, geographic area and years of experience. The name, telephone number and email address were collected strictly for the purpose of recruitment, sending questionnaires and reminders, and to inform them about the summary of findings if they wished. These personal details were kept until participants were informed about the study findings if they chose to, otherwise they were kept until the end of the study. However, profession/job title, geographic area and years of experience were published and reported anonymously.

Raw research data and personal data were password protected and stored on a shared secure University of Manchester Research Data Storage. These data were only accessible by the study team at the University of Manchester and were only be accessed using the University of Manchester owned encrypted computers. The identity of each member was anonymous to other members of the panel, and was known only to the research team.

However, aggregated and anonymous research data could be examined by all the research team and were stored on the secure University of Manchester personal data storage (P drive) and on a secure, cloud-based file sharing and synchronisation tool (Dropbox Business) between internal and external members of the research team.

5.3.7 Delphi procedure

5.3.7.1 First stage

In the first round of stage 1, panellists were asked to rate their level of agreement with the use of each indicator to assess prescribing and drug monitoring safety, using a five-point Likert scale where: 1=strongly disagree; 2=disagree; 3=neutral; 4= agree; 5=strongly agree. Panellists were asked to rate their agreement of including the indicator based on; (a) the indicator described a pattern of prescribing that may put patients at risk of harm; and (b) the indicator described a prescribing practice that was common in the UK. Participants were also given the opportunity to comment on each indicator and to suggest new indicators. Figure 5.1 shows a screenshot of the first-round questionnaire

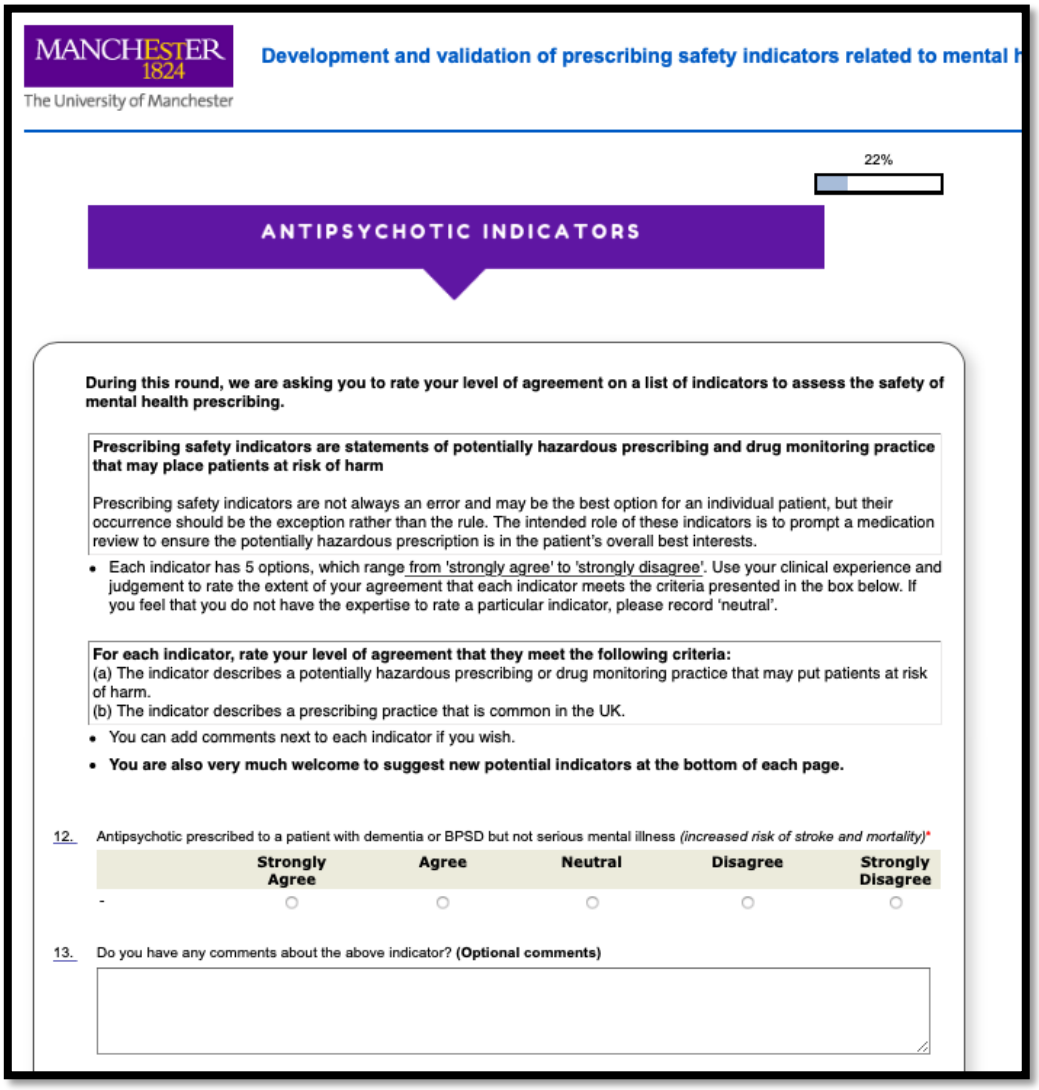

Figure 5.1: Screenshot of the first-round questionnaire

Following completion of the first round of questionnaires, the median agreement value was calculated for each indicator. In addition, the free-text comments provided by the experts were analysed qualitatively in order to modify, remove or introduce new indicators. The results from round 1 were summarised and returned to each expert, with their individual score, the group median agreement rating score and a summary of the free-text comments. For the second round, the panellists were asked to re-rate their level of agreement for all of the indicators based on the group comments and ratings. The agreement value was recalculated for each statement after this round. Figure 5.2 shows a screenshot of the second-round questionnaire

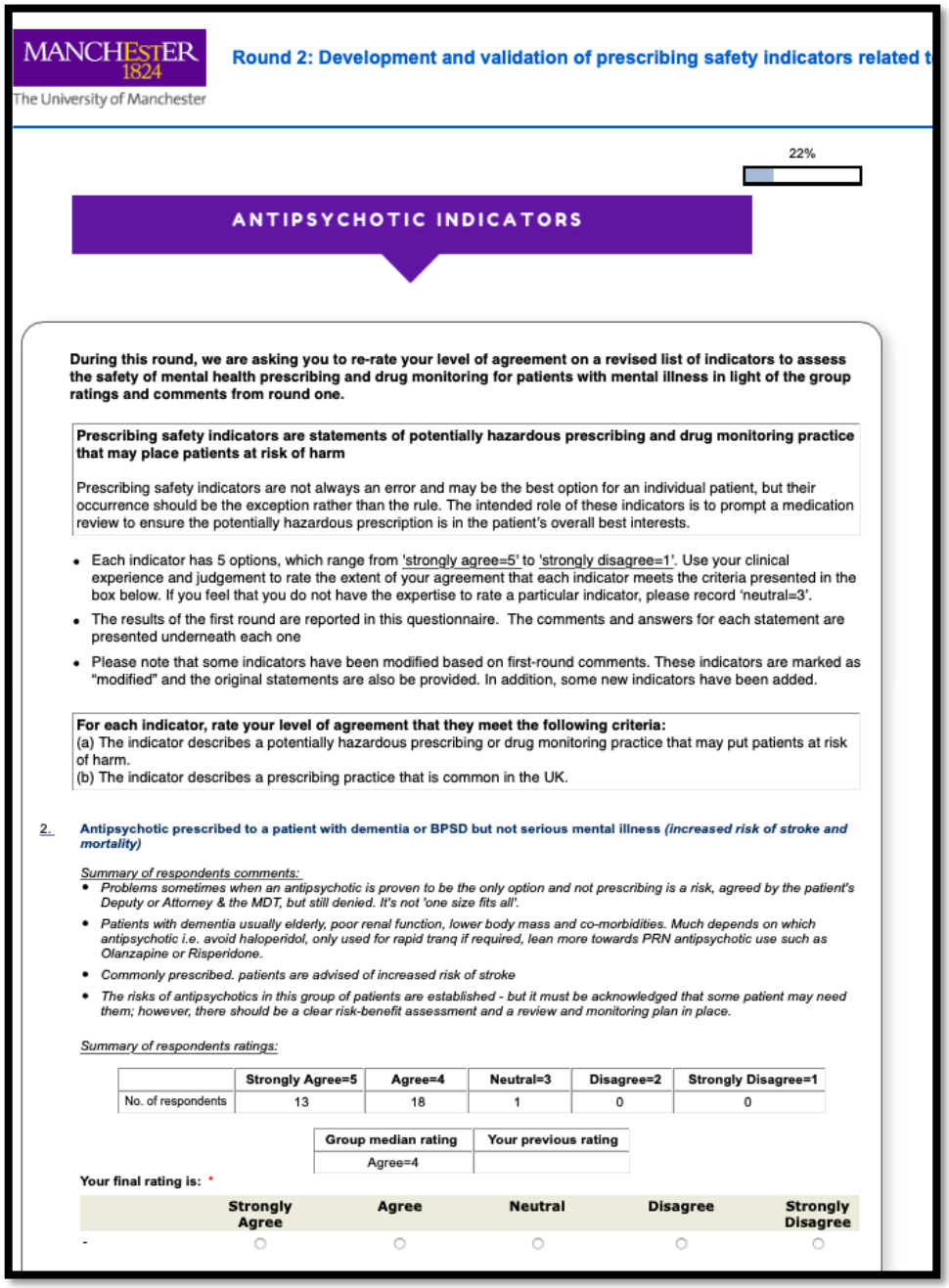

Figure 5.2: Screenshot of the second-round questionnaire

The final agreed list of indicators contained indicators that achieved consensus on acceptance, which was defined as at least 80% of participants rating the indicator as 4= agree or 5=strongly agree. The definition for consensus was defined as at least 80%, since this is what has been used in previous studies in the UK.[29,35,209,210]

5.3.7.2 Second stage

Panellists were asked to rate the clinical significance of each accepted indicator from stage 1, based on: 1) the severity of the potential harm to patients if the prescribing or monitoring practice occurred and; 2) the likelihood of the prescribing or monitoring

practice occurring, based on the UK National Patient Safety Agency Risk Matrix (Table 5.1).[402] This process is similar to previous publications.[29,35,210] The likelihood and severity scores were converted into 'risk scores'. Figure 5.3 shows a screenshot of the third-round questionnaire.

Table 5.1: Risk scoring = consequence x likelihood [402]

	Likelihood				
Consequence	1 Rare	2 Unlikely	3 Possible	4 Likely	5 Almost certain
5 Catastrophic	5	10	15	20	25
4 Major	4	8	12	16	20
3 Moderate	3	6	9	12	15
2 Minor	2	4	6	8	10
1 Negligible	1	2	3	4	5

Low Risk 1-3	Moderate risk 4-6	High risk 8-12	Extreme risk 15-25

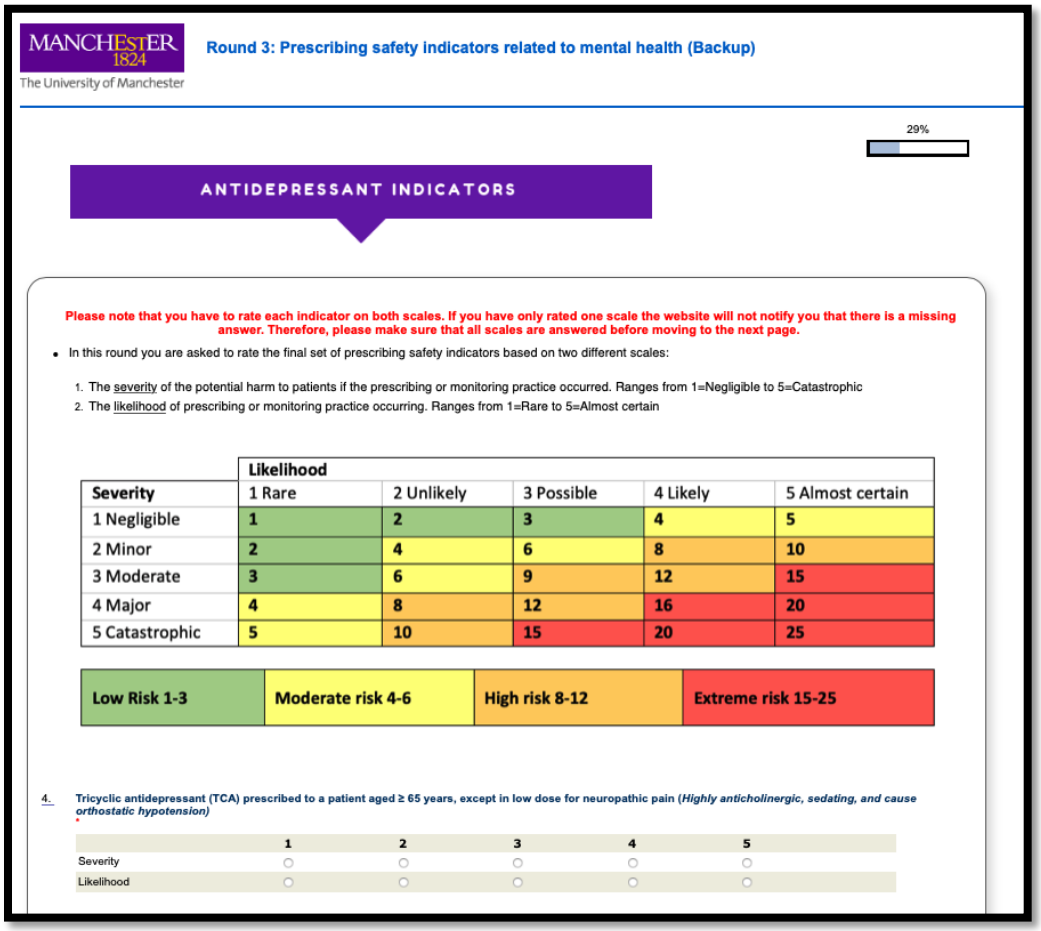

Figure 5.3: Screenshot of the third-round questionnaire

The risk score for each indicator was calculated by multiplying the severity and likelihood ratings for each member of the panel, and then by identifying the median risk score

between members. Indicators were categorised into four overall risk categories; low, moderate, high or extreme. Consensus was defined as at least 80% of participants rating the indicator in the upper categories (high or extreme), or the lower categories (low and moderate). Therefore, indicators were considered high or extreme risk when the overall median risk category for that item was high or extreme and 80% or more of the panellist rated the indicator as high or extreme risk. The statistical analyses were performed on the raw data using Microsoft Excel®. Figure 5.4 summaries the process of developing prescribing safety indicators related to mental health conditions and medications.

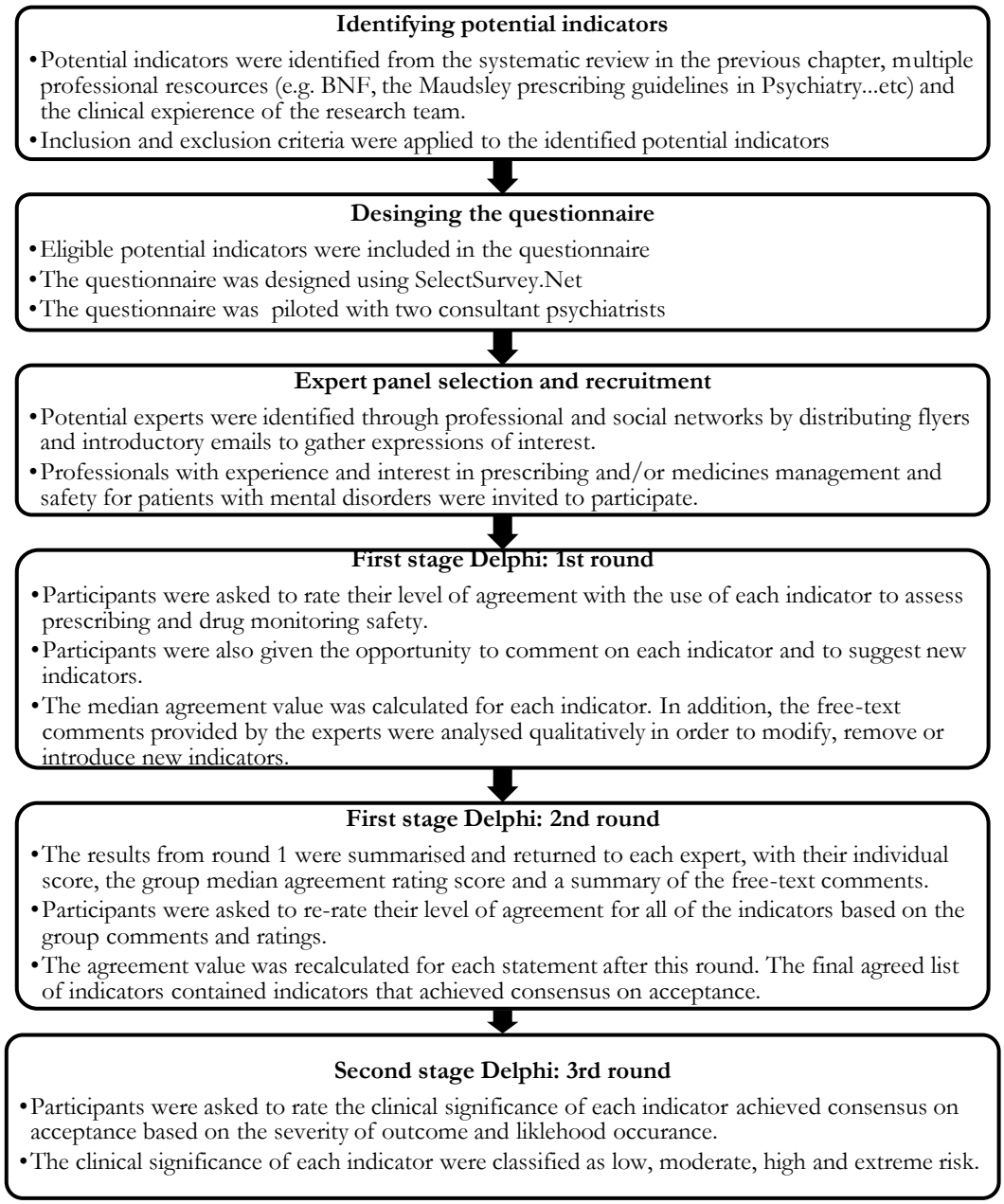

Figure 5.4: Summary of the process to develop prescribing safety indicators related to mental health conditions and medications

5.4 Results

5.4.1 First stage

The first stage of the e-Delphi was completed by 31 of the 32 experts who had originally agreed to take part. The expert panel comprised psychiatrists (n=6), mental health pharmacists (n=17), mental health nurses (n=7) and a general practitioner (n=1). Participants were from geographically diverse areas in the UK, with a range of professional grades. Table 5.2 summarises the characteristics of the expert panel.

Table 5.2: Characteristics of the expert panel

Characteristics	First stage	Second stage
Participants: n	31 members	29 members
Years of Experience: Median (IQR)	18 years (10.25-27)	17 years (10-25)
Region of practice: n (%)		
England: North	14 (45.2)	14 (48.3)
England: Midlands and East	10 (32.3)	8 (27.6)
England: South	3 (9.7)	3 (10.3)
England: London	2 (6.5)	2 (6.9)
Wales	1 (3.2)	1 (3.4)
Scotland	1 (3.2)	1 (3.4)
Profession: n (%)		
Psychiatrists	6 (19.4)	6 (20.7)
Mental Health Pharmacists	17 (54.5)	16 (55.2)
Mental Health Nurses	7 (22.6)	6 (20.7)
General Practitioners	1 (3.2)	1 (3.4)

IQR, The interquartile range.

A total of 101 potential prescribing safety indicators were included in the first round. After analysing the participants' free-text comments received in this round, 20 indicators were modified and 4 were merged to form 2 indicators. In addition, 5 new indicators were included based on panel members' suggestions following review by the research team (these indicators are marked with three asterisks in the results tables). Thus, the final number of potential indicators that were included in the second round was 104.

After two rounds of scoring, the final number of indicators that achieved consensus on acceptance (rated as 'agree' or 'strongly agree' by 80% of panellists) was 75 indicators. This list contained prescribing safety indicators from the following drug classes: antipsychotics (n=19), antidepressants (n=14), sedative, hypnotics and anxiolytics (n=8), mood stabilisers (n=22), antidementia (n=4), anticholinergic (n=6) and non-specific psychotropics (n=2). The indicators also covered a wide range of prescribing problems, including drug-disease-interactions (n=19), drug-drug interactions (DDIs) (n=18), inappropriate dose (n=12),

potentially inappropriate medications (PIMs) (n=7), inappropriate duration (n=4), omissions (n=4), polypharmacy (n=1), and inadequate monitoring (n=10). The full list of 75 indicators achieving agreement in stage 1 are provided in Table 5.3, and the 29 indicators that did not achieve consensus are provided in Table 5.4.

5.4.2 Second stage

The second stage of the e-Delphi was completed by 29 of the 31 participants who completed the first stage. Table 5.2 summarises the characteristics of the panel. From this stage, a total of 42 of the 75 indicators identified in stage 1 were considered high or extreme risk by consensus of the expert panel (39 indicators were considered as high-risk and 3 were extreme risk, with 80% of the panellists rating these indicators as high or extreme). These indicators are listed in Table 5.5. Figure 5.5 shows the steps taken in arriving at the final set of indicators.

The list of high and extreme risk prescribing safety indicators included different mental health related medication classes; antipsychotics (n=14), antidepressants (n=6), sedative, hypnotics and anxiolytics (n=6), mood stabilisers (n=8), anticholinergic (n=6) and non-specific psychotropics (n=2). These indicators also reflected different types of potentially hazardous prescribing; including drug-disease-interactions (n=12), drug-drug interactions (DDIs) (n=9), potentially inappropriate medications (PIMs) (n=3), inappropriate duration (n=4), inappropriate dose (n=4), omissions (n=4), polypharmacy (n=1), and inadequate monitoring (n=5).

Table 5.3. Prescribing safety indicators that achieved consensus on acceptance after first stage (round2):

Prescribing safety indicator	Type of problem	First stage	Second stage			
		Round 2: Agreement [a]	Median Severity	Median Likelihood	Median Risk Category	Agreement [b]
Antipsychotic						
1. Antipsychotic prescribed to a patient with dementia or BPSD but not serious mental illness (increased risk of stroke and mortality)	Drug-disease interaction	100%	4	4	High	93%
2. Prescribing antipsychotic with a QT-prolonging drug (risk of QT- prolongation that can lead to potentially fatal torsade de pointes arrhythmia) [c]	DDI	100%	4	4	Extreme	93%
3. Antipsychotic prescribed for at least 12 months without monitoring glucose, weight, or lipid profile within the previous year (risk of metabolic adverse effects)	Monitoring	97%	4	3	High	90%
4. Clozapine prescribed to a patient with a history of constipation and without a laxative (risk of worsening constipation and potentially fatal risk of intestinal obstruction, faecal impaction, and paralytic ileus)	Omission	94%	5	4	Extreme	97%
5. Prescribing Clozapine with other agents having a well-known potential to suppress bone marrow function (increase the risk and/or severity of bone marrow suppression)	DDI	94%	4	2	High	72%
6. Clozapine dose not adjusted in a patient started/stopped smoking/NRT (starting/stopping smoking can change Clozapine blood level, which can lead to sedation, hypotension and increased risk of neurological adverse effects including seizures)	Dosing	94%	4	4	Extreme	97%
7. Prescribing Haloperidol without monitoring ECG at baseline (risk of QTc prolongation and/or ventricular arrhythmias)	Monitoring	94%	4	3	High	100%
8. Risperidone prescribed to a patient with dementia and without psychotic illness for more than 6 weeks (increased risk of stroke and mortality)	Duration	87%	3	4	High	97%
9. Antipsychotic prescribed to a patient with prolonged QTc interval (risk of potentially fatal torsade de pointes arrhythmia)	Drug-disease interaction	87%	4	3	High	97%
10. Clozapine, Chlorpromazine, Quetiapine or Risperidone prescribed to a patient with postural hypotension, syncope or history of falls (increased risk of falls and fractures)	Drug-disease interaction	87%	4	4	High	93%
11. Clozapine prescribed with anticholinergic except for hypersalivation (risk constipation and potentially fatal risk of intestinal obstruction, faecal impaction, and paralytic ileus)	DDI	87%	4	3	High	83%
12. Prescribing more than one regular antipsychotic for more than 2 months excluding clozapine augmentation (increased risk of adverse effects)	Duration	87%	3	3	High	83%
13. Prescribing clozapine with CYP1A2 inhibiting substances e.g. Fluvoxamine, Ciprofloxacin, Perazine or hormonal contraceptives (risk of change in clozapine plasma level which can increase risk of adverse effects)	DDI	87%	4	3	High	79%
14. Single/combination antipsychotic(s) prescribed regularly a dose above 100% BNF maximum (increased risk of adverse effects)	Dosing	87%	4	4	High	86%
15. Clozapine initiation regime prescribed without blood pressure/pulse/temperature monitoring within the last week (risk of hypotension, hypertension, tachycardia and fever)	Monitoring	87%	4	2	High	66%
16. Antipsychotic other than Quetiapine, Aripiprazole or Clozapine prescribed to a patient with Parkinson's disease or with Lewy Body Disease (risk of severe extrapyramidal symptoms)	Drug-disease interaction	81%	4	3	High	93%

17.	Oral Haloperidol prescribed at a dose of more than 5 mg daily to a patient aged ≥ 65 years (risk of anticholinergic and extrapyramidal effects)	Dosing	81%	4	3	High	72%
18.	Risperidone prescribed at a dose of more than 3 mg to a patient aged ≥ 65 years (risk of anticholinergic and extrapyramidal effects	Dosing	81%	3	3	High	76%
19.	Antipsychotic, other than Asenapine, Aripiprazole, Clozapine, Lurasidone, Olanzapine and Quetiapine, newly prescribed for at least 6 months without monitoring prolactin (risk of hyperprolactinaemia)	Monitoring	81%	3	4	High	86%
Antidepressant							
20.	SSRI or SNRI prescribed with NSAID or antiplatelet to a patient without gastrointestinal protection (increased risk of gastrointestinal bleeding)	Omission	97%	4	3	High	97%
21.	Paroxetine or Venlafaxine prescription stopped abruptly where titration of dose would otherwise be required (risk of withdrawal reactions)	Dosing	94%	4	3	High	69%
22.	TCA prescribed to a patient with arrhythmia, cardiac conduction abnormalities, heart block, ischemic heart disease, recent MI or heart failure (risk of exacerbation of heart condition)	Drug-disease interaction	90%	5	3	High	76%
23.	SSRI or SNRI prescribed with NOAC or warfarin (Increased risk of bleeding	DDI	90%	4	3	High	93%
24.	Prescribing a serotonergic psychotropic medication with another serotonergic drug (increased risk of serotonin syndrome)	DDI	90%	4	4	High	100%
25.	TCA prescribed to a patient aged ≥ 65 years, except in low dose for neuropathic pain (highly anticholinergic, sedating, and cause orthostatic hypotension)	PIM	84%	4	3	High	76%
26.	SSRI prescribed to a patient with current or recent significant hyponatraemia, Na+ < 130 mmol/l. (increased risk of hyponatraemia)	Drug-disease interaction	84%	4	3	High	79%
27.	Prescribing Citalopram, Escitalopram, TCA or Trazadone with QT-prolonging drugs (risk of QT-prolongation that can lead to potentially fatal torsade de pointes arrhythmia) [c]	DDI	84%	4	3	High	90%
28.	Agomelatine prescribed without monitoring liver function tests prior to starting treatment and within 6 months of starting treatment (risk of liver toxicity)	Monitoring	84%	4	3	High	66%
29.	Prescribing Citalopram tablets >20 mg (16 mg drops) or Escitalopram >10 mg to a patient aged ≥65 years (risk dose-dependent QT interval prolongation)***	Dosing	84%	3	3	High	76%
30.	Antidepressant other than agomelatine initiated within 14 days of stopping MAOi (increased risk of serotonin syndrome) ***	DDI	84%	4	2	High	72%
31.	SNRI prescribed to a patient with uncontrolled hypertension (risk of blood pressure destabilisation)	Drug-disease interaction	81%	4	3	High	83%
32.	SSRI or SNRI prescribed to a patient with a history of peptic ulcer or bleeding disorders without gastroprotection (increased risk of gastrointestinal bleeding)	Omission	81%	4	3	High	86%
33.	Agomelatine prescribed to a patient with hepatic impairment or abnormal liver function tests (risk of liver toxicity)	Drug-disease interaction	81%	4	3	High	76%
Sedative, hypnotic and anxiolytic Indicators							
34.	Any sedative-hypnotic prescribed to a patient with a history of falls (increased risk of falling and fracture)	Drug-disease interaction	97%	4	3	High	97%
35.	Prescribing two benzodiazepines and/or Z-drugs concurrently (increased risk of falling and fracture)	DDI	97%	4	3	High	79%
36.	Benzodiazepine, Z-drug or sedating antihistamine prescribed to a patient with Dementia or cognitive impairment (CNS adverse effects)	Drug-disease interaction	94%	4	3	High	90%

37.	Benzodiazepine, Z-drug or sedating antihistamine for more than 1 month (risk of prolonged sedation, confusion, impaired balance, falls) (Risk of tolerance, and dependence with benzodiazepines and Z-drugs)	Duration	94%	3	4	High	93%
38.	Benzodiazepine or Z-drug prescribed to a patient aged ≥ 65 years (increased risk of falling and fracture)	PIM	87%	3	4	High	90%
39.	Benzodiazepine or Z-drug prescribed to a patient with hepatic impairment or cirrhosis (risk of accumulation and encephalopathy)	Drug-disease interaction	87%	4	3	High	90%
40.	Benzodiazepine or Z-drug prescribed to a patient with asthma, COPD or sleep apnoea (risk of exacerbation of respiratory failure)	Drug-disease interaction	84%	4	3	High	86%
41.	Benzodiazepine or Z-drug prescribed with a strong CYP3A4 inhibitor (increases exposure, which results in prolonged sedation)	DDI	81%	3	3	High	69%
Mood stabiliser							
42.	The formulation of lithium changed between liquid and solid without dose equivalent adjustment (risk of lithium toxicity which can cause tremor, dysarthria, ataxia and confusion)	Dosing	97%	4	3	High	76%
43.	Valproic acid prescribed to a woman of childbearing potential (risk of congenital malformations to the exposed foetus)	PIM	94%	5	3	High	83%
44.	Prescribing Lamotrigine with combined oral contraceptive (risk of decrease lamotrigine exposure and efficacy. Possible risk of failure of contraception)	DDI	94%	4	3	High	83%
45.	Lamotrigine dose not re-titrated after a treatment break of more than 5 days (risk of sedation, tremor, ataxia, fatigue and serious skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis)	Dosing	94%	4	3	High	86%
46.	Carbamazepine prescribed without monitoring U&E, LFT and FBC within the last 6 months (risk of liver dysfunction, agranulocytosis and aplastic anaemia)	Monitoring	94%	4	3	High	76%
47.	Valproate prescribed for at least 12 months without monitoring LFT and FBC within the last 12 months (risk of hepatotoxicity and hepatic failure, weight increase and thrombocytopenia)	Monitoring	94%	4	3	High	72%
48.	Lithium prescribed to a patient with AKI (risk of toxicity and exacerbation of renal failure)	Drug-disease interaction	90%	5	2	High	76%
49.	Lamotrigine initiated at a dose higher than 12.5mg/day or 25mg on alternate days to a patient already on Valproate (risk of sedation, tremor, ataxia, fatigue and serious skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis)	Dosing	90%	4	3	High	83%
50.	Prescribing Lithium with ACEi/ARB, NSAID or a diuretic (risk of lithium toxicity which can cause tremor, dysarthria, ataxia and confusion)	DDI	90%	4	3	High	90%
51.	Lithium prescribed in a patient with eGFR <30ml/min (risk of lithium toxicity)	Drug-disease interaction	90%	4	2	High	72%
52.	Prescribing Lithium without monitoring lithium plasma level within the last 6 months or within the last 3 months if the patient is aged ≥ 65 years or have a renal impairment or during the first year of treatment (risk of lithium toxicity which can lead to blurred vision, muscle weakness, coarse tremor, slurred speech, confusion, seizures and renal damage)	Monitoring	90%	4	3	High	83%
53.	Lithium prescribed for at least 6 months without monitoring U&E or thyroid function within the last 6 months (U&E: risk of lithium toxicity and renal impairment) (thyroid: risk of thyroid disorder)	Monitoring	90%	4	3	High	83%

54. Lithium dose not adjusted or omitted in a patient with a lithium concentration above the therapeutic range (>1 mmol/L) (risk of lithium toxicity which can lead to blurred vision, muscle weakness, coarse tremor, slurred speech, confusion, seizures and renal damage)	Dosing	90%	5	3	High	76%
55. Prescribing Carbamazepine with Warfarin or direct oral anticoagulant (risk of reducing anticoagulation effect which can cause blood clots)	DDI	87%	4	2	High	76%
56. Prescribing Carbamazepine with clozapine (risk of reducing clozapine concentration, risk of blood dyscrasias and risk of fatal pancytopenia or neuroleptic malignant syndrome)	DDI	87%	4	2	High	62%
57. Carbamazepine prescribed to a pregnant woman (increases the risk of neural tube defects)	PIM	87%	5	2	High	59%
58. Mood stabiliser (Lithium, Valproate, Lamotrigine, Carbamazepine) prescribed without performing pregnancy test/excluding pregnancy in a woman of child-bearing potential (risk of teratogenicity in case of pregnancy) *******	Monitoring	87%	4	3	High	79%
59. Lithium preparation not prescribed by brand (increased risk of toxicity or therapeutic failure)	Dosing	84%	3	3	High	69%
60. Lithium prescribed to a pregnant woman (risk of teratogenicity, including cardiac abnormalities)	PIM	84%	4	2	High	55%
61. Lithium prescribed to a patient with untreated hypothyroidism (risk of inducing thyroid disorder)	Drug-disease interaction	84%	4	2	High	66%
62. Lithium prescribed to a breastfeeding mother (present in milk and risk of toxicity in infants)	PIM	81%	4	2	High	59%
63. Prescribing Carbamazepine with oral or intravaginal contraceptives, patches or pure progestogen pills (risk of failure of contraception and risk of foetal malformation)	DDI	81%	4	2	High	86%
Antidementia						
64. Acetylcholinesterase inhibitors prescribed to a patient with bradycardia, heart block or recurrent unexplained syncope (risk of cardiac conduction failure, syncope and injury)	Drug-disease interaction	84%	4	3	High	66%
65. Prescribing two anticholinesterase inhibitors (risk of accumulation of side effects)	DDI	87%	4	2	High	59%
66. Anticholinesterase inhibitors prescribed with a drug with anticholinergic activity (illogical association of two antagonistic mechanisms)	DDI	84%	3	3	High	79%
67. Memantine prescribed at a dose >10 mg to a patient with eGFR < 29 mL/min (risk of increase Memantine concentration and risk of adverse effects)	Dosing	81%	4	3	High	76%
Anticholinergic						
68. A medication with medium/high anticholinergic activity prescribed to a patient with dementia or cognitive impairment (risk of exacerbation of cognitive impairment)	Drug-disease interaction	100%	4	3	High	90%
69. Prescribing two anticholinergics with at least one of them with moderate/high anticholinergic activity (increased risk of adverse effect)	DDI	100%	4	4	High	90%
70. A medication with medium/high anticholinergic activity prescribed to a patient with a history of urinary retention or benign prostatic hyperplasia (risk of urinary retention)	Drug-disease interaction	94%	4	3	High	90%
71. A medication with medium/high anticholinergic activity prescribed to a patient aged ≥ 65 years (risk of falling and fracture, acute confusion and urinary retention)	PIM	90%	4	4	High	97%
72. A medication with medium/high anticholinergic activity prescribed to a patient with constipation and without a laxative (risk of worsening constipation)	Omission	87%	4	3	High	90%
73. A medication with medium/high anticholinergic activity prescribed to a patient with angle closure glaucoma (risk of acute exacerbation of glaucoma and risk or permanent loss of vision)	Drug-disease interaction	84%	4	3	High	86%
Other						

74.	Four or more psychotropics prescribed to a patient for more than 3 months (increased risk of adverse effects)	Duration	90%	4	4	High	90%
75.	Three or more psychotropic drugs prescribed to a patient on an as required (PRN) basis (increased risk of adverse effects)	Polypharmacy	84%	4	3	High	86%

[a] Percentage of members rated the indicator as "agree" or "strongly agree". [b] Percentage of members rated the indicator as high or extreme.

[c] QT prolonging drugs: medications with known and possible risk of Torsades de Pointes according to crediblemeds.org.[403]

*** Indicator suggested by the panel in first round and were included in the second round.

ACEi, Angiotensin-converting-enzyme inhibitor; AKI, Acute kidney injury; ARB, Angiotensin receptor blocker; BNF, British National Formulary; BPSD, Behavioural and psychological symptoms of dementia; CNS, Central nervous system; COPD, Chronic Obstructive Pulmonary Disease; ECG, Electrocardiogram; eGFR, estimated Glomerular Filtration Rate; FBC, Full blood count; LFT, Liver function test; MAOi, Monoamine oxidase inhibitor; NOAC, New Oral Anticoagulant; NRT, Nicotine replacement therapy; NSAID, Nonsteroidal anti-inflammatory drug; SNRI, Serotonin–norepinephrine reuptake inhibitor; SSRI, Selective serotonin reuptake inhibitors; TCA, Tricyclic antidepressant; U&E, urea and electrolytes.

Table 5.4. Prescribing safety indicators that did not achieve consensus on acceptance after first stage (round2):

Prescribing safety indicator	First stage Round 2: Agreement [a]
Antipsychotic	
• **Antipsychotic prescribed to a patient aged > 65 years with active seizures (Lowers seizure threshold)**	77%
• **Antipsychotic prescribed to a patient with ADHD but without serious mental illness (increased risk of adverse effects)**	68%
• **Prescribing a low potency first-generation antipsychotic (e.g. chlorpromazine or levomepromazine.), Loxapine, or Depot antipsychotic to a patient with epilepsy (increased risk of seizure) –**	71%
• **Zuclopenthixol acetate prescribed in combination with regular antipsychotics (risk of QT- prolongation that can lead to potentially fatal torsade de pointes arrhythmia)**	77%
• **Olanzapine dose not adjusted in a patient started/stopped smoking/NRT (starting/stopping smoking can change Olanzapine blood level, which can lead to sedation, hypotension and increased risk of neurological adverse effects including seizures)**	71%
• **Clozapine dose not adjusted or omitted in a patient with a clozapine concentration above therapeutic range 600¬µg/L (increased risk of toxicity which can lead to sedation, hypotension, seizures, constipation leading to bowel obstruction, fatality)**	74%
• **Anticonvulsant prophylaxis not prescribed to a patient with clozapine plasma level above 500µg/L (risk of seizure)**	65%
Antidepressant	
• **Prescribing Bupropion or TCA to a patient with epilepsy (increased risk of seizure)**	77%
• **Antidepressant prescribed to a patient with type1 bipolar disorder without mood stabilisers (increases the risk of switching to mania and limited evidence of benefit)**	71%
• **Tricyclic antidepressant prescribed to a patient with postural hypotension, syncope or history of falls (risk of falls and fractures)**	74%
• **Two antidepressants, Other than mirtazapine and venlafaxine, prescribed to a patient for more than 2 months (increased risk of adverse reactions)**	68%

• **Patient diagnosed with moderate/severe depressive symptoms lasting at least three months without prescribing an antidepressant (increases the risk of emotional, behavioural and physical complications)**	77%
• **Patient diagnosed with persistent severe anxiety that interferes with independent functioning, without prescribing SSRI, SNRI or Pregabalin (increases the risk of emotional, behavioural and physical complications**	71%
Sedative, hypnotic and anxiolytic	
• **Benzodiazepine or Z-drug prescribed during pregnancy (Risk of neonatal withdrawal symptoms)**	71%
Mood stabiliser	
• **Prescribing Carbamazepine with strong CYP3A4 (Risk of carbamazepine toxicity which can cause dizziness, diplopia, ataxia and mental confusion) Strong CYP3A4 inhibitors include: Clarithromycin, telithromycin, nefazodone, itraconazole, ketoconazole, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir**	74%
Antidementia	
• **Rivastigmine patches prescribed at a dose >4.6mg/24 hours after a treatment break of >3 days (increase the risk of adverse reactions)**	71%
• **Acetylcholinesterase inhibitor prescribed with antiplatelet or NSAID without gastroprotection to a patient aged >65 years (increased risk of bleed) *****	77%
ADHD medication	
• **Any ADHD medication prescribed to a patient aged <5 years (Lack of evidence regarding long-term safety and effects on growth)**	71%
• **Dexamfetamine, Lisdexamfetamine or Methylphenidate prescribed to a patient with insomnia (Risk of CNS stimulation)**	48%
• **SR Methylphenidate prescribed two doses per day to a child, rather than one dose (risk of prolonged appetite suppression, sleep disturbance and effect on growth)**	48%
• **Methylphenidate MR not prescribed by brand (risk of changing drug concentration and decreasing the clinical effect)**	61%
• **A stimulant or atomoxetine prescribed to a patient with a heart problem, such as structural cardiac abnormalities; CVD or hypertension (risk of cardiovascular adverse events)**	58%
• **Any ADHD medication prescribed without monitoring heart rate and blood pressure within the last 6 months (Risk of raised heart rate and blood pressure)**	74%
• **Any ADHD medication prescribed to a patient aged <10 years without monitoring weight within the last 3 months (Risk of growth suppression)**	71%
• **Any ADHD medication prescribed to a patient aged >10 years without monitoring weight within the last 6 months (Risk of growth suppression)**	74%
• **Any ADHD medication prescribed to a patient aged <18 years without monitoring height within the last 6 months (Risk of growth suppression)**	58%
• **Stimulant medication prescribed to a patient with a history of substance misuse/risk of misuse diversion (increased risk of misuse) *****	68%
Anticholinergic	
• **Prescribing procyclidine, hyoscine, orphenadrine, atropine, trihexyphenidyl or pirenzepine for more than 2 months (increased risk of adverse effects)**	35%
Other	
• **Pseudoephedrine, Phenylephrine or Theophylline prescribed to a patient with insomnia (Risk of CNS stimulation)**	52%

[a] Percentage of members rated the indicator as "agree" or "strongly agree".

*** Indicator suggested by the panel in first round and were included in the second round.

ADHD, Attention deficit hyperactivity disorder; CNS, Central nervous system; NRT, Nicotine replacement therapy; NSAID, Nonsteroidal anti-inflammatory drug; SNRI, Serotonin–norepinephrine reuptake inhibitor; SSRI, Selective serotonin reuptake inhibitors; TCA, Tricyclic antidepressant.

Table 5.5: Prescribing safety indicators that were considered high or extreme risk to patient safety by at least 80% of the expert panel.

	Prescribing safety indicator	First stage	Second stage	
		Round 2: Agreement [a]	Risk Category	Agreement [b]
Antipsychotic				
1.	**Antipsychotic prescribed to a patient with dementia or BPSD but not serious mental illness (increased risk of stroke and mortality)**	100%	High	93%
2.	**Prescribing antipsychotic with a QT-prolonging drug (risk of QT- prolongation that can lead to potentially fatal torsade de pointes arrhythmia)**	100%	Extreme	93%
3.	**Antipsychotic prescribed for at least 12 months without monitoring glucose, weight, or lipid profile within the previous year (risk of metabolic adverse effects)**	97%	High	90%
4.	**Clozapine prescribed to a patient with a history of constipation and without a laxative (risk of worsening constipation and potentially fatal risk of intestinal obstruction, faecal impaction, and paralytic ileus)**	94%	Extreme	97%
5.	**Clozapine dose not adjusted in a patient started/stopped smoking/NRT (starting/stopping smoking can change Clozapine blood level, which can lead to sedation, hypotension and increased risk of neurological adverse effects including seizures)**	94%	Extreme	97%
6.	**Prescribing Haloperidol without monitoring ECG at baseline (risk of QTc prolongation and/or ventricular arrhythmias)**	94%	High	100%
7.	**Risperidone prescribed to a patient with dementia and without psychotic illness for more than 6 weeks (increased risk of stroke and mortality)**	87%	High	97%
8.	**Antipsychotic prescribed to a patient with prolonged QTc interval (risk of potentially fatal torsade de pointes arrhythmia)** [c]	87%	High	97%
9.	**Clozapine, Chlorpromazine, Quetiapine or Risperidone prescribed to a patient with postural hypotension, syncope or history of falls (increased risk of falls and fractures)**	87%	High	93%
10.	**Clozapine prescribed with anticholinergic except for hypersalivation (risk constipation and potentially fatal risk of intestinal obstruction, faecal impaction, and paralytic ileus)**	87%	High	83%
11.	**Prescribing more than one regular antipsychotic for more than 2 months excluding clozapine augmentation (increased risk of adverse effects)**	87%	High	83%
12.	**Single/combination antipsychotic(s) prescribed regularly a dose above 100% BNF maximum (increased risk of adverse effects)**	87%	High	86%
13.	**Antipsychotic other than Quetiapine, Aripiprazole or Clozapine prescribed to a patient with Parkinson's disease or with Lewy Body Disease (risk of severe extrapyramidal symptoms)**	81%	High	93%
14.	**Antipsychotic, other than Asenapine, Aripiprazole, Clozapine, Lurasidone, Olanzapine and Quetiapine, newly prescribed for at least 6 months without monitoring prolactin (risk of hyperprolactinaemia)**	81%	High	86%
Antidepressant				
15.	**SSRI or SNRI prescribed with NSAID or antiplatelet to a patient without gastrointestinal protection (increased risk of gastrointestinal bleeding)**	97%	High	97%
16.	**SSRI or SNRI prescribed with NOAC or warfarin (increased risk of bleeding)**	90%	High	93%
17.	**Prescribing a serotonergic psychotropic medication with another serotonergic drug (increased risk of serotonin syndrome)**	90%	High	100%
18.	**Prescribing Citalopram, Escitalopram, TCA or Trazadone with QT-prolonging drugs (risk of QT- prolongation that can lead to potentially fatal torsade de pointes arrhythmia)** [c]	84%	High	90%
19.	**SNRI prescribed to a patient with uncontrolled hypertension (risk of blood pressure destabilisation)**	81%	High	83%
20.	**SSRI or SNRI prescribed to a patient with a history of peptic ulcer or bleeding disorders without gastroprotection (increased risk of gastrointestinal bleeding)**	81%	High	86%
Sedative, hypnotic and anxiolytic Indicators				
21.	**Any sedative-hypnotic prescribed to a patient with a history of falls (increased risk of falling and fracture)**	97%	High	97%
22.	**Benzodiazepine, Z-drug or sedating antihistamine prescribed to a patient with dementia or cognitive impairment (CNS adverse effects)**	94%	High	90%

23.	**Benzodiazepine, Z-drug or sedating antihistamine for more than 1 month (Risk of prolonged sedation, confusion, impaired balance, falls) (risk of tolerance, and dependence with benzodiazepines and Z-drugs)**	94%	High	93%
24.	**Benzodiazepine or Z-drug prescribed to a patient aged ≥ 65 years (increased risk of falling and fracture)**	87%	High	90%
25.	**Benzodiazepine or Z-drug prescribed to a patient with hepatic impairment or cirrhosis (risk of accumulation and encephalopathy)**	87%	High	90%
26.	**Benzodiazepine or Z-drug prescribed to a patient with asthma, COPD or sleep apnoea (risk of exacerbation of respiratory failure)**	84%	High	86%
Mood stabiliser				
27.	**Valproic acid prescribed to a woman of childbearing potential (risk of congenital malformations to the exposed foetus)**	94%	High	83%
28.	**Prescribing Lamotrigine with combined oral contraceptive (risk of decrease lamotrigine exposure and efficacy. Possible risk of failure of contraception)**	94%	High	83%
29.	**Lamotrigine dose not re-titrated after a treatment break of more than 5 days (risk of sedation, tremor, ataxia, fatigue and serious skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis)**	94%	High	86%
30.	**Lamotrigine initiated at a dose higher than 12.5mg/day or 25mg on alternate days to a patient already on Valproate (risk of sedation, tremor, ataxia, fatigue and serious skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis)**	90%	High	83%
31.	**Prescribing Lithium with ACEi/ARB, NSAID or a diuretic (risk of lithium toxicity which can cause tremor, dysarthria, ataxia and confusion)**	90%	High	90%
32.	**Prescribing Lithium without monitoring lithium plasma level within the last 6 months or within the last 3 months if the patient is aged ≥ 65 years or have a renal impairment or during the first year of treatment (risk of lithium toxicity which can lead to blurred vision, muscle weakness, coarse tremor, slurred speech, confusion, seizures and renal damage)**	90%	High	83%
33.	**Lithium prescribed for at least 6 months without monitoring U&E or thyroid function within the last 6 months (U&E: risk of lithium toxicity and renal impairment) (thyroid: risk of thyroid disorder)**	90%	High	83%
34.	**Prescribing Carbamazepine with oral or intravaginal contraceptives, patches or pure progestogen pills (risk of failure of contraception and risk of foetal malformation)**	81%	High	86%
Anticholinergic				
35.	**A medication with medium/high anticholinergic activity prescribed to a patient with dementia or cognitive impairment (risk of exacerbation of cognitive impairment)**	100%	High	90%
36.	**Prescribing two anticholinergics with at least one of them with moderate/high anticholinergic activity (increased risk of adverse effect)**	100%	High	90%
37.	**A medication with medium/high anticholinergic activity prescribed to a patient with a history of urinary retention or benign prostatic hyperplasia (risk of urinary retention)**	94%	High	90%
38.	**A medication with medium/high anticholinergic activity prescribed to a patient aged ≥ 65 years (risk of falling and fracture, acute confusion and urinary retention)**	90%	High	97%
39.	**A medication with medium/high anticholinergic activity prescribed to a patient with constipation and without a laxative (risk of worsening constipation)**	87%	High	90%
40.	**A medication with medium/high anticholinergic activity prescribed to a patient with angle closure glaucoma (Risk of acute exacerbation of glaucoma and risk or permanent loss of vision)**	84%	High	86%
Other				
41.	**Four or more psychotropics prescribed to a patient for more than 3 months (increased risk of adverse effects)**	90%	High	90%
42.	**Three or more psychotropic drugs prescribed to a patient on an as required (PRN) basis (increased risk of adverse effects)**	84%	High	86%

[a] Percentage of members rated the indicator as "agree" or "strongly agree". [b] Percentage of members rated the indicator as high or extreme. [c] QT prolonging drugs: medications with known and possible risk of Torsades de Pointes according to crediblemeds.org.[403]

ACEi, Angiotensin-converting-enzyme inhibitor; ARB, Angiotensin receptor blocker; BNF, British National Formulary; BPSD, Behavioural and psychological symptoms of dementia; CNS, Central nervous system; COPD, Chronic Obstructive Pulmonary Disease; ECG, Electrocardiogram; NOAC, New Oral Anticoagulant; NRT, Nicotine replacement therapy; NSAID, Nonsteroidal anti-inflammatory drug; SNRI, Serotonin–norepinephrine reuptake inhibitor; SSRI, Selective serotonin reuptake inhibitors; TCA, Tricyclic antidepressant; U&E, urea and electrolytes.

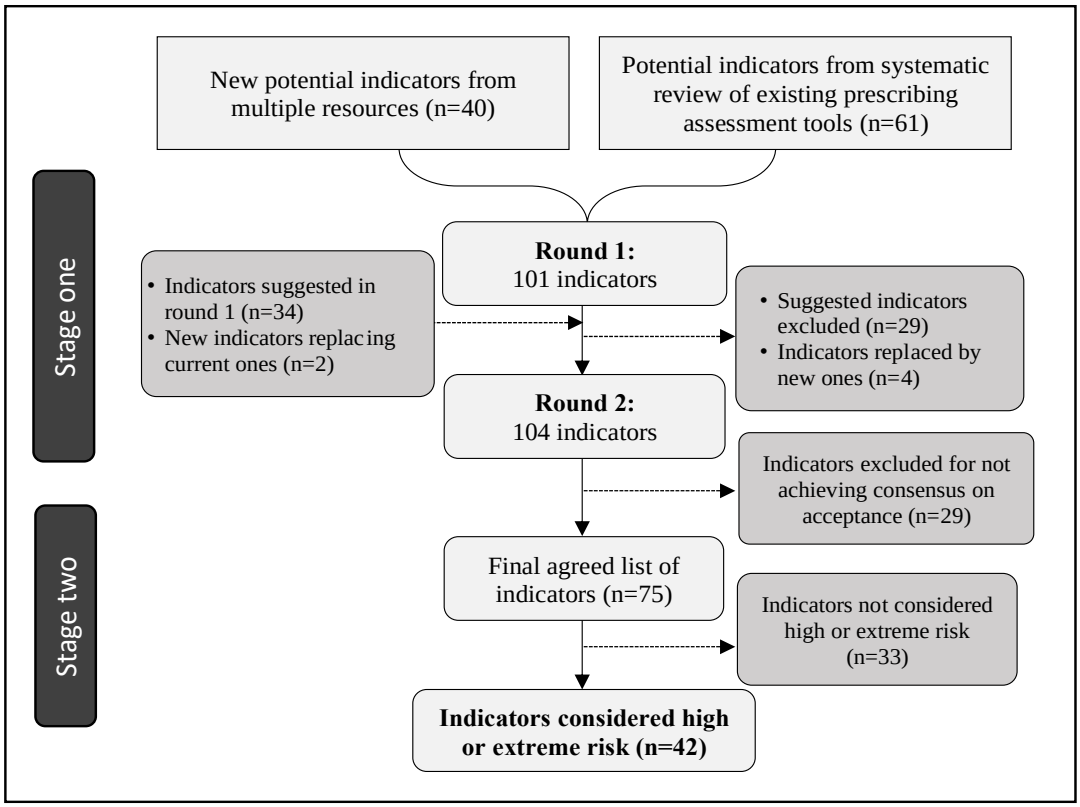

Figure 5.5: The steps taken in arriving at the final set of prescribing safety indicators

5.5 Discussion

To our knowledge, this is the first suite of prescribing safety indicators to be developed specifically for mental health related disorders and medications. A total of 75 prescribing safety indicators were identified that can be considered suitable to assess the safety of prescribing for this unique population. A subset of 42 prescribing safety indicators were considered a high or extreme risk to patient safety and could therefore be prioritised for development of improvement interventions. These indicators cover a broad range of prescribing and medication monitoring problems as well as different mental health related drug classes.

The topics covered in the developed suite of prescribing safety indicators contextualise contemporary safety concerns affecting the care of those with mental disorders and some issues that were not covered in the systematic review in Chapter 4. Examples include the risk of dementia with the use of anticholinergics,[404,405] the risk of cerebrovascular adverse events and mortality with the use of antipsychotics for behavioural and psychological symptoms of dementia (BPSD),[406] the risk of foetal congenital malformations due to exposing pregnant mothers to valproate,[148] and the risk of fatal intestinal obstruction, faecal impaction, and paralytic ileus with use of clozapine.[131]

The most frequently named therapeutic class in the high/extreme list was antipsychotics followed by mood stabilisers. These findings were foreseeable given the enduring risks posed with medication within these classes, such clozapine, lithium and valproate which are considered high risk medicines.[20,407] Accordingly, all the chosen inadequate medication monitoring indicators fell within these two classes. The presence and absence of indicators within classes was also affected by the frequency of how common medications were prescribed. For example, none of the indicators specified MAOi. When examining data concerning antidepressants dispensed in the UK in 2016, MAOi represented only 0.07% of all antidepressants. In comparison, selective serotonin reuptake inhibitors represented more than 50%, and were named in four out of six of the antidepressant indicators.[17]

While there are some indicators that could be better suited to a particular setting, others could be applicable to multiple settings that provide care to patients with mental disorders. The prescribing safety indicators presented in this chapter are not specific for a single setting and could be relevant to any setting that provides care for patients with mental illness, including primary care, hospitals, specialised inpatient and community mental health services, care homes and prisons. However, accordingly, the prescribing safety indicators

may require further work to be operationalised to specific health contexts and to provide evidence of their reliability and validity.[32,392]

Although Chapter 2 indicated that prescribing errors, inappropriate prescribing and preventable medication-related harm are common in patient with mental illness,[25-27] it also shown that most mental health medication safety research has focused on hospital settings, and there is an almost complete lack of data available on the safety of prescribing in primary care specifically for this population.[25,223,224] Accordingly, the next chapter will examine mental health related prescribing safety in primary care using a subset of the prescribing safety indicators developed in this chapter.

5.6 Conclusion

This chapter reports the first study to develop a suite of 75 prescribing safety indicators related to mental health disorders and medications that were agreed among an expert panel using the modified e-Delphi technique. Of these, 42 were identified as having high or extreme risk of patient harm and could therefore be prioritised for development of improvement interventions. These indicators incorporate different types of potentially hazardous prescribing and inadequate medication monitoring, and reflect current challenges associated with the pharmacological management of mental health disorders. The indicators have the potential to form the foundation of assessment of prescribing safety for patients with mental disorders in different settings, and be a catalyst for future safety improvement initiatives for this vulnerable population. The next chapter will apply a subset of the developed indicators into primary care health records to assess the safety of prescribing for people with mental disorders.

Chapter 6 : Evaluating the safety of mental health related prescribing in UK primary care using the Clinical Practice Research Datalink

The purpose of this chapter is to describe the aims, method, results and discussion of the cross sectional and longitudinal study which was designed to evaluate the safety of mental health related prescribing in UK primary care using mental health related prescribing safety indicators. This is the third and final study in this research programme and it was published in the BMJ Quality & Safety.[408]

6.1 Introduction

Primary care is often the first point of contact for people with mental illness with around 90% of adults managed entirely in primary care, including those with high levels of need and complexity.[62,89,90] However, there is evidence that these patients may experience poor quality care affecting both their physical and mental health care needs.[62,89] GPs may not always feel capable of managing patients with mental illness and making alterations to an established treatment, as many report feeling insufficiently trained or experienced in psychiatric services.[89,409]

However, as Chapter 2 illustrated, most medication safety research for patients with mental illness has focused on hospital settings, with little data available on the safety of prescribing in primary care specifically for this population.[25,223] As a result, this chapter will use a subset of the prescribing safety indicators developed in Chapter 5 (which were in turn based on the findings of Chapter 4) to examine mental health related prescribing safety in primary care, in order to examine the magnitude of the problem and to identify targets for improvement.

6.2 Aim and objectives

This chapter aims to pilot mental health related prescribing safety indicators in a large primary care database by examining the prevalence and patterns of different mental health related prescribing safety indicators in primary care in the UK and by measuring the reliability of these indicators to distinguish between practices for benchmarking purposes.

The objectives of this chapter were:

- To select and operationalise mental health related prescribing safety indicators to be applied to primary care health records,
- To examine the overall prevalence of individual mental health related prescribing safety indicators and a group of composite prescribing safety indicators,
- To examine variation in the prevalence between practices of individual mental health related prescribing safety indicators and a group of composite prescribing safety indicators,
- To examine the change in the prevalence of individual mental health related prescribing safety indicators and a group of composite prescribing safety indicators over time,
- To identify patient and practice level characteristics associated with the risk of being affected potentially hazardous prescribing and inadequate medication monitoring indicators.
- To assess the reliability of the prescribing safety indicators at practice level.

6.3 Methods

6.3.1 Study design

The study includes both longitudinal and cross-sectional components. A longitudinal analysis was used to examine the change in the prevalence of different types of mental health related potentially hazardous prescribing and inadequate medication monitoring indicators for general practice patients between 2009-2019. In addition, a cross sectional analysis was conducted to explore the variation in the frequency of these prescribing safety indicators between general practices in the 6- to 12- month period up to September 2019 and to identify patient and practice level characteristics associated with the risk of being affected by prescribing safety indicators.

6.3.2 Data source

Data used in this work were retrieved from the CPRD GOLD, a primary care database of anonymised routinely collected electronic health records from contributing general practices in the UK using Vision® software.[410] CPRD is funded by the MHRA and the National Institute for Health Research (NIHR), as part of the Department of Health and Social Care. CPRD GOLD has been used for extensive epidemiological research and it includes approximately 6.9% of the UK population, and is considered broadly representative of the general population in terms of age, sex and ethnicity.[410]

CPRD data include patients' demographics, diagnoses, prescriptions and test results. Recording and identification of diagnoses is implemented through the use of Read codes. Read codes are a coded thesaurus of clinical terms which are entered by clinicians to record patient findings. Drug prescriptions are entered into the database through the product code system which is a unique code for each treatment, selected by the GP.[410]

CPRD data is presented in separate data files. All files can be linked through a unique patient identifier number. A detailed description of the data available from the various dataset files used in this research is provided in Table 6.1.[410] In January 2020 build-up which was used in this study, the dataset included information from 887 practices (current and historic) and more than 21 million patients.

In addition, practice level index of multiple deprivation (IMD) were linked to the CPRD data. The IMD is one of the most complete and widely used approach to quantify relative

deprivation and affluence for small areas in the UK. The IMD provides data on different indicators across seven domains each of which reflects a different aspect of deprivation experienced by individuals living in an area. These are: income, employment, education and skills, health, housing, crime, access to services, and living environment.[411]

Table 6.1: An overview of the data files in the CPRD that were used in this study

File Name	Description
The Patient file	Contains basic patient demographics and patient registration details for the patients.
The Practice file	Contains details of each practice, including region and collection information.
The Clinical file	Contains medical history events. This file contains all the medical history data entered on the GP system, including symptoms, signs and diagnoses. This can be used to identify any clinical diagnoses, and deaths. Patients may have more than one row of data. The data is coded using Read codes, which allow linkage of codes to the medical terms provided.
The Test file	Contains records of test data on the GP system. The data is coded using a Read code, chosen by the GP, which will generally identify the type of test used.
The therapy file	Contains details of all prescriptions on the GP system. This file contains data relating to all prescriptions (for drugs and appliances) issued by the GP. Patients may have more than one row of data. Drug products and appliances are recorded by the GP using the Gemscript product code system

6.3.3 Selecting the prescribing safety indicators

As discussed in the previous chapter, the 42 developed high/extreme risk indicators were not specific for a single setting, and the feasibility of using the indicators in primary care databases were not explored during the Delphi study and therefore, they needed to be refined to specific health contexts. In addition, for practicality and time constraints during the PhD, a pragmatic approach was followed to reduce the number of indicators. Besides, it has been argued that too many indicators could lead to apathy.[412] The refinement process was based on the following considerations:

- Coverage and available data within the CPRD (n=7),
- The technical feasibility (i.e. the ability to extract and/or analyse the data from the database) (n=6),
- Whether the indicator had been explored in the previous published literature (n=3),
- Commonality and importance in primary care (n=4).

A subset of 22 prescribing safety indicators were deemed suitable for inclusion by the research team (WK, DS, DMA and RNK). Indicators were excluded if the data were not captured in the CPRD such as over the counter therapy (OTC), or if the indicator contained a medication usually prescribed by mental health trusts and might not be recorded in GP records such as clozapine and long-acting antipsychotic injections.[410,413] Also, some indicators were not selected because they have already been examined extensively in the literature. For example the use of antipsychotics for behavioural and psychological symptoms of dementia.[414]

6.3.4 Operationalising the prescribing safety indicators

In order to examine their prevalence, each prescribing safety indicator comprised a denominator and a numerator. The denominator included all patients with the potential to trigger an indicator because of an existing diagnosis, medication, age and/or sex. For example, with indicator P10, patients would be included in the denominator if they had a record of dementia, and, for indicator P11 patients would be included if they were aged older than 65. The numerator included patients who triggered the indicator by receiving the potentially hazardous prescription, having no record of the required monitoring, or having no record of the recommended prescription. Figure 6.1 shows the classifications of the 22 prescribing safety indicators. Table 6.2 lists the 22 included prescribing safety indicators with their operational definitions. Appendix (10)provides a draft summaries of the evidence-based for each mental health related prescribing safety indicator implemented in this chapter.

Additionally, three composite indicators were defined. For each composite indicator, patients were eligible to be included if they were 'at risk' on any one of the relevant individual indicators, and if a patient was eligible for more than one indicator they were counted once. Therefore, the composite indicators describe the number of patients triggering at least one of the relevant indicators divided by the number of patients with the potential to trigger any of the relevant indicators. The first composite consisted of all potentially hazardous prescribing indicators (P1-P18), the second consisted of all inadequate medication monitoring indicators (M1-M4), and the third consisted of all potentially hazardous prescribing indicators except P11 (specifically for the elderly) and P13 (specifically for female patients). The reason for excluding these two indicators was to allow relevant comparisons between genders and age groups in terms of the overall risk.

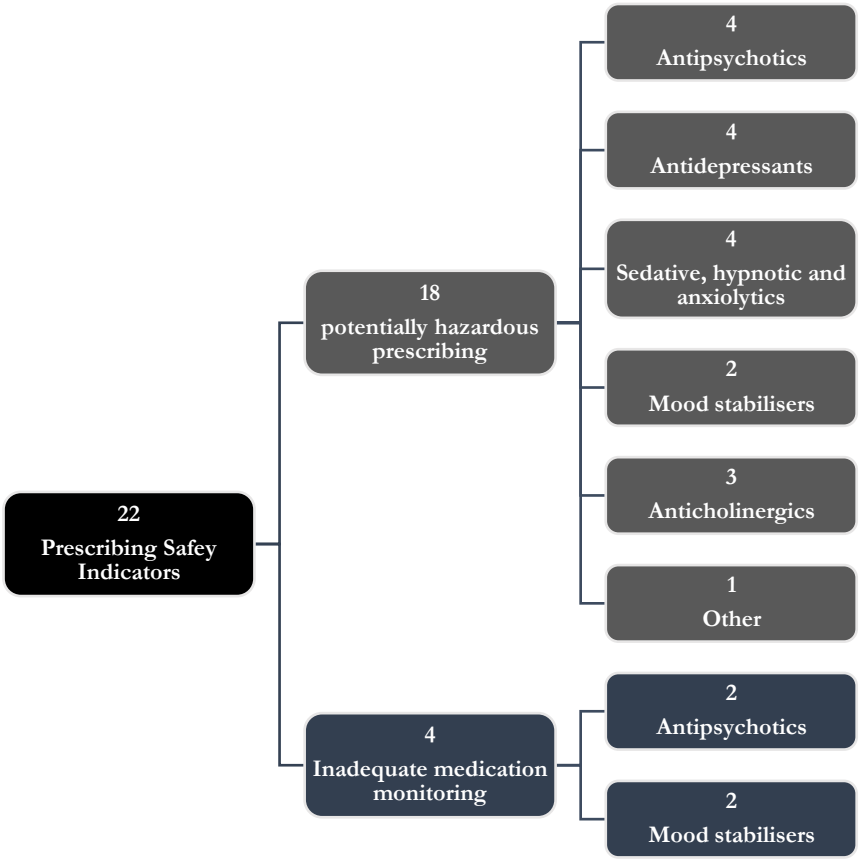

Figure 6.1: The classifications of the 22 prescribing safety indicators

Table 6.2: The description of the 22 prescribing safety indicators with their operational definitions

No	Prescribing safety indicator	Patients at risk of triggering the prescribing safety indicator (denominator)	Patients triggered the prescribing safety indicator (numerator)
	Antipsychotic		
P1	Prescribing antipsychotic with a QT-prolonging drug	Prescribed any antipsychotic within the 6 months leading up to the audit date	Prescribed any QT prolonging drug within the 6 months leading up to the audit date
P2	Risperidone prescribed to a patient with dementia and without psychotic illness for more than 6 weeks	Has a Read code for dementia before the 6 months leading up to the audit date and no read code for psychosis within the 9 months leading up to the audit date and prescribed risperidone within the 6 months leading up to the audit date	Prescribed risperidone for more than 6 weeks within the 6 months leading up to the audit date
P3	Prescribing more than one regular antipsychotic for 3 months or more, excluding clozapine augmentation	Prescribed more than one regular antipsychotic within the 6 months leading up to the audit date	Prescribed more than one regular antipsychotics for 3 months or more within the 6 months leading up to the audit date
P4	Antipsychotic other than quetiapine, aripiprazole or clozapine prescribed to a patient with Parkinson's disease or with Lewy Body Disease	Has a Read code for Parkinson's disease or Lewy Body Disease before the 6 months leading up to the audit date and prescribed any antipsychotic within the 6 months leading up to the audit date	Prescribed antipsychotic other than quetiapine, aripiprazole or clozapine within the 6 months leading up to the audit date
M1	Antipsychotic prescribed for at least 12 months without monitoring glucose, weight, or lipid profile within the previous year	Prescribed any antipsychotic between the 12-24 months leading up to the audit date and again within the 12 months leading up to the audit date	**M1a:** Have not had glucose test within the 12 months leading up to the audit date **M1b:** Have not had weight recorded within the 12 months leading up to the audit date

			M1c: Have not had lipid profile test within the 12 months leading up to the audit date
M2	Initiation of haloperidol without monitoring ECG at baseline	Prescribed haloperidol within the 6 months leading up to the audit date and not prescribed haloperidol in the 6-12 months before the audit date	Have not had ECG monitoring within the 9 months leading up to the audit date
	Antidepressant		
P5	Selective serotonin reuptake inhibitor (SSRI) or serotonin and norepinephrine reuptake inhibitor (SNRI) prescribed with an NSAID or antiplatelet agent to a patient without gastrointestinal protection	Prescribed any SSRI or SNRI AND Prescribed antiplatelet or NSAID within the 6 months leading up to the audit date	Not prescribed gastroprotection within the 6 months leading up to the audit date.
P6	SSRI or SNRI prescribed with a direct oral anticoagulant (DOAC) or warfarin	Prescribed SSRI or SNRI within the 6 months leading up to the audit date	Prescribed warfarin or DOAC concurrently with SSRI or SNRI during the quarter Prescribed warfarin or DOAC within the 6 months leading up to the audit date.
P7	Prescribing citalopram, escitalopram, TCA or trazadone with QT-prolonging drugs	Prescribed citalopram, escitalopram, TCA or trazadone within the 6 months leading up to the audit date	Prescribed any QT prolonging drug within the 6 months leading up to the audit date
P8	SSRI or SNRI prescribed to a patient with a history of peptic ulcer or bleeding disorders without gastroprotection	Has a Read code for peptic ulcer or bleeding disorders before the 6 months leading up to the audit date and prescribed SSRI or SNRI within the 6 months leading up to the audit date.	Not prescribed gastroprotection within the 6 months leading up to the audit date
	Sedative, hypnotic and anxiolytic Indicators		
P9	Any sedative-hypnotic prescribed to a patient with a history of falls	Has a Read code for falls before the 6 months leading up to the audit date	Prescribed any sedative-hypnotic within the 6 months leading up to the audit date
P10	Benzodiazepine, Z-drug or sedating antihistamine prescribed to a patient with dementia or cognitive impairment	Has a Read code for dementia before the 6 months leading up to the audit date	Prescribed benzodiazepine, Z-drug or sedating antihistamine within the 6 months leading up to the audit date
P11	Benzodiazepine or Z-drug prescribed to a patient aged ≥ 65 years	Aged more than 65 before the 6 months leading up to the audit date	Prescribed benzodiazepine or Z-drug within the 6 months leading up to the audit date
P12	Benzodiazepine or Z-drug prescribed to a patient with asthma, COPD or sleep apnoea	Has a Read code for asthma, COPD or sleep apnoea before the 6 months leading up to the audit date	Prescribed benzodiazepine or Z-drug within the 6 months leading up to the audit date
	Mood stabiliser		
P13	Valproic acid prescribed to a woman of childbearing potential	Female, aged ≥ 15 before the 6 months leading up to the audit date and ≤ 49 years before the 6 months leading up to the audit date	Prescribed valproic acid within the 6 months leading up to the audit date
P14	Prescribing lithium with an ACEi/ARB or a diuretic	Prescribed lithium within the 6 months leading up to the audit date	Prescribed ACEi/ARB or a diuretic within the 6 months leading up to the audit date
M3	Prescribing lithium without monitoring lithium plasma levels within the previous 6 months or within the last 3 months if the patient is aged ≥ 65 years or have a diagnosis of renal impairment or during the first year of treatment	**M3a**: Prescribed lithium in the 6-12 months leading up to the audit date and again in the 6 months leading up to the audit date	Have not had lithium level testing within the 6 months leading up to the audit date
		M3b: Aged ≥ 65 before the 6 months leading up to the audit date and prescribed lithium in the 3-6 months leading up to the audit date and again in the 3 months leading up to the audit date	Have not had lithium level testing in the 3 months leading up to the audit date
		M3c: Prescribed in the 3-6 months leading up to the audit date and again in the 3 months leading up to the audit date and NOT prescribed lithium in the 12-18 months leading up to the audit date	Have not had lithium level testing in the 3 months leading up to the audit date

		M3d: Prescribed lithium in the 3-6 months leading up to the audit date and again in the 3 months leading up to the audit date and has a Read code for renal impairment before the 6 months leading up to audit date.	Have not had lithium level testing in the 3 months leading up to the audit date
M4	Lithium prescribed for at least 6 months without monitoring U&Es or thyroid function within the last 6 months	Lithium prescribed in the 6-12 months leading up to the audit date and again within the 6 months leading up to the audit date	**M4a:** Have not had U&E testing in the 6 months leading up to the audit date **M4b:** Have not had thyroid function testing in the 6 months leading up to the audit date
	Anticholinergic		
P15	A medication with medium/high anticholinergic activity prescribed to a patient with dementia or cognitive impairment	Has a Read code for dementia or cognitive impairment before the 6 months leading up to audit date	Prescribed any medication with medium/high anticholinergic activity within the 6 months leading up to audit date.
P16	Mental health related medication with medium/high anticholinergic activity prescribed with another medication with medium/high anticholinergic activity	Prescribed mental health related medication with medium/high anticholinergic activity before the 6 months leading up to audit date	Prescribed any medication with medium/high anticholinergic activity within the 6 months leading up to audit date.
P17	Mental health related medication with medium/high anticholinergic activity prescribed to a patient with a history of urinary retention or benign prostatic hyperplasia	Has a Read code for urinary retention or benign prostatic hyperplasia before the 6 months leading up to audit date	Prescribed mental health related medication with medium/high anticholinergic activity before the 6 months leading up to audit date
	Other		
P18	Four or more psychotropics prescribed to a patient for more than 3 months	Prescribed 4 psychotropics within the 6 months leading up to the audit date	Prescribed 4 or more psychotropics for 3 months within the 6 months leading up to the audit date

6.3.5 Population

The base study population consisted of all patients registered with general practices contributing to the CPRD in the UK, who were deemed to be of research quality 12 months prior to the longitudinal start date (i.e. 1 January 2008) or 12 months prior to the cross-sectional audit date (i.e. 1 October 2018) and had data collected after the audit date (30 September 2019). Research quality was determined using the two sets of data quality criteria provided by the CPRD: acceptability for patients (i.e. registration status, recording of events, and valid age and gender) and up to standard (UTS) time for practices (i.e. continuity of recording).[410] Within the base population, data were extracted for all patients with the potential to trigger each prescribing safety indicator because of an existing diagnosis, medication, age and/or sex.

6.3.6 Clinical codes

Lists of codes were identified in order to capture all events (diagnosis, test and medication) stated in each prescribing safety indicators. A CPRD Code Browser is available to search Medical Dictionary for read codes to identify specific diagnoses and tests and Product Dictionary for product codes. The read codes were searched through the browser using read terms and the product codes were searched through the browser using drug substance

names and BNF chapter names. The Clinical Codes repository were also searched to identify relevant previously developed list of codes.[415]

After collating the list of codes for each relevant event to identify the population for each indicator, two pharmacists of the research team (RNK and DS) reviewed the lists and changes were made accordingly. A full list of the codes is available at TheClinicalCodes repository (https://clinicalcodes.rss.mhs.man.ac.uk).[415] A drug preparation algorithm published previously was used to prepare drug exposure data.[416,417]

6.3.7 Statistical Analysis

6.3.7.1 Cross-Sectional analyses

The proportion of patients triggering each prescribing safety indicator and composite indicator was calculated with 95% confidence intervals. To examine the variability in the prevalence of prescribing safety indicators between practices, the intraclass correlation coefficient (ICC) was estimated using an empty two-level logistic regression model and a two-level logistic regression model with patient variables (case-mix adjustment). The ICC estimates the proportion of the total variation in an indicator that is attributable to the variation between practices.[32]

In addition, we calculated the median odds ratio (MOR) for each indicator using the same case-mix model. The MOR is the median of all possible odd ratios of triggering an indicator in two patients with identical characteristics, but registered with two different practices. It can also be conceptualized as the increased risk that an individual would encounter when moving from one practice to another. The MOR is always equal to or higher than one. Higher MOR values indicate more variation between practices. The advantage of the MOR is that it is directly comparable with the ORs for patient and practice level variables.[418,419]

Furthermore, the reliability for each prescribing safety indicator and each composite indicator was estimated using the Spearman-Brown Prophecy formula defined as $(n * ICC)/(1 + (n - 1) * ICC)$, where n represents number of patients in the denominator per practice.[32] The reliability coefficient indicates if the observed practice-level variation is due to true practice differences or due to chance.[420] This indicates for an indicator with low ICC, higher numbers of 'patients at risk' are needed for a reliable comparison.[32] The reliability ranges between 0 and 1, where a higher value indicates a higher level of reliability.

Values greater than 0.7 are usually deemed to suggest adequate reliability.[30] The reliability for a theoretical practice (using the median number of patients in the denominator) was calculated to provide an overall estimate of reliability. The proportion of practices with a reliability measure greater than 0.7, 0.8 and 0.9 was measured. To visualise the variation between practices, funnel plots of the observed proportions and caterpillar plots of the shrunken practice-level residuals (with 95% CIs) from the case-mix model were generated for each prescribing safety indicator and each composite indicator with an overall reliability greater than 0.7 (Appendix (11)).

The associations between potentially hazardous prescribing (composite 3) and inadequate medication monitoring (composite 2) with both practice-level and patient-level variables were examined using two-level logistic regressions. Initially, unadjusted odds ratios (ORs) with 95% confidence intervals were calculated and then subsequently adjusted for patient and practice variables. Patient-level variables considered were age, sex, and number of repeat medications, which is defined as ≥3 prescriptions of the same medicine within the 12 months leading up to 30 September 2019.[421] Practice-level variables were number of patients per general practice (list size), practice level IMD quintile, and location of practice by country of the UK. The covariates were selected based on prior literature.[30,32] Composite 1 was not included in this analysis as P11 was not relevant to all age groups and P13 was not relevant to both genders.

6.3.7.2 Longitudinal analyses

The proportion of patients triggering each prescribing safety indicator (with 95% confidence intervals) and for the three composite indicators were measured using a series of consecutive cross-sectional analyses by calendar quarter from 2009 to the third quarter of 2019.

In addition, for each indicator, changes in the variation between practices over time was assessed by examining the ICCs of the first and last included quarters using an F-test to compare the variance in both quarters. Chi-square ($\chi 2$) tests were used to compare the prevalence of the first and last quarter of each prescribing safety indicator. All of the analyses were performed using Stata V.16 (StataCorp, College Station, TX). Funnel plots were created using a tool by Public Health England.[422]

6.3.8 Ethical approval

This study is based in part on data from the CPRD obtained under licence from the UK MHRA. The data is provided by patients and collected by the NHS as part of their care and support. The interpretation and conclusions contained in this study are those of the authors alone. The study and use of CPRD data were approved by the Independent Scientific Advisory Committee (ISAC) for MHRA database research, ref 19_234A (Appendix (9)).

6.4 Results

6.4.1 Cross-sectional analyses

A total of 361 general practices were eligible for inclusion with 3,001,877 registered patients. Most included practices were from Scotland (n=159, 42.97%), followed by England (n=99, 26.76%), Wales (n=98, 26.49%) and Northern Ireland (n=14, 3.78%). In total, 1,613,207 (53.74%) patients were at risk of triggering any one of the 22 prescribing safety indicators due to their age, sex, disease, and/or prescription. Table 6.3 shows the observed prevalence, ICCs and MOR of each prescribing safety indicator and composite indicator. Appendix (11)shows the variation between practices for each indicator and each composite indicator with adequate reliability before and after adjusting for patient characteristics.

Table 6.3: Summary of the observed prevalence and the variation between practices for each prescribing safety indicator and composite indicator

No.	Prescribing safety indicator	Observed Prevalence (95% CI)	Patients at risk of prescribing safety indicator (denominator)	Patients triggering prescribing safety indicator (numerator)	ICC (95% CI) Unadjusted	ICC (95% CI) Adjusted by patient level variables	MOR (95% CI)
Composite1	Prescribing indicators (P1-P18)	9.40 (9.36 to 9.45)	1,611,129	151,469	0.03 (0.03 to 0.03)	0.01 (0.01 to 0.02)	1.22 (1.20 to 1.24)
Composite2	Monitoring indicators (M1-M4)	90.19 (89.9 to 90.47)	42,879	38,671	0.26 (0.22 to 0.30)	0.27 (0.23 to 0.31)	2.84 (2.59 to 3.16)
Composite3	Prescribing indicators (P1-P18) excluding indicators specific for elderly or female (P11 and P13)	15.48 (15.41 to 15.56)	882,653	136,664	0.02 (0.02 to 0.03)	0.01 (0.01 to 0.01)	1.21 (1.20 to 1.24)
P1	Prescribing antipsychotic with a QT-prolonging drug	48.14 (47.74 to 48.55)	57,998	27,923	0.02 (0.02 to 0.03)	0.01 (0.01 to 0.02)	1.21 (1.18 to 1.25)
P2	Risperidone prescribed to a patient with dementia and without psychotic illness for more than 6 weeks	90.15 (88.41 to 91.71)	1,310	1,181	0.00	0.00	1.00
P3	Prescribing more than one regular antipsychotic for 3 months or more, excluding clozapine augmentation	41.82 (40.23 to 43.42)	3,735	1,562	0.04 (0.02 to 0.07)	0.02 (0.01 to 0.05)	1.32 (1.2 to 1.52)
P4	Antipsychotic other than quetiapine, aripiprazole or clozapine prescribed to a patient with Parkinson's disease or with Lewy Body Disease	49.41 (45.81 to 53.02)	763	377	0.04 (0.01 to 0.23)	0.04 (0.01 to 0.23)	1.46 (1.16 to 2.58)
P5	Selective serotonin reuptake inhibitor (SSRI) or serotonin and norepinephrine reuptake inhibitor (SNRI) prescribed with an NSAID or antiplatelet agent to a patient without gastrointestinal protection	35.41 (35.02 to 35.8)	58,327	20,653	0.02 (0.02 to 0.03)	0.03 (0.02 to 0.03)	1.34 (1.3 to 1.39)
P6	SSRI or SNRI prescribed with a direct oral anticoagulant (DOAC) or warfarin	3.09 (3.02 to 3.15)	279,073	8,618	0.02 (0.01 to 0.02)	0.01 (0.01 to 0.01)	1.20 (1.17 to 1.24)
P7	Prescribing citalopram, escitalopram, TCA or trazadone with QT-prolonging drugs	41.86 (41.58 to 42.15)	113,097	47,348	0.02 (0.02 to 0.03)	0.02 (0.01 to 0.02)	1.27 (1.24 to 1.3)
P8	SSRI or SNRI prescribed to a patient with a history of peptic ulcer or bleeding disorders without gastroprotection	38.57 (37.59 to 39.55)	9,567	3,690	0.02 (0.01 to 0.03)	0.01 (0 to 0.03)	1.19 (1.11 to 1.33)
P9	Any sedative-hypnotic prescribed to a patient with a history of falls	12.29 (12.13 to 12.46)	157,711	19,390	0.04 (0.03 to 0.05)	0.03 (0.02 to 0.03)	1.33 (1.29 to 1.37)
P10	Benzodiazepine, Z-drug or sedating antihistamine prescribed to a patient with dementia or cognitive impairment	20.16 (19.64 to 20.68)	23,099	4,656	0.05 (0.04 to 0.07)	0.05 (0.04 to 0.06)	1.49 (1.42 to 1.58)

No.	Prescribing safety indicator	Observed Prevalence (95% CI)	Patients at risk of prescribing safety indicator (denominator)	Patients triggering prescribing safety indicator (numerator)	ICC (95% CI) Unadjusted	ICC (95% CI) Adjusted by patient level variables	MOR (95% CI)
P11	Benzodiazepine or Z-drug prescribed to a patient aged ≥ 65 years	6.39 (6.33 to 6.46)	524,083	33,502	0.05 (0.04 to 0.06)	0.05 (0.04 to 0.05)	1.47 (1.42 to 1.51)
P12	Benzodiazepine or Z-drug prescribed to a patient with asthma, COPD or sleep apnoea	5.72 (5.65 to 5.78)	452,338	25,857	0.05 (0.04 to 0.06)	0.04 (0.04 to 0.05)	1.45 (1.41 to 1.5)
P13	Valproic acid prescribed to a woman of childbearing potential	0.20 (0.19 to 0.21)	647,979	1,284	0.05 (0.03 to 0.07)	0.03 (0.02 to 0.05)	1.34 (1.24 to 1.47)
P14	Prescribing lithium with an ACEi/ARB or a diuretic	18.63 (17.19 to 20.14)	2,743	511	0.01 (0 to 0.66)	0.01 (0 to 0.68)	1.14 (1 to 99.91)
P15	A medication with medium/high anticholinergic activity prescribed to a patient with dementia or cognitive impairment	17.44 (16.95 to 17.93)	23,099	4,028	0.03 (0.02 to 0.03)	0.03 (0.02 to 0.04)	1.32 (1.26 to 1.39)
P16	Mental health related medication with medium/high anticholinergic activity prescribed with another medication with medium/high anticholinergic activity	90.64 (89.94 to 91.31)	7,054	6,394	0.11 (0.07 to 0.16)	0.12 (0.08 to 0.18)	1.92 (1.69 to 2.24)
P17	Mental health related medication with medium/high anticholinergic activity prescribed to a patient with a history of urinary retention or benign prostatic hyperplasia	10.33 (10.09 to 10.57)	62,974	6,506	0.03 (0.02 to 0.03)	0.01 (0.01 to 0.02)	1.19 (1.14 to 1.24)
P18	Four or more psychotropics prescribed to a patient for more than 3 months	41.70 (41.08 to 42.33)	24,005	10,011	0.03 (0.03 to 0.04)	0.03 (0.02 to 0.04)	1.34 (1.29 to 1.4)
M1	Antipsychotic prescribed for at least 12 months without monitoring glucose, weight, or lipid profile within the previous year	91.61 (91.34 to 91.87)	41,253	37,791	0.42 (0.37 to 0.47)	0.43 (0.38 to 0.48)	4.50 (3.87 to 5.33)
M1a:	Antipsychotic prescribed for at least 12 months without monitoring glucose within the previous year	83.55 (83.19 to 83.91)	41,253	34,467			
M1b:	Antipsychotic prescribed for at least 12 months without monitoring weight within the previous year	54.92 (54.44 to 55.4)	41,253	22,657			
M1c:	Antipsychotic prescribed for at least 12 months without monitoring lipid profile within the previous year	61.93 (61.46 to 62.4)	41,253	25,549			
M2	Initiation of haloperidol without monitoring ECG at baseline	92.57 (89.57 to 94.93)	404	374	0.45 (0.14 to 0.8)	0.47 (0.17 to 0.79)	5.64 (2.29 to 37.19)

No.	Prescribing safety indicator	Observed Prevalence (95% CI)	Patients at risk of prescribing safety indicator (denominator)	Patients triggering prescribing safety indicator (numerator)	ICC (95% CI) Unadjusted	ICC (95% CI) Adjusted by patient level variables	MOR (95% CI)
M3	Prescribing lithium without monitoring lithium plasma levels within the previous 6 months or within the last 3 months if the patient is aged ≥ 65 years or have a diagnosis of renal impairment or during the first year of treatment	24.30 (22.67 to 25.99)	2,613	635	0.24 (0.19 to 0.31)	0.26 (0.2 to 0.33)	2.73 (2.33 to 3.3)
M3a	Prescribing lithium without monitoring lithium plasma levels within the previous 6 months	18.61 (17.11 to 20.19)	2,525	470			
M3b	Prescribing lithium without monitoring lithium plasma within the last 3 months if the patient is aged ≥ 65 years	29.05 (24.9 to 33.48)	451	131			
M3c	Prescribing lithium without monitoring lithium plasma levels within the last 3 months if the patient has a diagnosis of renal impairment	38.68 (32.09 to 45.59)	212	82			
M3d	Prescribing lithium without monitoring lithium plasma levels within the last 3 months during the first year of treatment	30.6 (26.2 to 35.28)	415	127			
M4	Lithium prescribed for at least 6 months without monitoring U&Es or thyroid function within the last 6 months	33.50 (31.66 to 35.38)	2,525	846	0.17 (0.12 to 0.23)	0.17 (0.12 to 0.23)	2.16 (1.89 to 2.56)
M4a	Lithium prescribed for at least 6 months without monitoring U&Es within the last 6 months	21.35 (19.76 to 23)	2,525	539			
M4b	Lithium prescribed for at least 6 months without monitoring thyroid function within the last 6 months	30.53 (28.74 to 32.37)	2,525	771			

6.4.1.1 Prevalence of composite indicators

The composite that only contained prescribing-related indicators (Composite 1, P1-P18), 151,469 of 1,611,129 (9.4%, 95% CI 9.36% to 9.45%) at-risk patients were affected by at least one potentially hazardous prescription. For the composite that only included monitoring indicators (Composite 2, M1-M4), 38,671 of 42,879 (90.19%, 95% CI 89.9% to 90.47%) at-risk patients were affected by at least one potentially hazardous medication-monitoring episode. For composite 3 (P1-P18 excluding P11 and P13), 136,664 of 882,653 (15.48%, 95% CI 15.41% to 15.56%) patients received at least one potentially hazardous prescription.

6.4.1.2 Prevalence of individual prescribing safety indicators

The proportion of patients triggering each indicator varied considerably across the 22 prescribing safety indicators from 0.20 % to 92.57%. For the potentially hazardous prescribing indicators, the prevalence ranged from 0.2% to 90.6%. For the inadequate monitoring indicators, the prevalence ranged from 24.3% to 92.6%. Of those that that triggered at least one indicator, the majority triggered just one indicator (n=110,144, 65.65%), 20.92% (n= 35,093) triggered two indicators, 8.01% (n=13,439) triggered three indicators, and 5.43% (n=9,108) triggered at least four indicators.

6.4.1.3 Variation between practices

Variation between practices in terms of the observed prevalence of potentially hazardous prescribing measured by prescribing composite (P1-P18, composite 1) ranged from 3.24% to 24.06% (median 9.32%, IQR 7.6-11.23%). However, when measured using the ICC, 3% of this variation was attributable to differences between practices, and only 1% persisted after adjusting for patient characteristics. The remaining 99% was due to unmeasured differences between patients. The MOR value was 1.22 (95% CI 1.20 to 1.24). For the monitoring composite (M1-M4, composite 2) the observed prevalence ranged from 33.33% to 100% (median 91.81%, IQR 84.54-96.86%), with 27% of variation being due to differences between practices after adjusting for patient characteristics and MOR 2.84 (95% CI 2.59 to 3.16). Figure 6.2 shows the proportion of patients receiving potentially hazardous prescribing for each general practice and Figure 6.3 show the proportion of patients experiencing inadequate medication monitoring for each general practice.

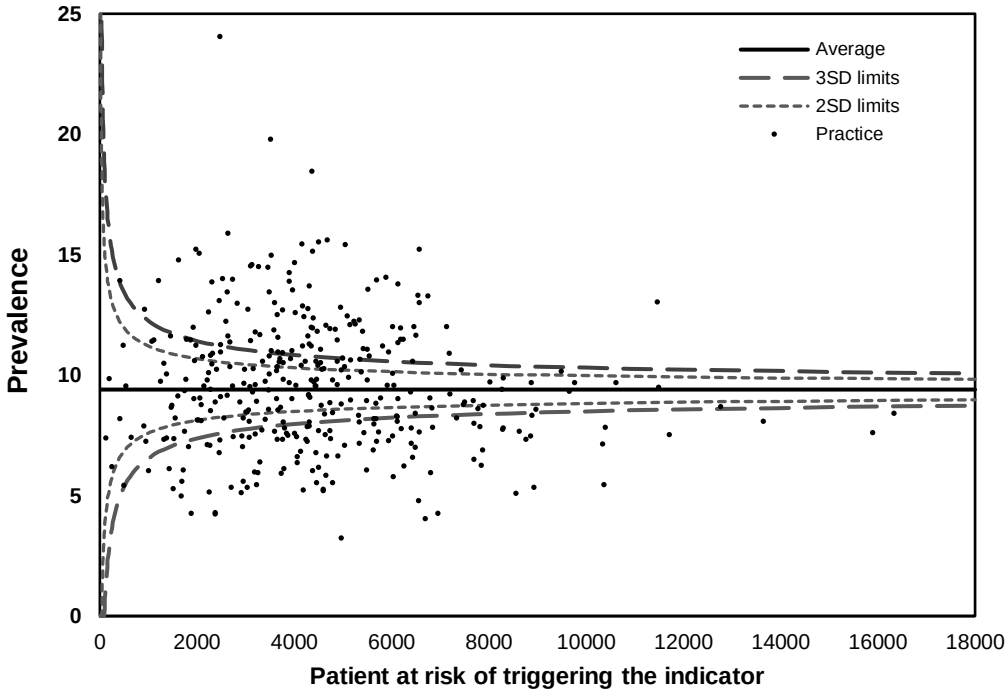

Figure 6.2: Proportion of patients receiving at least one potentially hazardous prescribing (composite 1), for each general practice

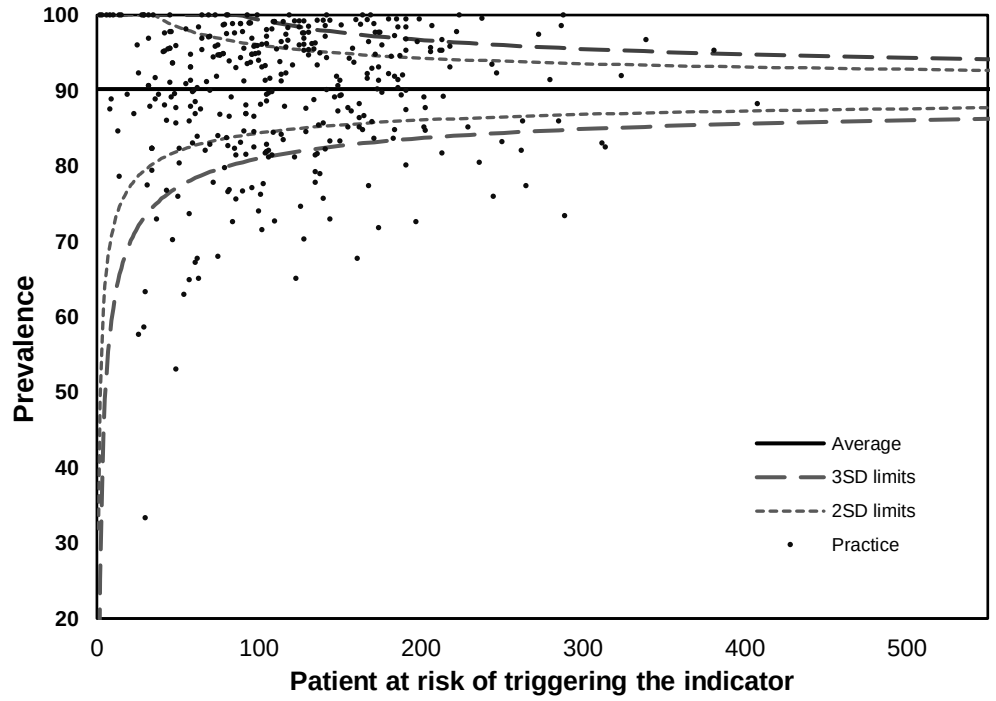

Figure 6.3: Proportion of patients experiencing at least one inadequate medication monitoring (composite 2), for each general practice.

Of the 22 prescribing safety indicators, 8 prescribing indicators and 3 monitoring indicators had reliability scores lower than the recommended level of 0.7 for a practice that was of median size of all practices implying inadequate reliability. The proportion of practices with adequate reliability for the remaining indicators ranged from 66.2% to 100%. However, all composite indicators had reliability scores above 0.9, with over 99% of practices having reliability >0.7. Table 6.4 shows the reliability for a theoretical practice with median number of patients and the proportion of practices with a reliability measure greater than 0.7, 0.8 and 0.9.

Table 6.4: The reliability of the prescribing safety indicators

No.	Prescribing safety indicator	Reliability*	% of practices with reliability >0.7	% of practices with reliability >0.8	% of practices with reliability >0.9
Composite1	Prescribing indicators (P1-P18)	0.99	100%	100%	99%
Composite2	Monitoring indicators (M1-M4)	0.97	99%	98%	96%
Composite3	Prescribing indicators excluding indicators specific for elderly or female (P11 and P13)	0.98	100%	99%	98%
P1	Prescribing antipsychotic with a QT-prolonging drug	0.77	70%	37%	2%
P2	Risperidone prescribed to a patient with dementia and without psychotic illness for more than 6 weeks	0.00	0%	0%	0%
P3	Prescribing more than one regular antipsychotic for 3 months or more, excluding clozapine augmentation	0.26	0%	0%	0%
P4	Antipsychotic other than quetiapine, aripiprazole or clozapine prescribed to a patient with Parkinson's disease or with Lewy Body Disease	0.08	0%	0%	0%
P5	Selective serotonin reuptake inhibitor (SSRI) or serotonin and norepinephrine reuptake inhibitor (SNRI) prescribed with an NSAID or antiplatelet agent to a patient without gastrointestinal protection	0.78	70%	41%	3%
P6	SSRI or SNRI prescribed with a direct oral anticoagulant (DOAC) or warfarin	0.92	97%	91%	67%
P7	Prescribing citalopram, escitalopram, TCA or trazadone with QT-prolonging drugs	0.86	90%	74%	23%
P8	SSRI or SNRI prescribed to a patient with a history of peptic ulcer or bleeding disorders without gastroprotection	0.30	0%	0%	0%
P9	Any sedative-hypnotic prescribed to a patient with a history of falls	0.93	92%	82%	66%
P10	Benzodiazepine, Z-drug or sedating antihistamine prescribed to a patient with dementia or cognitive impairment	0.76	66%	37%	3%
P11	Benzodiazepine or Z-drug prescribed to a patient aged ≥ 65 years	0.98	100%	100%	99%
P12	Benzodiazepine or Z-drug prescribed to a patient with asthma, COPD or sleep apnoea	0.98	99%	99%	98%
P13	Valproic acid prescribed to a woman of childbearing potential	0.99	100%	99%	98%
P14	Prescribing lithium with an ACEi/ARB or a diuretic	0.04	0%	0%	0%
P15	A medication with medium/high anticholinergic activity prescribed to a patient with dementia or cognitive impairment	0.59	23%	5%	0%
P16	Mental health related medication with medium/high anticholinergic activity prescribed with another medication with medium/high anticholinergic activity	0.69	43%	15%	0%
P17	Mental health related medication with medium/high anticholinergic activity prescribed to a patient with a history of urinary retention or benign prostatic hyperplasia	0.79	73%	44%	9%
P18	Four or more psychotropics prescribed to a patient for more than 3 months	0.66	39%	12%	0%

M1	Antipsychotic prescribed for at least 12 months without monitoring glucose, weight, or lipid profile within the previous year	0.99	99%	99%	98%
M2	Initiation of haloperidol without monitoring ECG at baseline	0.44	24%	6%	0%
M3	Prescribing lithium without monitoring lithium plasma levels within the previous 6 months or within the last 3 months if the patient is aged ≥ 65 years or have a diagnosis of renal impairment or during the first year of treatment	0.66	42%	16%	1%
M4	Lithium prescribed for at least 6 months without monitoring U&Es or thyroid function within the last 6 months	0.55	18%	3%	0%

* For a theoretical practice (using the median number of patients in the denominator)

When investigating variation between practices in the prevalence of individual prescribing safety indicators, after controlling for patient characteristics, the highest variation for a prescribing related indicator was for P16 (related to prescribing two medications with anticholinergic activity) with ICC=0.12 and MOR=1.92 (95% CI 1.69 to 2.24). However, the highest variation for prescribing related indicator with adequate reliability (>0.7) was for P10 and P11 (both related to benzodiazepine or Z-drug prescribing) with ICC=0.05 for both prescribing safety indicators and MOR=1.49 (95% CI 1.42 to 1.58) and 1.47 (95% CI 1.42 to 1.51), respectively. However, for individual monitoring related indicators with adequate reliability, the highest variation was observed for M1 (related to monitoring the physical health of patients receiving an antipsychotic) with ICC=0.43 and MOR=4.50 (95% CI 3.87 to 5.33).

6.4.1.4 Patient and practice characteristics associated with potentially hazardous prescribing indicators (composite 3)

Table 6.5 shows the prevalence of patients triggering potentially hazardous prescribing indicators (composite 3, P1-P18 excluding P11 and P13) by patient- and practice-level characteristics, and the unadjusted and adjusted odds ratios (with 95% CIs) derived from the two-level logistic regression model.

Table 6.5: Prevalence of patients receiving at least one potentially hazardous prescribing (Composite 3) by patients and practices level characteristics and multilevel logistic regression unadjusted and adjusted odds ratios (95% CIs).

Variable (No at risk)	% Prevalence (95% CI)	Odds ratio (95% CI)	
		Unadjusted	Adjusted
Age:			
<25 (128,141)	3.98% (3.87 to 4.08)	1	1
25-34 (118,374)	9.92% (9.75 to 10.09)	2.62 (2.53 to 2.71)	2.22 (2.14 to 2.30)
35-44 (115,374)	13.91% (13.71 to 14.11)	3.89 (3.77 to 4.02)	2.34 (2.26 to 2.42)
45-54 (135,518)	17.73% (17.53 to 17.94)	5.22 (5.06 to 5.38)	2.03 (1.96 to 2.09)
55-64 (134,562)	19.68% (19.47 to 19.89)	5.89 (5.71 to 6.07)	1.60 (1.55 to 1.65)
65-74 (120,225)	19.49% (19.27 to 19.72)	5.92 (5.74 to 6.11)	1.16 (1.12 to 1.20)
>=75 (130,459)	22.87% (22.64 to 23.1)	7.41 (7.18 to 7.64)	1.11 (1.08 to 1.15)
Sex			
Male (400,029)	12.19% (12.09 to 12.29)	1	1

Female (482,624)	18.21% (18.10 to 18.32)	1.6 (1.58 to 1.62)	1.43 (1.41 to 1.45)
No of drugs on repeat prescription:			
0 or 1 (361,502)	3.66% (3.60 to 3.72)	1	1
2-4 (232,723)	13.16% (13.02 to 13.30)	3.94 (3.86 to 4.03)	3.99 (3.91 to 4.08)
5-7 (133,179)	23.41% (23.18 to 23.64)	7.98 (7.81 to 8.15)	9.16 (8.95 to 9.38)
8-10 (80,072)	32.47% (32.15 to 32.80)	12.55 (12.26 to 12.84)	15.52 (15.12 to 15.93)
>10 (75,177)	47.41% (47.05 to 47.76)	23.54 (23.01 to 24.08)	30.22 (29.44 to 31.02)
List size			
<6000 (130,159)	16.22% (16.02 to 16.42)	1	1
6001-9000 (270,949)	16.38% (16.24 to 16.52)	1.04 (0.97 to 1.12)	1.03 (0.98 to 1.08)
9001-12000 (210,388)	15.62% (15.46 to 15.77)	0.99 (0.91 to 1.08)	1.02 (0.96 to 1.08)
>12000 (271,157)	14.13% (14.00 to 14.26)	0.88 (0.81 to 0.96)	1.01 (0.95 to 1.07)
Practice level index of multiple deprivation quintile:			
1 least deprived (151,968)	13.22% (13.05 to 13.39)	1	1
2 (140,183)	15.28% (15.09 to 15.47)	1.19 (1.08 to 1.31)	1.08 (1.01 to 1.15)
3 (169,054)	15.00% (14.83 to 15.17)	1.18 (1.07 to 1.29)	1.03 (0.96 to 1.09)
4 (195,532)	16.26% (16.10 to 16.43)	1.31 (1.19 to 1.43)	1.08 (1.01 to 1.15)
5 most deprived (225,916)	16.82% (16.66 to 16.97)	1.37 (1.25 to 1.51)	1.10 (1.03 to 1.17)
Country:			
England (247,545)	12.98% (12.84 to 13.11)	1	1
Northern Ireland (35,773)	22.02% (21.59 to 22.45)	1.91 (1.67 to 2.18)	1.47 (1.33 to 1.63)
Scotland (328,773)	16.94% (16.81 to 17.07)	1.34 (1.26 to 1.43)	1.17 (1.11 to 1.23)
Wales (270,562)	15.14% (15.01 to 15.28)	1.19 (1.11 to 1.28)	0.95 (0.91 to 1.00)

All of the patient-level characteristics included in the analysis were significantly associated with the risk of receiving potentiality hazardous prescribing in the univariable and multivariable models.

In the univariate model, the risk of receiving potentially hazardous prescribing was increasing with age and the number of repeat prescriptions. After adjustment, the number of repeat prescriptions continued to have the same relationship; the prevalence of hazardous prescribing in patients receiving 0-1 repeat prescriptions was 3.66% compared with 47.41% in those with >10 repeat prescriptions (adjusted OR 30.22, 95% CI 29.44 to 31.02). However, with age, the risk of potentially hazardous prescribing increased with increasing age until 35-44 years old (adjusted OR 2.34, 95% CI 2.26 to 2.42) and then began decreasing. Women were found to have higher odds of receiving potentiality hazardous prescribing than men (18.21% vs 12.19% in men, adjusted OR 1.43, 95% CI 1.41 to 1.45). For the practice-level characteristics, it was observed that patients from the most deprived localities had higher odds of receiving potentially hazardous prescribing compared to patients from the least deprived localities (adjusted OR 1.10, 95% CI 1.03 to 1.17). In comparison to England, patients in Northern Ireland were at the highest risk (adjusted OR 1.47, 95% CI 1.33 to 1.63), followed by Scotland (adjusted OR 1.17 95% CI 1.11 to 1.23).

6.4.1.5 Patient and practice characteristics associated with inadequate medication monitoring indicators (composite 2)

Table 6.6 presents the prevalence and odds ratios for inadequate medication monitoring indicators (Composite 2, M1-M4). Similar to the potentially hazardous prescribing composite, women were found to have a higher risk of experiencing inadequate medication monitoring than men (adjusted OR 1.12, 95% CI 1.05 to 1.20). However, the opposite was observed with respect to age and polypharmacy. Patients with >10 prescriptions had a lower risk of inadequate medication monitoring than patients with 0-1 repeat prescription (adjusted OR 0.35, 95% CI 0.29 to 0.41), and patients aged >74 had a lower risk than patients aged <25 (adjusted OR 0.40, 95% CI 0.31 to 0.51). No significant association was observed for the practice list size, country, and the risk of experiencing inadequate medication monitoring.

Table 6.6: Prevalence of patients experienced at least one inadequate medication monitoring (Composite 2) by patients and practices level characteristics and multilevel logistic regression unadjusted and adjusted odds ratios (95% CIs).

Variable (No at risk)	% Prevalence (95% CI)	Odds ratio (95% CI)	
		Unadjusted	Adjusted
Age:			
<25 (2,034)	96.31% (95.40 to 97.09)	1	1
25-34 (4,663)	95.86% (95.25 to 96.41)	0.80 (0.60 to 1.05)	0.85 (0.64 to 1.12)
35-44 (6,372)	92.91% (92.25 to 93.52)	0.45 (0.35 to 0.58)	0.52 (0.40 to 0.67)
45-54 (8,558)	90.37% (89.73 to 90.99)	0.31 (0.25 to 0.40)	0.39 (0.30 to 0.50)
55-64 (8,274)	87.59% (86.86 to 88.29)	0.24 (0.19 to 0.30)	0.31 (0.24 to 0.40)
65-74 (6,051)	85.46% (84.54 to 86.34)	0.19 (0.15 to 0.25)	0.26 (0.20 to 0.34)
>=75 (6,927)	89.07 % (88.31 to 89.80)	0.28 (0.22 to 0.36)	0.40 (0.31 to 0.51)
Sex			
Male (17,280)	90.01% (89.56 to 90.45)	1	1
Female (25,599)	90.31% (89.94 to 90.67)	1.05 (0.98 to 1.13)	1.12 (1.05 to 1.20)
No of drugs on repeat prescription:			
0 or 1 (4,208)	95.58% (94.91 to 96.18)	1	1
2-4 (12,283)	92.29% (91.80 to 92.76)	0.52 (0.44 to 0.62)	0.57 (0.48 to 0.68)
5-7 (10,016)	89.70% (89.08 to 90.29)	0.37 (0.31 to 0.43)	0.45 (0.38 to 0.53)
8-10 (7,216)	88.84% (88.10 to 89.56)	0.32 (0.27 to 0.38)	0.42 (0.36 to 0.50)
>10 (9,156)	86.48% (85.76 to 87.17)	0.26 (0.22 to 0.30)	0.35 (0.29 to 0.41)
List size:			
<6000 (6,829)	90.10% (89.37 to 90.80)	1	1
6001-9000 (14,279)	91.15% (90.78 to 91.62)	1.15 (0.84 to 1.56)	1.12 (0.82 to 1.53)
9001-12000 (10,448)	88.32% (87.69 to 88.93)	0.82 (0.58 to 1.17)	0.83 (0.58 to 1.17)
>12000 (11,323)	90.74% (90.19 to 91.26)	0.98 (0.68 to 1.41)	1.08 (0.74 to 1.58)
Practice level index of multiple deprivation quintile:			
1 least deprived (5,653)	86.87% (85.97 to 87.74)	1	1
2 (6,799)	90.04% (89.31 to 90.74)	1.48 (0.98 to 2.24)	1.57 (1.03 to 2.41)
3 (7,884)	91.53% (90.89 to 92.13)	1.88 (1.25 to 2.82)	1.87 (1.23 to 2.84)
4 (9,904)	90.93% (90.35 to 91.49)	1.77 (1.20 to 2.63)	1.85 (1.23 to 2.76)
5 most deprived (12,639)	90.32% (89.79 to 90.83)	1.56 (1.06 to 2.29)	1.65 (1.11 to 2.46)
Country			
England (9,790)	90.18% (89.85 to 90.77)	1	1
Northern Ireland (2,552)	85.89% (84.48 to 87.22)	0.69 (0.37 to 1.28)	0.73 (0.39 to 1.38)
Scotland (18,489)	89.68% (89.23 to 90.12)	1.11 (0.82 to 1.50))	1.14 (0.84 to 1.55)
Wales (12,048)	91.87% (91.37 to 92.36)	1.25 (0.90 to 1.73)	1.28 (0.92 to 1.78)

6.4.1.6 Patient and practice characteristics associated with each individual prescribing safety indicators

Table 6.7 and Table 6.8 shows the two-level multivariable logistic regression analysis for each prescribing safety indicator. Several observations can be extracted from these tables. For instance, it was observed that the risk of triggering lithium related inadequate monitoring indicators (M3 and M4) for patients registered with practices from the most deprived areas was significantly higher than patients registered with practices from the least deprived areas. In addition, it has been noticed that for P4, P9, P11, and P12 the odds of triggering the indicator for Northern Ireland is more than double the odds in England. However, for P16, the odds for Northern Ireland is half the odds in England.

Table 6.7: Two-level multivariable logistic regression analysis for each potentially hazardous indicator.

Variable	P1		P2		P3		P4		P5		P6		P7		P8		P9	
	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI
Age:																		
<25	1.00		-		1.00		1.00		1.00		1.00		1.00		1.00		1.00	
25-34	1.09	(1.00-1.19)	-		1.60	(1.09-2.37)	2.28	(0.13-39.41)	0.73	(0.65-0.83)	2.84	(1.65-4.88)	0.94	(0.86-1.03)	1.08	(0.66-1.78)	1.56	(1.40-1.73)
35-44	1.01	(0.93-1.10)	-		2.93	(2.01-4.26)	3.61	(0.26-49.67)	0.53	(0.47-0.60)	4.78	(2.84-8.04)	0.70	(0.65-0.77)	0.64	(0.40-1.01)	1.69	(1.53-1.87)
45-54	0.84	(0.77-0.91)	-		3.13	(2.16-4.54)	3.72	(0.28-50.18)	0.44	(0.39-0.49)	7.04	(4.21-11.76)	0.56	(0.51-0.61)	0.46	(0.30-0.72)	1.35	(1.23-1.48)
55-64	0.65	(0.59-0.70)	1.00		2.80	(1.92-4.08)	5.89	(0.45-76.52)	0.41	(0.37-0.46)	9.67	(5.79-16.13)	0.44	(0.40-0.47)	0.44	(0.28-0.68)	0.94	(0.85-1.03)
65-74	0.45	(0.41-0.49)	1.66	(0.60-4.58)	2.13	(1.42-3.19)	4.59	(0.36-58.78)	0.49	(0.43-0.55)	19.88	(11.92-33.16)	0.31	(0.29-0.34)	0.43	(0.27-0.67)	0.63	(0.58-0.69)
>=75	0.46	(0.42-0.50)	1.16	(0.47-2.83)	0.66	(0.43-1.02)	3.63	(0.28-46.35)	0.62	(0.55-0.70)	42.33	(25.39-70.56)	0.30	(0.27-0.33)	0.48	(0.30-0.75)	0.52	(0.47-0.57)
Sex																		
Male	1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Female	0.91	(0.87-0.94)	1.17	(0.79-1.72)	0.65	(0.56-0.75)	1.32	(0.98-1.78)	0.84	(0.81-0.88)	0.66	(0.63-0.69)	1.07	(1.04-1.10)	1.16	(1.05-1.28)	1.31	(1.26-1.35)
No of repeat drugs:																		
0 or 1	1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00	
2-4	4.39	(4.13-4.66)	8.31	(3.10-22.31)	20.59	(7.52-56.33)	0.34	(0.12-0.98)	0.69	(0.64-0.74)	4.53	(3.63-5.65)	2.23	(2.13-2.34)	0.21	(0.17-0.27)	5.05	(4.71-5.40)
5-7	8.36	(7.83-8.93)	6.83	(2.85-16.36)	33.86	(12.39-92.53)	0.32	(0.12-0.90)	0.40	(0.37-0.43)	12.23	(9.85-15.20)	3.81	(3.63-4.01)	0.08	(0.06-0.10)	9.98	(9.29-10.72)
8-10	12.24	(11.39-13.16)	8.65	(3.62-20.67)	31.26	(11.40-85.75)	0.21	(0.08-0.58)	0.25	(0.23-0.27)	20.61	(16.59-25.60)	5.76	(5.47-6.08)	0.04	(0.03-0.06)	18.02	(16.74-19.39)
>10	21.92	(20.38-23.58)	8.56	(3.67-19.98)	41.88	(15.31-114.51)	0.23	(0.08-0.62)	0.12	(0.11-0.13)	35.37	(28.52-43.86)	10.35	(9.81-10.91)	0.02	(0.02-0.03)	36.07	(33.58-38.75)
List size																		
<6000	1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00	
6001-9000	1.07	(1.02-1.13)	1.24	(0.68-2.25)	0.90	(0.73-1.10)	0.77	(0.47-1.24)	1.00	(0.94-1.06)	1.03	(0.95-1.10)	1.02	(0.98-1.06)	0.89	(0.77-1.04)	1.07	(1.02-1.13)
9001-12000	1.07	(1.01-1.13)	1.27	(0.66-2.42)	0.84	(0.67-1.05)	0.76	(0.46-1.24)	0.95	(0.89-1.01)	1.07	(0.99-1.15)	0.99	(0.95-1.03)	0.85	(0.72-1.00)	1.10	(1.04-1.16)
>12000	1.05	(0.99-1.11)	1.44	(0.76-2.72)	0.81	(0.64-1.01)	0.77	(0.46-1.27)	0.95	(0.89-1.01)	1.04	(0.97-1.13)	1.03	(0.99-1.07)	0.85	(0.72-1.00)	0.96	(0.92-1.02)
Practice level IMD:																		
1 least deprived	1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00	
2	1.02	(0.95-1.09)	1.35	(0.72-2.50)	1.22	(0.93-1.60)	0.91	(0.54-1.53)	1.08	(1.01-1.16)	0.98	(0.90-1.06)	1.04	(1.00-1.09)	0.91	(0.76-1.09)	1.01	(0.96-1.07)
3	1.03	(0.96-1.10)	2.26	(1.16-4.42)	0.88	(0.67-1.15)	0.91	(0.54-1.52)	1.07	(1.00-1.14)	0.97	(0.89-1.05)	0.94	(0.90-0.98)	0.95	(0.80-1.12)	0.88	(0.83-0.93)
4	1.02	(0.96-1.09)	1.41	(0.79-2.52)	0.94	(0.72-1.21)	1.29	(0.79-2.12)	1.13	(1.06-1.20)	0.99	(0.92-1.06)	0.96	(0.92-1.01)	0.83	(0.70-0.98)	0.93	(0.88-0.98)
5 most deprived	1.04	(0.98-1.11)	1.23	(0.72-2.10)	1.05	(0.82-1.34)	0.97	(0.59-1.58)	1.05	(0.98-1.11)	0.87	(0.81-0.94)	0.98	(0.94-1.03)	0.90	(0.77-1.05)	0.83	(0.79-0.87)
Country:																		
England	1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Northern Ireland	1.36	(1.24-1.49)	0.72	(0.36-1.42)	1.32	(0.95-1.82)	3.71	(1.74-7.89)	1.18	(1.08-1.28)	0.80	(0.71-0.89)	1.37	(1.28-1.46)	0.68	(0.54-0.85)	2.03	(1.89-2.17)
Scotland	0.94	(0.90-0.99)	1.27	(0.77-2.08)	0.76	(0.63-0.92)	1.17	(0.80-1.73)	1.10	(1.05-1.16)	0.82	(0.77-0.88)	0.87	(0.84-0.90)	0.79	(0.69-0.91)	1.22	(1.17-1.28)
Wales	0.94	(0.89-0.99)	1.29	(0.76-2.19)	0.86	(0.70-1.06)	1.05	(0.71-1.55)	1.29	(1.22-1.35)	0.91	(0.86-0.97)	0.86	(0.83-0.89)	1.10	(0.95-1.27)	0.96	(0.92-1.00)

Variable	P10		P11		P12		P13		P14		P15		P16		P17		P18	
	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI
Age:																		
<25	1.00		-		1.00		1.00		-		1.00		1.00		1.00		1.00	
25-34	1.44	(0.46-4.49)	-		3.52	(3.26-3.81)	0.98	(0.79-1.21)	1.00		0.61	(0.16-2.25)	6.53	(4.62-9.23)	2.58	(1.65-4.04)	1.13	(0.94-1.37)
35-44	2.72	(1.05-7.05)	-		3.99	(3.70-4.31)	1.13	(0.93-1.37)	0.76	(0.34-1.73)	2.37	(0.95-5.93)	10.10	(7.15-14.26)	2.65	(1.72-4.08)	1.61	(1.35-1.92)
45-54	2.52	(1.04-6.13)	-		3.04	(2.81-3.28)	1.37	(1.12-1.67)	1.89	(0.91-3.93)	2.35	(1.01-5.48)	13.52	(9.67-18.89)	1.71	(1.13-2.58)	1.72	(1.45-2.05)
55-64	2.26	(0.95-5.36)	-		2.09	(1.93-2.26)	-		2.79	(1.36-5.70)	1.89	(0.83-4.30)	11.44	(8.35-15.68)	1.35	(0.91-2.02)	1.63	(1.37-1.94)
65-74	1.47	(0.62-3.47)	1.00		1.62	(1.50-1.75)	-		2.90	(1.40-5.98)	0.98	(0.43-2.22)	8.95	(6.57-12.21)	0.90	(0.60-1.34)	1.13	(0.94-1.35)
>=75	1.19	(0.51-2.80)	1.04	(1.02-1.07)	1.55	(1.43-1.68)	-		3.47	(1.67-7.21)	0.67	(0.30-1.52)	5.98	(4.44-8.05)	0.69	(0.46-1.03)	0.71	(0.59-0.85)
Sex																		
Male	1.00		1.00		1.00		-		1.00		1.00		1.00		1.00		1.00	
Female	1.16	(1.08-1.24)	1.78	(1.73-1.82)	1.55	(1.51-1.59)	-		0.73	(0.59-0.90)	1.18	(1.10-1.27)	2.57	(2.15-3.06)	2.25	(2.03-2.48)	0.69	(0.65-0.73)
No of repeat drugs:																		
0 or 1	1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		-	
2-4	2.05	(1.66-2.53)	2.99	(2.83-3.17)	3.40	(3.24-3.57)	16.29	(13.57-19.56)	3.55	(0.85-14.87)	3.25	(2.49-4.24)	3.28	(2.35-4.58)	3.47	(3.02-3.99)	1.00	
5-7	3.34	(2.74-4.08)	5.43	(5.14-5.74)	7.43	(7.06-7.82)	40.81	(33.41-49.84)	9.48	(2.30-39.12)	5.65	(4.37-7.30)	4.07	(2.93-5.66)	6.92	(6.02-7.94)	4.80	(4.19-5.49)
8-10	5.15	(4.22-6.28)	9.48	(8.97-10.02)	13.33	(12.63-14.07)	78.03	(62.65-97.20)	15.05	(3.64-62.30)	8.72	(6.75-11.26)	4.52	(3.19-6.40)	11.95	(10.39-13.74)	7.98	(6.96-9.14)
>10	8.78	(7.22-10.68)	19.00	(17.99-20.07)	26.86	(25.51-28.29)	118.58	(95.02-147.98)	27.17	(6.59-111.97)	15.06	(11.68-19.42)	5.00	(3.61-6.94)	21.59	(18.83-24.76)	13.07	(11.44-14.93)
List size																		
<6000	1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00	
6001-9000	1.11	(1.00-1.24)	1.03	(0.99-1.06)	0.97	(0.94-1.01)	0.87	(0.73-1.03)	0.91	(0.66-1.24)	1.14	(1.01-1.28)	0.91	(0.70-1.20)	0.97	(0.89-1.05)	1.05	(0.97-1.15)
9001-12000	1.12	(1.00-1.25)	1.07	(1.03-1.11)	0.99	(0.95-1.03)	0.90	(0.76-1.08)	1.12	(0.81-1.56)	1.12	(0.99-1.26)	0.99	(0.74-1.33)	0.95	(0.87-1.04)	1.02	(0.93-1.12)
>12000	1.04	(0.93-1.17)	0.96	(0.93-1.00)	0.90	(0.86-0.94)	0.85	(0.71-1.01)	1.05	(0.76-1.47)	1.19	(1.05-1.34)	0.93	(0.70-1.24)	1.01	(0.92-1.10)	1.06	(0.97-1.17)
Practice level IMD:																		
1 least deprived	1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00	
2	0.94	(0.84-1.06)	0.99	(0.95-1.03)	1.01	(0.97-1.06)	1.03	(0.84-1.27)	1.33	(0.93-1.89)	1.01	(0.89-1.14)	1.46	(1.06-2.00)	1.04	(0.94-1.14)	1.21	(1.09-1.34)
3	0.87	(0.78-0.98)	0.84	(0.80-0.87)	0.92	(0.88-0.97)	0.96	(0.79-1.17)	1.12	(0.79-1.61)	1.01	(0.89-1.13)	1.20	(0.90-1.60)	1.08	(0.99-1.19)	1.02	(0.92-1.14)
4	0.97	(0.87-1.08)	0.84	(0.81-0.87)	0.92	(0.88-0.96)	0.96	(0.79-1.16)	1.22	(0.87-1.72)	1.10	(0.98-1.23)	1.54	(1.16-2.05)	1.14	(1.04-1.24)	1.00	(0.91-1.11)
5 most deprived	0.83	(0.74-0.92)	0.78	(0.75-0.81)	0.86	(0.82-0.90)	0.97	(0.81-1.17)	1.31	(0.94-1.82)	0.95	(0.84-1.06)	1.87	(1.40-2.50)	1.19	(1.10-1.30)	1.07	(0.98-1.18)
Country:																		
England	1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Northern Ireland	1.92	(1.64-2.24)	2.65	(2.52-2.80)	2.07	(1.95-2.21)	0.75	(0.56-1.02)	0.80	(0.49-1.28)	0.99	(0.83-1.18)	0.55	(0.36-0.85)	1.05	(0.91-1.20)	1.28	(1.14-1.44)
Scotland	1.26	(1.16-1.38)	1.27	(1.23-1.31)	1.42	(1.37-1.47)	0.80	(0.69-0.92)	0.82	(0.62-1.08)	1.01	(0.92-1.10)	1.14	(0.91-1.44)	1.13	(1.06-1.22)	0.83	(0.77-0.90)
Wales	1.41	(1.28-1.54)	1.10	(1.06-1.13)	0.98	(0.94-1.01)	0.98	(0.84-1.13)	0.94	(0.70-1.26)	0.78	(0.71-0.86)	0.77	(0.60-0.99)	0.97	(0.90-1.05)	1.13	(1.04-1.23)

* IMD= Index of Multiple Deprivation

Table 6.8: Two-level multivariable logistic regression analysis for each inadequate medication monitoring indicator.

Variable	M1		M2		M3		M4	
	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI
Age:								
<25	1.00		1.00		1.00		1.00	
25-34	1.05	(0.79-1.41)	9.64	(0.40-232.93)	1.78	(0.65-4.89)	0.76	(0.29-2.03)
35-44	0.62	(0.47-0.81)	9.61	(0.42-220.24)	0.85	(0.32-2.25)	0.75	(0.30-1.90)
45-54	0.49	(0.38-0.64)	36.27	(1.65-798.05)	0.90	(0.34-2.34)	0.76	(0.31-1.90)
55-64	0.42	(0.32-0.54)	10.73	(0.74-154.71)	0.81	(0.31-2.10)	0.64	(0.26-1.59)
65-74	0.36	(0.28-0.47)	6.09	(0.51-73.19)	0.95	(0.36-2.50)	0.47	(0.19-1.18)
>=75	0.51	(0.40-0.67)	18.83	(1.66-213.00)	1.19	(0.45-3.14)	0.56	(0.22-1.42)
Sex								
Male	1.00		1.00		1.00		1.00	
Female	1.10	(1.02-1.18)	1.09	(0.48-2.46)	1.04	(0.86-1.26)	0.74	(0.62-0.88)
No of drugs on repeat prescription:								
0 or 1	1.00		1.00		1.00		1.00	
2-4	0.63	(0.53-0.76)	1.36	(0.08-23.70)	0.95	(0.54-1.65)	0.68	(0.43-1.08)
5-7	0.47	(0.39-0.56)	0.32	(0.03-3.14)	0.92	(0.53-1.61)	0.58	(0.36-0.92)
8-10	0.41	(0.34-0.49)	0.26	(0.03-2.37)	1.12	(0.63-1.98)	0.64	(0.40-1.05)
>10	0.32	(0.26-0.38)	0.18	(0.02-1.51)	1.13	(0.64-1.99)	0.83	(0.51-1.34)
List size								
<6000	1.00		1.00		1.00		1.00	
6001-9000	1.14	(1.03-1.28)	0.14	(0.02-1.14)	1.06	(0.81-1.40)	0.85	(0.66-1.10)
9001-12000	0.82	(0.73-0.91)	0.16	(0.02-1.41)	0.67	(0.49-0.91)	0.67	(0.51-0.88)
>12000	1.16	(1.03-1.30)	0.15	(0.02-1.30)	1.00	(0.75-1.34)	0.86	(0.66-1.13)
Practice level IMD:								
1 least deprived	1.00		1.00		1.00		1.00	
2	1.38	(1.22-1.58)	15.02	(1.57-143.51)	1.88	(1.34-2.64)	0.94	(0.70-1.26)
3	1.55	(1.36-1.76)	1.80	(0.52-6.17)	1.83	(1.30-2.57)	1.00	(0.75-1.35)
4	1.40	(1.25-1.59)	2.74	(0.82-9.18)	2.22	(1.61-3.08)	1.47	(1.12-1.94)
5 most deprived	1.30	(1.15-1.45)	3.23	(0.93-11.18)	3.33	(2.43-4.56)	1.81	(1.39-2.37)
Country:								
England	1.00		1.00		1.00		1.00	
Northern Ireland	0.71	(0.61-0.81)	-		0.58	(0.38-0.88)	0.74	(0.50-1.10)
Scotland	1.02	(0.93-1.12)	0.56	(0.20-1.58)	0.82	(0.65-1.05)	1.05	(0.83-1.32)
Wales	1.47	(1.32-1.64)	1.13	(0.35-3.59)	0.61	(0.47-0.80)	0.67	(0.52-0.86)

* IMD= Index of Multiple Deprivation

6.4.2 Longitudinal analyses

For the longitudinal analysis, 323 general practices and 4,483,449 patients were included during the study period. Most included practices were from Scotland (n=147, 45.51%), followed by Wales (n=82, 25.39), England (n=80, 24.77%), and Northern Ireland (n=14, 4.33%).

Table 6.9 shows the change over time in prevalence and variation between practices for each prescribing safety indicator and composite indicator (quarterly changes in each prescribing safety indicator prevalence between 2009 and 2019 are shown in Appendix (11)). The data indicated a steady increase in the proportion of patients receiving potentially hazardous prescribing between 2009 and 2019. The percentage for composite 1 (P1-P18) increased by 40.32% from 6.77% to 9.50%. The percentage of patients receiving potentially inadequate medication monitoring (composite 2, M1-M4), increased by 14.77% from 78.52% to 90.12%. Figure 6.4 and Figure 6.5 show the proportion of patients receiving potentially hazardous prescribing and inadequate medication monitoring for each quarter from 2009 to 2019. There were significant increases in the prevalence of 9 individual indicators, significant reductions in the prevalence of 9 further indicators, and no significant difference in the remaining 4 indicators ($p > 0.05$). Seasonal variation was observed for lithium monitoring indicators (M3 and M4), where fewer patients triggered the indicators in the first quarter of each year (i.e. more people receive the monitoring).

Between 2009 and 2019, the variation in the prevalence between practices reduced significantly for patients receiving potentially hazardous prescribing (composite 1, P1-P18) (ICC 0.05 to 0.03, $p < 0.001$), but it increased for patients receiving inadequate medication monitoring (composite 2, M1-M4) (ICC 0.20 to 0.25, $p < 0.001$). There was a significant increase in the variation of 7 individual indicators, significant reductions in the variation of 8 indicators, and no significant difference in 7 indicators ($p > 0.05$).

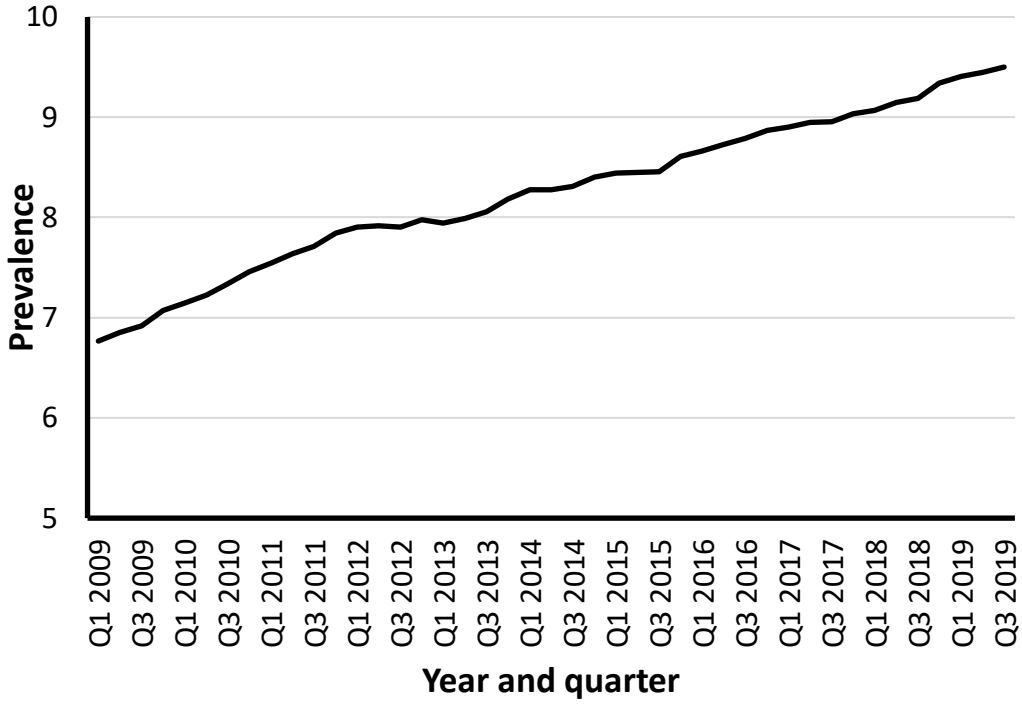

Figure 6.4: Proportion of patient receiving at least one potentially hazardous prescribing (composite 2), for each quarter between 2009 and 2019

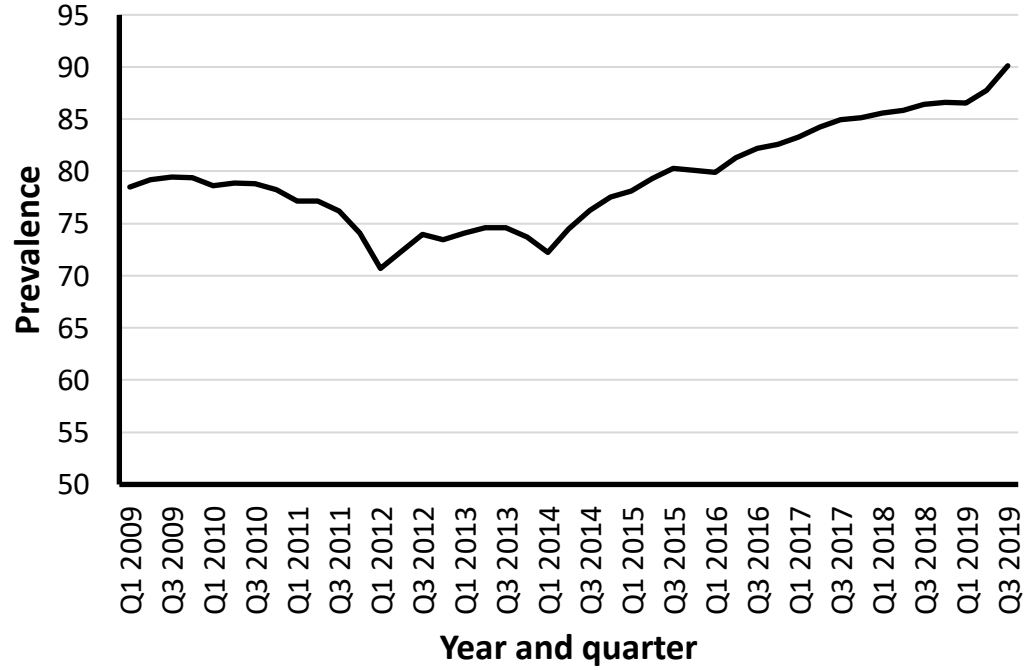

Figure 6.5: Proportion of patient experiencing at least one inadequate medication monitoring (composite 3), for each quarter between 2009 and 2019

Table 6.9: summary of the change over time in the prevalence and the variation between practices for each prescribing safety indicator and composite indicator

No.	Prescribing safety indicator	Change in prevalence				Change in variation between practices		
		Prevalence (%) Q1 2009*	Prevalence (%) Q3 2019	Absolute change (% of change)	χ2 test, p-value	ICC, Q1 2009	ICC, Q3 2019	F-test for difference in variances, p-value
Composite1	Prescribing indicators (P1-P18)	6.77	9.50	+2.73 (+40.32)	<0.001	0.045	0.029	<0.001
Composite2	Monitoring indicators (M1-M4)	78.52	90.12	+11.6 (+14.77)	<0.001	0.199	0.253	<0.001
Composite3	Prescribing indicators excluding indicators specific for elderly or female (P11 and P13)	14.16	15.61	+1.45 (+10.24)	<0.001	0.034	0.023	<0.001
P1	Prescribing antipsychotic with a QT-prolonging drug	45.50	48.35	+2.85 (+6.26)	<0.001	0.022	0.022	0.419
P2	Risperidone prescribed to a patient with dementia and without psychotic illness for more than 6 weeks	90.26	90.03	-0.23 (-0.25)	0.909	0.000	0.000	0.868
P3	Prescribing more than one regular antipsychotic for 3 months or more, excluding clozapine augmentation	37.47	41.59	+4.12 (+11)	<0.001	0.041	0.041	0.285
P4	Antipsychotic other than quetiapine, aripiprazole or clozapine prescribed to a patient with Parkinson's disease or with Lewy Body Disease	60.44	49.51	-10.93 (-18.08)	<0.001	0.132	0.048	0.566
P5	Selective serotonin reuptake inhibitor (SSRI) or serotonin and norepinephrine reuptake inhibitor (SNRI) prescribed with an NSAID or antiplatelet agent to a patient without gastrointestinal protection	57.30	35.43	-21.87 (-38.17)	<0.001	0.014	0.024	<0.001
P6	SSRI or SNRI prescribed with a direct oral anticoagulant (DOAC) or warfarin	1.81	3.11	+1.3 (+71.82)	<0.001	0.012	0.016	<0.001
P7	Prescribing citalopram, escitalopram, TCA or trazadone with QT-prolonging drugs	51.83	41.93	-9.9 (-19.1)	<0.001	0.030	0.020	<0.001
P8	SSRI or SNRI prescribed to a patient with a history of peptic ulcer or bleeding disorders without gastroprotection	44.01	38.40	-5.61 (-12.75)	<0.001	0.017	0.018	0.083
P9	Any sedative-hypnotic prescribed to a patient with a history of falls	11.60	12.40	+0.8 (+6.9)	<0.001	0.049	0.039	<0.001
P10	Benzodiazepine, Z-drug or sedating antihistamine prescribed to a patient with dementia or cognitive impairment	18.89	20.16	+1.27 (+6.72)	0.001	0.054	0.053	0.001
P11	Benzodiazepine or Z-drug prescribed to a patient aged ≥ 65 years	8.04	6.43	-1.61 (-20.02)	<0.001	0.057	0.048	<0.001
P12	Benzodiazepine or Z-drug prescribed to a patient with asthma, COPD or sleep apnoea	4.55	5.79	+1.24 (+27.25)	<0.001	0.061	0.048	<0.001
P13	Valproic acid prescribed to a woman of childbearing potential	0.20	0.20	0 (0)	0.549	0.051	0.045	<0.001
P14	Prescribing lithium with an ACEi/ARB or a diuretic	18.57	18.48	-0.09 (-0.48)	0.929	0.065	0.000	0.921
P15	A medication with medium/high anticholinergic activity prescribed to a patient with dementia or cognitive impairment	20.51	17.49	-3.02 (-14.72)	<0.001	0.055	0.026	<0.001
P16	Mental health related medication with medium/high anticholinergic activity prescribed with another medication with medium/high anticholinergic activity	92.73	90.54	-2.19 (-2.36)	<0.001	0.062	0.114	<0.001
P17	Mental health related medication with medium/high anticholinergic activity prescribed to a patient with a history of urinary retention or benign prostatic hyperplasia	8.40	10.39	+1.99 (+23.69)	<0.001	0.029	0.025	<0.001
P18	Four or more psychotropics prescribed to a patient for more than 3 months	30.30	41.87	+11.57 (+38.18)	<0.001	0.028	0.033	<0.001
M1	Antipsychotic prescribed for at least 12 months without monitoring glucose, weight, or lipid profile within the previous year	80.03	91.52	+11.49 (+14.36)	<0.001	0.328	0.414	<0.001
M2	Initiation of haloperidol without monitoring ECG at baseline	93.80	92.35	-1.45 (-1.55)	0.380	0.000	0.493	0.034
M3	Prescribing lithium without monitoring lithium plasma levels within the previous 6 months or within the last 3 months if the patient is aged ≥ 65 years or have a diagnosis of renal impairment or during the first year of treatment	31.46	24.17	-7.29 (-23.17)	<0.001	0.062	0.257	<0.001
M4	Lithium prescribed for at least 6 months without monitoring U&Es or thyroid function within the last 6 months	44.45	33.42	-11.03 (-24.81)	<0.001	0.092	0.176	0.785

*Except for M3 and M4 where we used the third quarter (Q3) of 2009 for comparison because of the seasonal variation.

6.5 Discussion

This study aimed to pilot mental health related prescribing safety indicators into large primary care database by examining the prevalence and patterns of different mental health related prescribing safety indicators in primary care in the UK and by measuring the reliability of the indicators to distinguish between practices. It has been found that mental health related potentially hazardous prescribing and inadequate medication monitoring is common in primary care, with considerable variation between general practices for some indicators even after controlling for differences in patient characteristics. Variations were higher for indicators related to benzodiazepine and Z-drug prescribing, and monitoring the physical health of patients receiving antipsychotics. In addition, the analyses identified a subset of 11 prescribing safety indicators with adequate reliability to be used for benchmarking purposes.

This work has also examined the change over time in the prevalence of each indicators, and it was found that the proportion of patients triggering composite indicators for potentially hazardous prescribing and inadequate monitoring has been increasing over the study period, though the absolute change in most individual indicators has been mainly small. However, 2 indicators, M1 and P18, showed a large increase, 11.49% and 11.57%, respectively. In contrast, 3 indicators, P4, P5 and M4, showed a large and steady reduction, 10.93%, 21.87% and 11.03%, respectively. Therefore, this could suggest that specific targeted intervention could be needed for those indicators that have been increasing over time, as well as learning from any changes where indicator prevalence was decreasing.

Measuring and identifying a safety issue is the first step toward positively changing practice.[138] The information obtained by the indicators may enable health providers and policy makers to examine different aspects regarding prescribing safety, identifying improvement targets, supporting development of improvement efforts to help reduce medication related harm, prioritising efforts for patients with increased risk of triggering the indicators and addressing avoidable health inequalities. This work could also be regarded as a baseline prevalence to evaluate prescribing safety for people with mental illness is improving in primary care.[32] However, it is important to consider that the identification of prescribing safety indicators does not necessarily imply error and sometimes the seemingly hazardous prescribing might be the patients' most suitable option.[252] Still, in general they are not considered good practice and should be avoided

where possible.[30] Indeed, these findings related to the high rates of potentially inadequate medication monitoring are concerning as there is not usually a clinical justification for them.[32] However, medication monitoring may be affected by patient engagement, quality of data recording, or that the monitoring is performed and documented in other settings such as secondary care. Nevertheless, current NICE guidelines indicate that primary care should be responsible for antipsychotics (M1) and lithium (M3 and M4) monitoring after the first 12 months of therapy or when the patient's condition has stabilised.[127,423]

The low reliability for some indicators indicates that some practices had inadequate numbers of patients 'at risk' to be used for comparison with others. However, the composite indicators showed adequate reliability across all or most practices. Therefore, for the purposes of benchmarking, composite indicators along with individual reliable indicators could be used, as we can be more confident that the they correctly define practices as having above average or below average rates of hazardous prescribing and inadequate monitoring.[30] However, it is important to recognise the multiple disadvantages of composite indicators (i.e. they do not always provide an accurate reflection of the full picture).[424,425] Nevertheless, the reliability estimate provided is only relevant to compare practices on an aggregated level (meso-level) and therefore individual prescribing safety indicators with low reliability could still be used to identify patients at risk of harm for improvement interventions on a patient level (micro-level) and also to assess the safety nationally or to compare it internationally (macro-level).[426]

6.6 Conclusion

This chapter presents the first work to specifically assess the safety of mental health related prescribing in primary care using a tailored suite of prescribing safety indicators. The findings suggest that potentially hazardous prescribing and inadequate medication monitoring are common in those with mental illness in primary care with high variation between practices for some indicators, and that between 2009 and 2019 the prevalence of some of the prescribing safety indicators has increased. The information obtained by the indicators may enable health providers to identify improvement targets that align with current national priorities and support development of improvement efforts to help reduce medication related harm for people with mental illness. This study has also identified a subset of indicators and composite indicators with good reliability making them fit for use in benchmarking.

Chapter 7 : General discussion and conclusions

In this chapter, the findings from the studies presented in this thesis are discussed in relation to the aims of the thesis and in the context of the wider literature. The strengths and limitations of the studies are outlined. The implications of the findings detailed in this thesis and recommendations for future research are then provided.

The overall aim of this PhD programme of was to assess the safety of prescribing for people with mental illness through the development and implementation of a suite of prescribing safety indicators related to mental health conditions and medications, and to use the findings to set an agenda for future research, policy and practice. In order to achieve this aim, six objectives were set. The aim and objectives were achieved by conducting a series of three studies.

The first study (Chapter 4) focused on the first objective and involved a systematic review to identify a comprehensive list of potential mental health related prescribing safety indicators from the existing published literature that could be later used in the formal consensus exercise to develop a tailored indicator suite. The second study (Chapter 5), which focused on the second and third objectives was a consensus-based study using the e-Delphi method to develop a suite of prescribing safety indicators related to mental health disorders and medications and assess the risk of the developed indicators. The third and final study (Chapter 6) focused on the fourth and fifth objectives, by operationalising and applying selected prescribing safety indicators developed in Chapter 5 that are relevant to primary care in order to assess the safety of mental health related prescribing in this setting across the UK. Chapter 6 involved (a) examining the overall prevalence, the variation between practices in the prevalence and the change of the prevalence over time of a suite of mental health related prescribing safety indicators and a group of composite prescribing safety indicators, (b) identifying patient and practice level characteristics that are associated with the risk of being affected by composite prescribing safety indicators, and (c) measuring the reliability of individual and composite prescribing safety indicators at practice level. Later in this chapter, recommendations will be provided to inform clinical practice, policy makers and future research to fulfil the sixth and final objective.

7.1 Summary of the key findings

7.1.1 Identifying potential prescribing safety indicators related to mental health disorders and medications (Chapter 4)

The first study presented in Chapter 4 provided insight into the existing prescribing assessment tools in the literature by systematically reviewing published evidence in order to identify a list of potential mental health related safety indicators. This was required because of the fragmented literature concerning mental health related prescribing indicators present in studies of broader patient groups that could be valuable for the development of a specific set for people with mental illness.

The systematic review identified 79 unique studies that developed, validated or updated a set of explicit indicators or criteria that measured prescribing in terms of safety or quality. A subset of 70/79 studies contained a total of 1386 mental health related prescribing indicators and of these, 245 were selected as potential mental health related prescribing safety indicators as they described prescribing or medication monitoring practices that could be hazardous and may put patients at significant risk of harm. These 245 potential prescribing safety indicators covered multiple prescribing problems including potentially inappropriate medication with a specific condition or a specific population, drug-drug interactions, inappropriate dose and duration, omission and inadequate monitoring. The list of potential indicators also covered different medication categories, including antidepressants, sedative, hypnotic and anxiolytics, antipsychotics, mood stabilisers, ADHD medications, anticholinergics, anti-dementia, and non-mental health medications with mental health conditions.

The list of potential prescribing safety indicators was selected from different types of studies with different purposes, settings and populations. It also provided a summary of the methods used by included studies to develop and validate prescribing indicators, which informed the design of Chapter 5 of this thesis. For instance, the review reported that almost half of the studies used the Delphi method for the validation of the indicators and half of those studies used a modified version of the Delphi. The review findings also highlighted that 95% of included studies used process indicators to assess prescribing, with only 5% reporting outcome indicators which is not surprising since medication prescribing is a health care process and therefore most prescribing assessment indicators are process-oriented.[138]

The systematic review confirmed that a suite of prescribing safety indicators specific to psychotropic medications and populations with mental illness had not been developed, with only one set with broad indicators being available relating to quality of prescribing.[278] In addition, there were important gaps in the literature which informed the second study presented in Chapter 5:

- the majority of the included studies did not target patients with mental illness or clinical practice within specialist mental health settings,
- the extracted indicators were not reviewed with experts in mental health, therefore, may not reflect all prescribing risks in the mental health context,
- the majority of the potential indicators were developed for application to elderly populations, therefore, other populations were under-represented,
- the identified indicators might not fully represent wider areas of risk in psychiatry.

Accordingly, there was a need to develop a new set of prescribing safety indicators specifically for application to patients with mental illness that addresses broad areas of potentially hazardous prescribing and drug monitoring in this population, and to undergo consensus-based refinement and validation with experts in mental health and medication management.

7.1.2 Developing a suite of prescribing safety indicators related to mental health disorders and medications. (Chapter 5)

The second study presented in Chapter 5 introduced the first agreed suite of prescribing safety indicators developed specifically for mental health related disorders and medications. A total of 75 prescribing safety indicators were identified that can be considered suitable to assess the safety of prescribing for this unique population after two eDelphi rounds with 29 expert panellists. This suite covered a broad range of contemporary safety concerns affecting the care of those with mental disorders under a range of different mental health related medication classes. It also addressed the coverage limitation for the tools reported in Chapter 4, which allowed developing a more comprehensive suite. For instance, including indicators for pregnant and breastfeeding women. Furthermore, the presented indicators are not specific for a single setting and could be relevant to any setting that provides care for patients with mental illness, including primary care, hospitals, specialised inpatient and community mental health services, care homes and prisons. However,

accordingly, the prescribing safety indicators may require further work to be operationalised to specific health contexts.[32,392]

In addition, by assessing their severity of harm and the likelihood of the prescribing safety indicator occurring in clinical practice, this study identified a subset of 42 prescribing safety indicators that were considered to be high or extreme risk for patient care which can be prioritised for development of improvement interventions. These 42 indicators comprised different types of hazardous prescribing, including drug-disease-interactions (n=12), drug-drug interactions (DDIs) (n=9), potentially inappropriate medications (PIMs) (n=3), inappropriate duration (n=4), inappropriate dose (n=4), omissions (n=4), polypharmacy (n=1), and inadequate monitoring (n=5). They also covered different mental health related medication classes including antipsychotics (n=14), antidepressants (n=6), sedative, hypnotics and anxiolytics (n=6), mood stabilisers (n=8), anticholinergic (n=6) and non-specific psychotropics (n=2).

However, even though a comprehensive definition of mental disorders has been used in this work and no disorders were purposely excluded, some disorders were not specifically mentioned in the developed list of indicators, such as insomnia, personality disorders and schizophrenia. However, patients with these disorders will likely be included in some indicators if they were prescribed psychotropics.

7.1.3 Evaluating the safety of mental health related prescribing in UK primary care (Chapter 6)

This study identified a subset of 22 mental health related prescribing safety indicators from the 42 high/extreme risk indicators in Chapter 5 that were considered feasible to apply into electronic primary care health records, before applying these into the CPRD. The 22 indicators included 18 potentially hazardous prescribing indicators and 4 inadequate medication monitoring indicators.

Chapter 6 indicated that mental health related potentially hazardous prescribing and inadequate medication monitoring commonly affects patients in primary care. In the third quarter of 2019, the potentially hazardous prescribing composite indicator was triggered by 9.4% of patients at risk, and by 90.2% of the patients at risk for the inadequate medication monitoring composite indicator. The proportion of patients triggering each individual indicator varied considerably across the 22 prescribing safety indicators from 0.2 % to 92.6%.

Between practices, the variation in the prevalence for the prescribing composite indicator ranged from 3.2% to 24.1%. Even though this variation is large in absolute terms,[32,392,420,427] only a small part of this variation was attributed to differences between practices (3%), which suggest small but statistically and clinically significant variation between practices.[392] The reported ICC was 0.03 (95% CI 0.03 to 0.03) and the MOR 1.22 (95% CI 1.20 to 1.24). In addition, higher levels of between-practice variation in prevalence was observed for individual indicators. For the monitoring composite indicator, the variation was higher with an ICC = 0.27 (95% CI 0.23 to 0.31) after adjusting for patient characteristics and MOR = 2.84 (95% CI 2.59 to 3.16). This suggests larger amount (27%) of the variation attributed to practice-level differences.

In spite of the modest variation for the prescribing indicators, all composite indicators had a strong reliability (> 0.9) to distinguish between practices. This research also identified a subset of 10 individual potentially hazardous prescribing indicators and one inadequate medication monitoring indicator with adequate reliability (> 0.7) for comparative feedback for improvement purposes. The 5 prescribing indicators and one monitoring indicator with strong reliability (> 0.9) may therefore be more suitable for high stakes evaluation such as pay for performance.[30,392,428]

The findings in 6.4.1.4 and 6.4.1.5 reported the estimated odds ratios for patient and practice characteristics associated with the risk of triggering both the prescribing and monitoring composite indicators from the univariate (unadjusted) and multivariate (adjusted) models. Patients with more than 10 multiple repeat prescriptions, patients aged 35-44, females, patients registered with practices from the most deprived areas and patients in Northern Ireland had the greatest risk of receiving potentially hazardous prescribing, and patients aged <35 and females had the greatest risk of receiving inadequate medication monitoring.

The findings in 6.4.2 showed that the proportion of patients triggering composite indicators for potentially hazardous prescribing and inadequate monitoring has been increasing over time. However, when considering individual indicators, only 8 out of the 18 prescribing related indicators showed a significant increase in their prevalence over the study period, with the remaining 10 indicators either showing significant reduction (n=7) or no change (n=3). In addition, the increase in the monitoring composite was influenced by only one indicator related to the monitoring of metabolic syndrome for patients prescribed antipsychotics. For the remaining monitoring indicators, there were significant decreases in two of them and no change in one.

7.2 Interpretation of key findings in the context of existing knowledge

7.2.1 Overall interpretation and contribution

Prescribing safety indicators represent a valuable tool to assess and monitor the safety of prescribing in populations with mental illness. Measuring and identifying a safety issue is the first step toward positively changing practice.[138] The findings of this thesis therefore allow focus to turn to how these indicators may be deployed and utilised effectively, efficiently and sustainably in routine clinical practice and as part of wider services and interventions to improve prescribing safety.[429]

Patient safety incidents including preventable medication-related harm can cause suffering and distress for patients and healthcare professionals.[430] For patients, this could include death or life-threatening injury.[431] This work contributes to reducing mental health related medication-related harm and benefit patients with mental disorders and healthcare practitioners by raising the profile of medication safety in mental illness and drive forward the safety agenda across mental health care settings. The findings of this research contribute to endeavours to achieve the goals of the WHO Third Global Patient Safety Challenge "Medication Without Harm", by developing a comprehensive suite of indicators to better understand, monitor and improve high risk prescribing.[39,50] This project also supports the efforts of the Medicines Safety Improvement Programme which was introduced in the NHS Patient Safety Strategy, by developing indicators that could be incorporated into current effective sustainable improvement interventions.[234] This programme of work provides a foundation on which mental health related prescribing safety can be assessed along with more in-depth insights into the prevalence and nature of prescribing safety risks for people with mental disorders.

While previous research in primary care examined the overall safety of prescribing, this work aimed to specifically assess mental health related prescribing which encapsulated more unique medication safety risks for this vulnerable population that link physical to mental health. This approach facilitated examination of the safety of prescribing more comprehensively for this vulnerable patient population, and provided a clearer estimate of the magnitude of the safety concerns. The findings generated in this thesis highlight priority areas for future intervention and recommendations for future research towards reducing medication related harm for people with mental disorders in primary care. In addition, the indicators developed in this research could also measure the impact of the

current developments from the NHS Long Term Plan in primary care to support people with mental illness, such as Primary care Networks and the newly developed service for reviewing medications including psychotropics.[89,165]

Polypharmacy is one of the three key action areas to protect patients from harm named by the WHO Third Global Patient Safety Challenge,[39] and Chapter 6 in this thesis has identified that increasing polypharmacy was found to have the strongest relationship with receiving mental health related potentially hazardous prescribing. This risk value is at least three times higher than estimated in previous research in the general population in primary care,[30,32,432,433] stressing the importance of reducing inappropriate polypharmacy in this population.

Although the presented suite of prescribing safety indicators in the programme of research has been developed for application in the UK, the clinical scenarios addressed in the suite could be relevant in other countries. In addition, this thesis has also provided several subsets of prescribing indicators at different stages of the programme of research (Figure 7.1) in the development process that can be used as a foundation for researchers from around the globe to select relevant indicators for validation for their specific countries and health settings. Thus, this programme of research helps address the WHO challenge internationally. However, as conducted in the Chapter 5 Delphi work, the suite of prescribing safety indicators might need to be adapted to allow for variations in clinical guidelines, medication availability and prescribing behaviours before testing and validation.[173,197] Morris et al. described the process to validate prescribing indicators developed in the US for application in the UK.[336]

In addition, because the database search strategy in Chapter 4 did not include any mental health terms, the list of included studies (Table 4.2) can be used as a source to identify indicators across a broad range of clinical conditions (other than mental illness) for populations across different settings. For example, researchers have created suites of prescribing safety and quality indicators for chronic kidney disease and type two diabetes.[302,314,434,435]

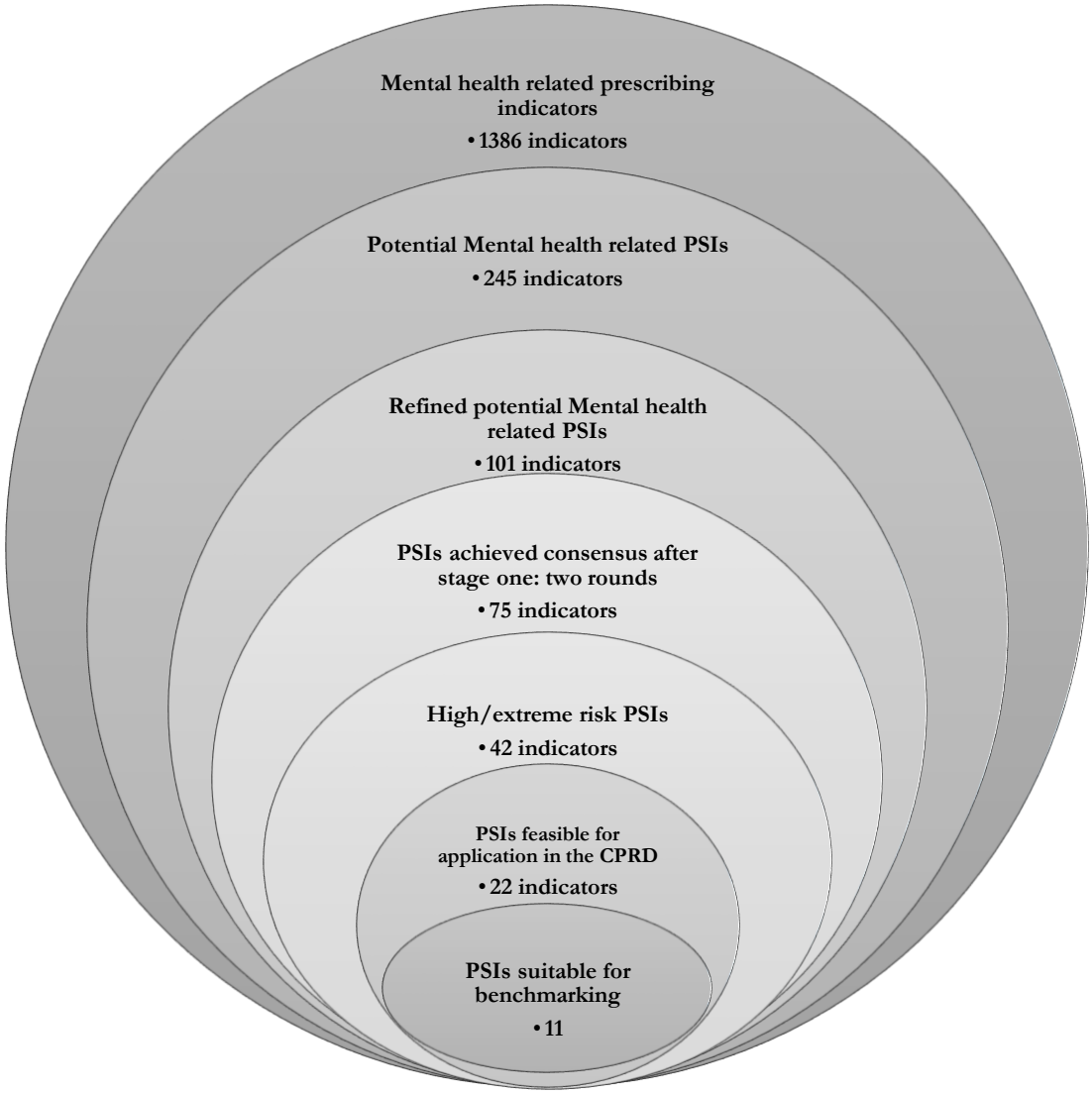

Figure 7.1: Summary of the mental health related prescribing indicators subsets developed in this programme of work

PSI= Prescribing Safety Indicators

7.2.2 The development of mental health related prescribing safety indicators

Chapter 4 identified an observed increase in new explicit, patient-level suites of prescribing indicators being published for use across various patient populations over time. This might be a result of increased implementation of electronic health records worldwide [436] and improvements in the quality of these records which may make operating electronic searches using prescribing indicators more feasible.[246] It also indicates an increasing emphasis on the quality and safety of healthcare, as noted in the wider literature.[437] A contributory factor to this rise might also be because indicators are used for audit and feedback purposes, which may be one of the more effective strategies to improve prescribing quality and quality of healthcare.[438] However, suites of prescribing indicators relevant to those with mental health illness have remained uncommon, and a specific suite of prescribing safety indicators tailored to mental health illness and medications remained absent.

When comparing our suite of indicators from Chapter 5 with published broader suites of prescribing safety indicators in the UK, it is apparent that several mental health specific prescribing safety concerns have not been addressed before.[29,35,173,209] This includes the risk of QT prolongation and torsade de pointes arrhythmia with antipsychotics and antidepressants, and the risk of clozapine toxicity with smoking cessation.[20,133] These might be partially explained by involving experts more focused on managing mental disorders in developing the current suite. Additionally, previous studies concerning the development of prescribing safety indicators in the UK targeted specific settings, such as primary [29,209] [30,173] and secondary care.[35,210] Similarly, an exclusion criterion that was mentioned in some of the previous studies that developed prescribing safety indicators was the feasibility of extracting the required data from the targeted setting.[29,209] Our prescribing safety indicators were not limited to a specific setting and were not refined for data collection. The reason for this is that our aim was to develop prescribing safety indicators that are relevant to populations with mental disorders regardless of the setting. We believe that the feasibility of measuring each indicator should be reviewed in the context of the specific targeted setting and data source when they are decided, as has been done in Chapter 6 (6.3.3 Selecting the prescribing safety indicators), where indicators were selected according to their relevance to primary care and their feasibility and data availability using CPRD. For instance, if the developed indicators were planned to be incorporated into the Medication Safety Dashboard developed for use in primary care in the NHS, all the indicators that contain information on clinical conditions or medication monitoring would not currently

be feasible for implementation as the dashboard is restricted to using prescription processing data.[233] In contrast, diagnostic information would be available from other primary care sources such as the CPRD and other EHRs, as explained in Chapter 6.[410] In addition, in the future, advances in databases and clinical information systems may create further opportunities for implementation of indicators,[173] such as development of linked electronic medical records between primary, secondary and social care to create a comprehensive record of prescribed medications.[439]

7.2.3 Mental health prescribing safety in UK primary care

Multiple studies have investigated the safety of prescribing in primary care in the UK or Ireland using more general (non-mental health specific) suites of prescribing safety indicators.[30,32,432,433] Prevalence in these studies ranged from 5.3% using 13 potentially hazardous prescribing indicators in the UK to 15.1% using 6 indicators in Ireland. However, comparing these rates to ours is not relevant due to the different indicators and focus of our suite on those with mental illness; only 3 mental health prescribing safety indicators were examined in previous studies (Table 7.1). However, the only indicator similarly observed and could be suitable for comparison is the lithium monitoring indicator from Stocks et al., where they observed a prevalence of 19.3% for inadequate lithium monitoring which is consistent with our sub-indicator (M3a: monitoring lithium plasma levels within the previous 6 months, 18.6%).[32] However, this is lower than our overall lithium monitoring indicator (M3: monitoring lithium plasma levels within the previous 6 months or within the last 3 months if the patient is aged ≥65 years or has a diagnosis of renal impairment or during the first year of treatment, 24.3%). As for the other two indicators, as mentioned in 6.3.3 , a similar indicator to these two from our eDelphi was excluded from the work in Chapter 6 as it has been examined extensively in a previous publication.[414]

Table 7.1: Mental health related prescribing safety indicators applied into primary care data in previous research in the UK

Indicator	Prevalence
Risperidone/olanzapine* prescribed in over 65s with dementia but not psychosis [30]	**2.8%**
Diagnosis of dementia, age >65, no psychosis diagnosis and prescribed antipsychotics [32]	**8.1%**
Repeat lithium without lithium concentration check [32]	**19.3%**

The prevalence of the inadequate medication monitoring composite indicator was influenced predominantly by one indicator related to the monitoring of metabolic syndrome for patients prescribed antipsychotics, where 91.61% of patients at risk did not receive the required monitoring. When examining the monitoring of the individual metabolic parameters for this indicator, 83.55% of patients at risk did not have a record for serum glucose monitoring, 61.93% did not have a record for monitoring serum lipid profile and 54.92% did not have a record for monitoring weight. In 2012, a meta-analysis of 48 studies examining metabolic screening practices in those taking antipsychotics showed that in routine clinical practice, metabolic monitoring is historically low in people prescribed antipsychotic medication monitoring, even after guideline implementation. Across studies, serum lipids were monitored in 22.2% of the population, glucose in 44.3%, and weight in 47.9%. In addition, monitoring was not significantly higher in case-record versus database studies.[440] Therefore, the quality of documentation might not be the main cause for the high prevalence of inadequate monitoring, and a future research priority should focus on identifying underlying reason(s) for this on the path to improvement. It has been suggested that historically one of the factors was lack of clarity as to who is responsible to conduct the monitoring.[441] A report in 2020 published preliminary findings of a survey on the barriers to attending physical health checks for people with SMI. The most commonly reported barriers were lack of motivation, low confidence/low mood and medication side effects.[442] A POMH-UK audit reported that in 2006 only 11% of patients received adequate monitoring for all metabolic syndrome measures and in 2012 only 34% received the required monitoring.[443]

7.2.3.1 Variation between practices

It has previously been suggested that there are large variations in mental health prescribing between general practices in the UK.[444-447] However, the variation in the prevalence of prescribing safety indicators has only been examined in the UK using a general (non-mental health specific) sets of prescribing safety indicators, and reported comparable marked variation between practices.[30,32] In 2015, a study assessing the prevalence of a general set of prescribing safety indicators in UK primary care reported an ICC = 0.04 (95% CI 0.03 to 0.04).[32] Similarly, in Scotland, a study assessing the prevalence of a set of NSAIDs related prescribing safety indicators in 2015 reported an ICC = 0.03 (95% CI 0.02 to 0.07).[392] As reported in section 7.1.3 these show small but significant variation between practices.

For the monitoring composite indicator prevalence reported in Chapter 6, variation between practices was higher than previously reported using a general set of four monitoring related prescribing safety indicators, where the ICC was estimated to be 0.17 (95% CI 0.15 to 0.19) compared to 0.26 (95% CI 0.22 to 0.30) in this research.[32] This indicates that for people with mental illness a greater proportion of this variation can be attributed to practice level differences in relation to the total variation, and therefore indicating more potential for improvement by implementing focused practice-level interventions to narrow the gap between practices, and by learning from high performing practices.[32,448,449]

When examining variation in rates within individual indicators, values were higher for indicators related to benzodiazepine and Z-drugs prescribing (P10: ICC=0.05 (95% CI 0.04 to 0.07) and MOR=1.49 (95% CI 1.42 to 1.58); P11: ICC=0.5 (95% CI 0.04 to 0.06), MOR= 1.47 (95% CI 1.42 to 1.51)) and monitoring the physical health of patients receiving antipsychotics (M1: ICC=0.43 (95% CI 0.37 to 0.47) and MOR=4.50 (95% CI 3.87 to 5.33)). A recent cross-sectional study found practice-level variation in benzodiazepine and Z-drug prescribing in England and reported that part of this variation was due to the indications for benzodiazepine and Z-drug prescribing and socioeconomic status using the practice IMD.[450]

7.2.3.2 Characteristics associated with prescribing safety risk

It has consistently been reported that the risk of receiving potentially hazardous prescribing in primary care increases with age.[30,32,432] In contrast to this finding, we found that after adjustment, the risk of receiving mental health related potentially hazardous prescribing for patients aged 25 to 64 is higher than older patients, with the highest risk for patients aged 35 to 44. A report published in 2013, found that between 2011 and 2012, mortality rate among adults in contact with mental health services in England was 3.6 times higher than the general population. However, the report also observed that the highest difference in rates was for patient aged 30 to 39, with mortality rate almost 5 times higher than the general population.[5] These findings might not be related, but they raise concerns regarding the quality of care provided for this population.

Although the findings of this research were consistent with previous studies in that polypharmacy was strongly associated with increasing risk of receiving potentially hazardous prescribing in the multilevel logistic regression analysis,[30,32,432,433] our estimated risk were found to be much higher than previously reported. The odds of receiving at least

one mental health related potentially hazardous prescribing were estimated after adjustment in Chapter 6 to be 30 times higher in people with more than 10 repeat prescriptions in comparison to people with one or no repeat prescriptions (adjusted OR 30.22; 95% CI 29.44 to 31.02). Previous research in the general population in primary care reported odds ratio after adjustment ranging from 1.35 to 10.[30,32,432,433] In addition, in Chapter 6, indicator P18 was related to polypharmacy and describes prescribing four or more psychotropics for longer than 3 months. It has been reported in the cross-sectional analysis that 41.7% of patients at risk triggered the indicator, and over the study period the prevalence increased from 30.3% to 41.9%.

Both findings emphasise the importance of addressing polypharmacy for people with mental illness. Several factors contribute to polypharmacy for this population, such as poor health behaviours and multimorbidity. In addition, mental illness is more common in more deprived areas,[71] and therefore those patients might be restricted in their choice of healthy options.[451] Moreover, multiple psychotropics medications are associated with clinically significant withdrawal reactions and an increase in relapse of the illness being treated after discontinuation.[452] Therefore, tackling polypharmacy for people with mental illness could be more complicated than the general population. Deprescribing is a strategy to reverse the potential harm of receiving too many inappropriate medicines to improve patient function and generate a higher quality of life and it can be defined as *"the planned and supervised process of dose reduction or stopping of medicines that might be causing harm, or no longer be of benefit*". It has been suggested that deprescribing is underdeveloped in mental health care.[453]

As for the monitoring composite indicator, the opposite was found for the age and number of repeat prescriptions variables, where patients aged less than 25 and those with one or no repeat prescription were at greatest risk of triggering a monitoring indicator. This finding was consistent with a previous publication using different medication monitoring indicators in the UK.[32] Besides, another study in the US on patient behaviour to incomplete medication monitoring found similar results. Furthermore, this US study also conducted semi-structured patient interviews and suggested that the reason behind this could be because older and sicker patients may have more contact with the health care system, and therefore have more opportunities for testing.[454] Additionally, since our composite monitoring indicator was influenced by one indicator (M1) one possible reason for increasing the risk for younger population is that the QOF indicators on monitoring lipid and glucose for patients with schizophrenia, bipolar affective disorder and other psychoses were limited to patients aged 40 and over.[301] Despite this NICE guidance indicates that

weight, lipid and glucose should be monitored every 6 months for children and young patients on antipsychotics.[455] One more possible reason for these findings, is that the monitoring for younger population may also be conducted in other settings (such as CYPMHS) and were not therefore documented properly in GP records. Another study in the US also found that most children prescribed antipsychotics did not receive the recommended glucose and lipid screening.[456]

This programme of work also reported in section 6.4.1.6 patient and practice characteristics associated with risk of triggering each prescribing safety indicator, which allow identification of further targets for improvement. For instance, it was detected that the risk of triggering lithium related inadequate monitoring indicators (M3 and M4) for patients registered with practices from the most deprived areas was significantly higher than patients registered with practices from least deprived areas (M3: adjusted OR 3.33 (95% CI 2.43-4.56); M4: adjusted OR 1.81 (95% CI 1.39-2.37). Between 2005 and 2006, a study explored the differences in the achievement of QOF indicators targets between the least and most deprived areas using the IMD, reporting that one of the greatest reductions was for lithium monitoring indicators, where it was observed that there was a decrease between 8.9% to 12% in the proportion of patients receiving lithium monitoring in the most deprived areas in comparison to the most affluent areas. It has been implied that shorter practice opening hours and fewer training practices between most and least deprived areas may contribute to these inequalities. Therefore, more targeted interventions could be applied in those areas to improve the quality of care.[457]

7.2.3.3 Change in prescribing safety over time

The change in the prevalence of prescribing safety indicators over time in primary care has been examined in two previous publications.[392,432] These studies reported similar reductions in the proportion of patients affected by the indicators related to prescribing of gastroprotection (P5 and P8). One of the studies also reported similar seasonal variation with lithium monitoring indicators (M3 and M4) which has been suggested to relate to preparation for the QOF return at the end of the financial year (i.e. end of March).[32,392,432] A study reported that the QOF financial deadline increases the pressure and prompts a *'nightmare climate'* to fulfil the remaining tasks.[458]

Even though all composite indicators showed a significant increase over the study period, it would be more appropriate to examine the trend of individual indicators to determine what drives this. Two indicators, M1 (related to monitoring the physical health of patients

receiving antipsychotics) and P18 (related to prescribing multiple psychotropics for more than 3 months) showed a large increase by 11.49% and 11.57%, respectively. A steady increase of the prevalence of M1 has been noted since 2014. Further investigation should determine whether this may be related to the retirement or modification of similar QOF indicators pertaining to the monitoring of physical health of people with serious mental illness in all UK nations in 2014.[459-461] In England, the indicators to monitor cholesterol, blood glucose and body mass index (BMI) were retired from the QOF in 2014.[462] Research commissioned by NHS England in 2018 found almost 20% reduction in the proportion of patients receiving lipid monitoring after the retirement of this indicator.[463] It has also been reported that removing financial incentives from clinical indicators could lead to decline in performance level in the US and the UK.[464] However, the POMH-UK reported that there has been an increase in the proportion of patients prescribed antipsychotics who received the required metabolic syndrome monitoring between 2006 and 2012 in mental health trusts. These findings could indicate inadequate communication between primary care and mental healthcare services,[462] and suggest that the monitoring is documented in these trusts rather than in primary care. That being said, in Chapter 6 during the time period before 2012 there was also an improvement in the required monitoring for patients in primary care for M1.

As for P18, a similar increasing trend related to psychotropic polypharmacy has been observed in the US.[160] This finding is also consistent with other reports indicating there has been substantial growth in the proportion of individuals worldwide using medications for mental illness,[14-17] and also emphasize the importance of rational prescribing and deprescribing as discussed in section 7.2.3.2.

In contrast, indicator P7 (related to prescribing some antidepressants with other QT-prolonging drugs) appeared to contain a turning point in frequency from 2012, where there was a gradual and constant decrease in the proportion of patients receiving the potentially hazardous combination. This improvement coincides with the concerns and alerts published by the MHRA and European Medicines Agency (EMA) at the end of 2011 regarding the risk of QT interval prolongation with citalopram and escitalopram, and other known medications that prolong QT interval such as tricyclic antidepressants and antipsychotics.[120,465] A similar but smaller reduction was also noticed with indicator P1, which also relates to the risk of QT prolongation (prescribing antipsychotic with another QT-prolonging drug).

7.3 Strengths of the work presented in this thesis

This programme of work presents the first suite of mental health specific prescribing safety indicators that were based on scientific evidence and expert consensus, and that could be refined for application into different settings and different countries. This work also demonstrates the feasibility and reliability of applying a subset of the indicators into a representative UK based primary care database, and their change over time. This research programme provides essential information about the extent of prescribing safety in patients with mental illness in primary care and facilitates identification of target areas for improvement. The research followed an integrative stepwise approach, whereby findings from each step informed the subsequent step.

Identifying the potential prescribing safety indicators involved conducting a systematic review which is considered the gold standard to search, evaluate and summarise the best available evidence regarding a question.[309] The systematic review (Chapter 4) was the first study to identify a list of potential prescribing safety indicators related to mental health disorders and medications that may be used to assess the safety of prescribing. The review included searching seven databases along with the reference lists of included studies for a comprehensive literature search with no limitation on languages to avoid language bias, no restriction on health settings or age group to capture the widest range of prescribing indicators and using a long-time frame of 28 years. In addition, the list of potential indicators was not restricted to practice in a specific country.

Developing the suite of prescribing safety indicators involved using a structured consensus method which allow acquiring the most reliable consensus of opinion, which is one of the most commonly used method to develop indicators. The e-Delphi study (Chapter 5) was the first to develop a suite of prescribing safety indicators specifically for mental health disorders and medications. This study followed an established approach which had been used to develop prescribing indicators in the past.[29,259] The strengths of this study include using information from various sources including the existing literature and other professional resources to identify new potential indicators. In addition, this study considered including indicators of all three aspects of prescribing safety, including prescribing safety incidents of commission, omission as well as inadequate medication monitoring. This allowed a more comprehensive evaluation of prescribing safety. Another strength of this study was that it included broader indicators related to mental health medication and conditions and was not solely limited to psychotropic prescribing. Also, the expert panel involved specialised health practitioners with a diversity of professions and of

considerable experience in mental health care, which allowed inputs from different perspectives including the option to suggest new indicators in the early round.

The third study (Chapter 6), examined the safety of mental health related prescribing in a large population over 11 years and evaluated variation in the prevalence of prescribing safety indicators between general practices across the UK nations using a database that is considered broadly representative of the general population in terms of age, sex and ethnicity.[410] In this research, mixed-effect (i.e. multi-level) models were used, which facilitate revealing the true underlying variation between practices.[466] In addition, this research used funnel plots to illustrate the variation between practices which has been endorsed as a graphical aid for institutional comparisons by Sir David Spiegelhalter "*to avoid spurious ranking of institutions into league tables*".[467,468]

7.4 Limitation of the work presented in this thesis

A number of limitations were identified for the systematic review presented in Chapter 4. Despite efforts to enhance the comprehensiveness of the review by using a rigorous and thorough search strategy, it cannot be confirmed that the review located all relevant studies. The screening process was conducted by one author, which can increase the likelihood of discarding relevant articles.[469] However, searching the reference lists of the included studies helped minimise this risk. Due to the heterogeneity of the included studies objectives and methods, we did not formally assess the methodological quality of the included studies. In addition, even though most studies used a consensus approach to develop their indicators, to our knowledge, there are currently no formal tools to assess the quality of consensus-based studies. However, certain aspects of the quality of the included studies were discussed in the findings, such as the methods used to select indicators and the process to validate the indicators. Nevertheless, in the context of this programme of research, assessing the methodological quality of the included studies in the systematic review was not essential, as the identified potential indicators will go through further development and validation.

Not all of the identified mental health related indicators in Chapter 4 were considered to have high clinical importance and may be likely to cause significant risk of harm, and they therefore might not be appropriate to assess the safety of prescribing. Accordingly, we attempted to select indicators, based on the clinical experience of the research team, which could be used to assess the safety of prescribing in for the review and for the e-Delphi

study. However, it is important to recognise limitations in our process of prescribing safety indicator selection. Firstly, the selection process was carried out by two mental health pharmacists using their clinical experience, knowledge of prescribing safety indicators and the published literature. Secondly, some indicators that targeted the elderly or a specific medication were modified to cover all ages or a drug class, respectively if another indicator was present describing this association that the team felt was more appropriate, which we carried out based on the same sources of information. Together, these potential limitations in our selection process mean that we cannot therefore exclude the possibility that we may have overlooked or misinterpreted practice in both ours and other countries that other professional groups may have addressed, and therefore, there is a possibility of not including potentially relevant indicators in the first round of ratings that could have been considered important by the panel. In order to minimise the risk, the Delphi survey was piloted with two consultant psychiatrists, and also members of the expert panel were encouraged to suggest new potential indicators in the first round of the e-Delphi.

Another potential limitation is that the composition of the eDelphi expert panel might have had an impact on the findings of this study. There were more mental health pharmacists than any other profession, and primary care was under-represented with only one general practitioner. Therefore, our indicators may not fully reflect specific prescribing challenges in primary care for those with mental illness. We attempted to compile a panel with different stakeholders with the same interest in managing mental health medications. A further limitation is that the number of rounds for each stage were selected before starting the study, and the views of the panel were only sought once in regards to the risk of harm associated with each indicator in phase 2. This was due to the time constraints and the burden on the members of the expert panel to take part. However, this approach had been successfully used previously for the development of prescribing safety indicators for primary care.[29]

Another important limitation was that members of the expert panel were not provided with the evidence base for the indicators and they were asked to rate the potential indicators solely based on their knowledge and experience. Nevertheless, the supporting evidence for each indicator was reviewed by the research team. In addition, as previous research has observed, the evidence base for some of the indicators was weak,[209] and this is principally the reason why consensus approaches are warranted.[273] Although in some areas more robust evidence is emerging, such as recent pharmacoepidemiological studies which provide a stronger evidence base to support indicators related to the use of anticholinergics and the risk of dementia.[404,405] Appendix (10)provides a draft summaries of the evidence-

based for each mental health related prescribing safety indicators implemented in Chapter 6.

In regard to the cross-sectional analysis, several limitations must be acknowledged. Due to the nature of medical records, the study could only examine coded events in health records, which could differ from the care actually delivered. For example, in a prescribing safety indicator where the absence of a test or prescription is the numerator, the resulting potential bias may be overestimating the prevalence of potentially hazardous care if care was delivered but not documented or if it was delivered outside of primary care. This is particularly relevant for monitoring indicators as some tests could take place in secondary care settings or in other specialist mental health settings. Although, as mentioned in section 6.5 , NICE guidance specified that GPs should be responsible for the monitoring when the care is transferred from secondary care under shared care arrangements after one year of treatment or when the patient's condition has stabilised.[127] Conversely, when the presence of a test or prescription is the numerator, underestimation is the more likely bias. Hence, this would raise the need to document more effectively. Furthermore, practices are not essentially representative of all the practices in their country, particularly that small number of practices were included in some regions. For instance, the shift of practices from Vision® to EMIS® clinical systems have led to reduction of practices contributing to the CPRD GOLD in England.

Concerning the longitudinal analysis presented in Chapter 6, it is important to point out that an increase in the prevalence of prescribing safety indicators over time does not necessary imply a deterioration in mental health care quality. Prescribing safety indicators present only one facet of healthcare and several factors might affect their prevalence. Additionally, as the quality of data recording has improved over time, this may have driven changes in the prescribing safety indicator prevalence.[410,470] Therefore, the trends observed should be interpreted with caution. However, to minimise this risk, only practices who were deemed up-to-standard 12 month prior to the longitudinal analyses period and up until after the period were included in the analyses.

Overall, an inherent limitation of prescribing safety indicators is that they do not consider patients' preferences, individual needs and circumstances. For instance, it will not take into account patients who do not attend their appointments for monitoring. Accordingly, prescribing safety indicators are used to alert health care professionals to any potential hazardous prescribing or inadequate monitoring, and cannot substitute shared decision-making processes between clinicians and patients. Therefore, this highlights the need to

conduct further research to explore their clinical relevance, predictive validity and practical implementation in clinical practice.

7.5 Implications for policy and practice

7.5.1 At national and local level

The prescribing safety indicators developed in this programme of work could be used to monitor and identify targets for improvement on a national or a local level, as with the Medication Safety Dashboard in England, the National Therapeutic Indicators in Scotland, the National Prescribing Indicators in Wales, the QOF in England, and the POMH-UK.[36-38,233] The information obtained by the prescribing safety indicators may enable health providers to scrutinize crucial aspects concerning prescribing for people with mental disorders, understand local practices, identify improvement targets, support development of improvement efforts, and help reduce medication related harm.

The prescribing safety indicators developed in this thesis could also measure the impact of the current developments from the NHS Long Term Plan in primary care to support people with mental illness, such as Primary care Networks and the newly developed robust service for reviewing medications including psychotropics.[89,165] Moreover, they could also be used to examine the impact of the COVID-19 pandemic on prescribing and monitoring safety, particularly since some practices and recommendations were altered due to the pandemic.[471,472]

Our findings in Chapter 6 provide a baseline prevalence to evaluate if prescribing safety for people with mental illness is improving in primary care.[32] It also provides a subset of prescribing safety indicators with high reliability to distinguish between practices, and therefore could be used to identify practices with high prevalence to investigate and practice with low prevalence to learn from. As one of the three NHS Patient Safety Strategy aims "insight" involves using new digital technologies to support learning from what does and does not go well. The identified indicators in this thesis could therefore help achieve this aim. Table 7.2 lists the mental health related prescribing safety indicators that achieved good reliability at practice level.

Table 7.2: The mental health related prescribing safety indicators with good reliability at practice level

No.	Prescribing safety indicator
P1	Prescribing antipsychotic with a QT-prolonging drug
P5	Selective serotonin reuptake inhibitor (SSRI) or serotonin and norepinephrine reuptake inhibitor (SNRI) prescribed with an NSAID or antiplatelet agent to a patient without gastrointestinal protection
P6	SSRI or SNRI prescribed with a direct oral anticoagulant (DOAC) or warfarin
P7	Prescribing citalopram, escitalopram, TCA or trazadone with QT-prolonging drugs
P9	Any sedative-hypnotic prescribed to a patient with a history of falls
P10	Benzodiazepine, Z-drug or sedating antihistamine prescribed to a patient with dementia or cognitive impairment
P11	Benzodiazepine or Z-drug prescribed to a patient aged ≥ 65 years
P12	Benzodiazepine or Z-drug prescribed to a patient with asthma, COPD or sleep apnoea
P13	Valproic acid prescribed to a woman of childbearing potential
P17	Mental health related medication with medium/high anticholinergic activity prescribed to a patient with a history of urinary retention or benign prostatic hyperplasia
M1	Antipsychotic prescribed for at least 12 months without monitoring glucose, weight, or lipid profile within the previous year

Since 2015, the CPRD in collaboration with the Royal College of General Practitioners (RCGP) provides reports to practices that illustrate the trend in a select list of prescribing safety indicators over time and benchmark their rate against other practices. This project currently uses a limited number of indicators with the intention to add more indicators in the future.[473,474] A qualitative study found that the reports were generally useful to support patient safety. However, evaluating the impact by quantifying the change in prescribing behaviours has not been conducted yet.[474] The identified prescribing safety indicators in this thesis with adequate reliability (Table 7.2) could be incorporated into these reports for benchmarking.

Patient level interventions, which will be discussed in the next section, such as the pharmacist-led safety medication dashboard (SMASH) and PINCER also provide practice-level summary comparative data including time-trended analyses with other practices and the national average.[42,48] Being an outlier can be an important motivator and highlight priority areas to change prescribing behaviour and improve quality.[475] A Cochrane

systematic review concluded that audit and feedback leads to potentially important improvements in professional practice.[476]

7.5.2 At patient level

The prescribing safety indicators presented in this thesis could be applied on a patient level data to identify individuals at risk of medication-related harm and help towards achieving the WHO Global Patient Safety Challenge of reducing the level of severe, avoidable harm related to medicines. With the expansion of electronic medical records and improvements in the information technology infrastructure, it is becoming more feasible to measure prescribing safety continuously allowing for real time feedback on prescribing safety using prescribing safety indicators to identify patients who are currently at risk of preventable drug related harm.[45] This has been demonstrated with the PINCER and SMASH interventions (latter based on PINCER prescribing safety indicators), the Data-Driven Quality Improvement in Primary Care (DQIP) program and the Effective Feedback to Improve Primary Care Prescribing Safety (EFIPPS).[33,39-44] These successful approaches utilise multi-faceted interventions, which appear to be more effective than a single strategy.[45] Table 7.3 summarise the main elements that encompass these interventions, their outcomes and whether they included any mental health related indicators.

Table 7.3: summary of interventions that utilises prescribing safety indicators

Intervention	Main elements	Findings	Mental health related prescribing safety indicators
PINCER [48]	(a) electronically searching clinical records to identify patients at risk of hazardous prescribing. (b)trained pharmacists provide an educational outreach intervention and agree an action plan for reviewing patients identified. (c) pharmacists working with, and supporting, general practice staff to implement the agreed action plan.	In July 2020 PINCER National Rollout progress report, showed a 14.4% reduction in the absolute number of patients triggering at least one prescribing safety indicator.	In the latest version (PINCER 3) one mental health related indicator was included.
SMASH [42]	(a) trained clinical pharmacists works in the general practices as members of the practice team to deliver the intervention; (b) a web-based, daily updated dashboard that generate a list of patients	An interrupted time series analysis reported that the SMASH intervention can provide sustained reduction in potentially hazardous prescribing, and a reduction in the variation between practices.	No mental health related indicators were included

	triggering the indicator. Along with educational material for each indicator; (c) review patients whose records triggered the indicators, and initiate remedial actions or advise GPs on action plans.		
DQIP [41]	(a) a single educational outreach visit. (b) a web-based IT tool to identify patients and support review. (c) financial incentives for general practices to review patients with high-risk prescribing.	41% reduction (from a rate of 3.7% before the intervention to 2.2% at the end of the intervention) in the odds of triggering the potentially hazardous prescribing composite indicator.	No mental health related indicators were included
EFIPPS [43,44]	(a) educational materials. (b) feedback of performance on the targeted indicators. (c) theory-informed behaviour change intervention.	12% reduction in the odds of triggering potentially hazardous prescribing using the first two components, and 14% using the three components.	One mental health related indicator was included.

However, in these four mentioned interventions, only two mental health related indicators were included. Therefore, it is essential to incorporate more mental health related indicators into these interventions to improve the safety for people with mental illness. In addition, the indicators could also be used to help identify and prioritise patients who would benefit from the new structured medication review and medicines optimisation service by primary care networks. For instance, the CPRD and RCGP reports that were discussed in the previous section also provide a list of patients at the practice that triggered one of the included indicators to facilitate structured medication reviews.[473,474] The developed mental health specific indicators in this thesis (not only the ones with adequate reliability) could be used to serve the same purpose.

Also, the proposed prescribing safety indicators could be used for targeted CDS alerts. The developed indicators could alert prescribers to prescribing practices that have the greatest potential to cause harm,[35,210] and could eventually reduce hazardous prescribing rather than using untargeted alerts which can cause alert fatigue.[244] For instance, the PINCER indicators are already embedded into CDS systems like OptimiseRx.[477] Research is currently underway to evaluate the effectiveness and cost-effectiveness of using similar (non-mental health specific) prescribing safety indicators for CDS alerts in primary care and secondary care.[34,478,479]

7.5.3 Supporting different mental health safety issues

Several studies have explored means to improve different aspects of medication safety issues for patients with mental illness, including; specialist mental health clinical pharmacy teams in primary care to improve medicines optimisation,[228] improved and greater collaboration between GPs and secondary care,[480] increased knowledge and skills training for managing mental disorders in primary care,[480] and better communication between GPs and psychiatrists to help improve metabolic monitoring for patients prescribed antipsychotics.[481] We envisage that our prescribing safety indicators may be used to guide these improvement efforts and assessing these safety concerns before and after any new improvement initiative. The indicators could also play an important role in developing the new planned services for reviewing medications delivered by the Primary Care Networks.[89] The identified risk factors in Chapter 6 such as age and polypharmacy could also be used to guide the design of this or similar services specifically for people with mental illness.

Consideration should be given to the better integration of pharmacy services and the use of pharmacists' expert skills and training in improving prescribing and monitoring for people with mental disorders in these interventions. Pharmacists play a key role in improving patient safety and several studies evaluated and reviewed the impact of pharmacists and pharmacy services on patients with mental illness and demonstrated improvements in the outcomes, prescribing practices, patient satisfaction, and resource use.[482-488] Also as mentioned in 7.5.2 , pharmacists have a key role in SMASH [42] and PINCER[48] successful interventions. There has also been recent policy recommendations to further integrate clinical pharmacists into primary care, including Primary Care Networks, and there have also been calls to have more specialist mental health pharmacists designated in primary care.[89,489] The developed mental health related prescribing safety indicators in this thesis may be a way to help them focus their efforts and identify patients at risk of harm.

7.6 Recommendations for future research (in order of priority)

7.6.1 Piloting the prescribing safety indicators into different settings at patient level

This programme of research in Chapter 6 provided evidence on the reliability and feasibility of applying the indicators into a large research database. However, in accordance with the Medical Research Council (MRC) framework for developing and evaluating complex interventions it is important to first pilot the developed mental health related prescribing safety indicators in clinical practice before incorporating into new or existing interventions to search records to identify patients at risk of harm. However, as discussed in Chapter 5, the feasibility of using the indicators in clinical practice was not explored in the Delphi study. Therefore, piloting may explore the practicality and acceptability of using the indicators in routine clinical practice and may help form the foundations of future interventions.[305] Research could investigate the views of healthcare staff on accessing, using and responding to these mental health related prescribing safety indicators data to improve prescribing and medication monitoring practices in different settings.[490-493] It is also important to examine the ability to change prescribing of each individual indicator and to explore the barriers and enablers to changing prescribing, particularly as many of the medications involved in this prescribing safety indicator suite may have been initiated by specialists in psychiatry with mental health teams involved in ongoing care. Several studies have used qualitative data and mixed method approaches (i.e. qualitative and quantitative) to explore the implementation of general (non-mental health specific) prescribing safety indicators in primary care as a part of different approaches to improve prescribing safety, and may therefore be used as a guide for this research goal.[490-493] For example, the DQIP pilot led to excluding indicators with limited changes in practice,[493] and the PINCER indicators have also been updated as a result of early pilot work.[48] A subset of the indicators developed in this thesis has also been deployed in English and Welsh prisons to evaluate their implementation and use in practice.[494]

Using unaltered versions of previously proven interventions in primary care to improve prescribing in the general population for populations with mental disorders might not be appropriate due to the unique characteristics of mental health care and therefore adjustments might be needed. Therefore, work might also be needed on the development phase of the MRC framework to modify existing interventions or to develop new ones.[305]

For instance, in mental health care different care providers might be involved, including community mental health teams, social workers, substance misuse services alongside usual primary care teams. Some medications involved in the suite developed in this thesis may have been initiated by psychiatry specialists, and involve shared care arrangements concerning ongoing prescribing and monitoring that may differ across localities, such as antipsychotics prescribed by specialists.[143] A Swedish qualitative study on prescribing psychotropic prescribing in primary care illustrated the complexity of the process as numerous factors were deemed important, many of which were not related to the patient's medical needs. In addition, psychiatry was characterised as a more imprecise field than other specialties and to require individual considerations to a greater extent, with a participant in a focus group stating that "*Psychiatry is not a science like others*".[495] Therefore, alternative approaches to patient consultation and medication review or more targeted interventions (such as intervention to reduce antipsychotic prescribing to patients with dementia [496]) or services (such as pharmacist-led clozapine clinics [497,498]) might need to be developed to improve some prescribing patterns. The findings in Chapter 6 could help prioritising the more relevant indicators. For example, M1 indicates high rates of inadequate metabolic monitoring and it also has been increasing over time. The same can be observed with P18, prescribing four or more psychotropics for more than 3 months.

Prescribing safety is of importance to a wide range of stakeholders and achieving the optimal use of medications is complex due to competing priorities of different stakeholders.[499,500] Therefore, it might be essential to combine the views and experiences of different stakeholders including patients, the public, healthcare professionals, health service commissioners and policymakers, alongside the published literature to co-produce strategies to guide developing new remedial interventions that involve use of prescribing safety indicators towards improving prescribing safety for people with mental illness. Including patients is becoming more common in co-developing health services and research.[501] It is important to evaluate the acceptability of using new and existing interventions to patients as well as healthcare professionals when incorporating the developed indicators. Research to better understand patient perspectives on the risks and benefits of hazardous prescribing is required.[392] Patient perspectives can be elicited to help identify the attributes that are most important to patients. Priorities and views on quality of care might differ between patients and healthcare providers, and therefore, involving patients is recommend as a way to improve quality and safety.[502,503] It has been reported that healthcare providers believe that patients play an important role in actively enhancing safety.[504] However, a study reported that mental health service users experience difficulties

in raising safety concerns that leads to missing potentially useful information.[505] The NHS Patient Safety Strategy acknowledges the significance of involving patients, their carers and the public in improving the patient safety, and therefore, a framework has been developed to explain how organisations should involve patients in patient safety.[506] Further research also needs to evaluate the effectiveness, cost-effectiveness and sustainability of these different interventions using robust research methods such as randomised control trials. The indicators could also be used as an outcome to quantify the impact of these interventions.

The presented indicators in Chapter 5 could also be implemented in other settings such as hospitals, community mental health services and prisons. A recent study investigating safety incidents reported to the National Reporting and Learning System in mental health hospitals in England and Wales between 2010 and 2017 found that prescribing-related medication incidents were frequently reported and have emerged as an important target for improvement.[227] Therefore, future research could also explore the implementation and practical use of the indicators in mental hospitals and psychiatric units in general hospitals to set the foundation to design and implement interventions to improve prescribing and medication monitoring for people with mental disorders. The indicators could also be included in the POMH-UK quality improvement programmes.

Furthermore, a UK based study investigated the impact of implementing a general set of prescribing safety indicators as a CDS on the computerised physician order entry in three general hospitals and found that it was associated with clinically important reductions in the rate of potentially hazardous prescribing.[34] Similar work could be attempted to test the impact of this intervention on patients with mental disorders using mental health specific prescribing safety indicators. With the expansion of e-prescribing system in mental health trusts, the presented prescribing safety indicators in this thesis could act as a priority list for CDS developers.[165]

Moreover, studies have always indicated that mental illness among prisoners is higher than the general population, with evidence of higher rates, inappropriate and unsafe prescribing of psychotropic in prisons.[507-509] Therefore, the reported prescribing safety indicators could also play an important role in prisons to improve prescribing and monitoring safety.

7.6.2 Clinical relevance and predictive validity

Prescribing safety indicators, according to Donabedian's conceptual framework, are process indicators. Therefore, these indicators must have an evidence-based link with an outcome. Although the presented prescribing safety indicators in this programme of research have been validated in a consensus study and might have adequate face and content validity, there is a need to systematically quantify the predictive validity in terms of patient risk using robust pharmacoepidemiological methods. In other words, research needs to examine if reducing the prevalence of the prescribing safety indicator would actually improve patient outcomes, such as hospitalisation and mortality. Work is already underway to test the predictive validity of a general set of primary care prescribing safety indicators for estimating the risk of adverse events and hospitalisations.[510]

7.6.3 Healthcare quality and safety indicator repository

Quality and safety indicators are being developed and used by researchers, healthcare professionals and policy makers around the globe to assess and improve healthcare safety and quality. In recent years, advances in electronic health records have led to developing and using more sophisticated indicators of quality and safety, and their use became more widespread.[138,246] Therefore, it is becoming increasingly important to share these indicators and the work that has been done into them, to help interested stakeholders to easily find suitable indicators fit for their specific purpose. However, there is no global repository to hold lists of these indicators. Efforts could be made to establish an international electronic repository for healthcare quality and safety indicators where researchers, policy makers, quality officers, or any healthcare professional with role in quality management can upload their indicators. For example, an online repository of clinical codes were developed to improve the validity of research using electronic medical records and to enable researchers to build on previous work.[415]

The repository can ask the uploader to determine if they are structure, process or outcome indicators, which speciality they are relevant to (i.e. mental health, cardiovascular, etc.), which aspect of quality they measure (i.e. access, effectiveness, safety, etc.), which stage of care they assess (i.e. screening, diagnosis, management, etc.), which setting is targeted (i.e. primary care, community pharmacy, etc.), if they require patient level data or aggregated data, which country they were developed for, how they were developed and validated, and what is the rational and evidence base for them. Table 7.4 summarise the proposed information that need to be provided when uploading an indicator into the repository.

Table 7.4: Proposed information to be requested when uploading an indicator into the repository

Information to be submitted into the database
• Indicator description
• Operational definition (numerator/denominator)
• Type of indicator
• Speciality
• Aspect of quality
• Stage of care
• Setting
• Type of data
• Country
• Development method
• Rationale
• Evidence-base
• ICD codes (if applicable)
• Medication codes (if applicable)

7.6.4 Developing further prescribing safety indicators

It was recognised in the first stage of the e-Delphi process in Chapter 4, indicators related to the paediatric population did not reach consensus, due to a large proportion of expert panel ratings falling in the neutral category. When examining first round free-text comments, it was evident that several participants felt that they did not have sufficient experience with this population and relevant medication groups (such as ADHD medications) to rate this category. Therefore, to address this issue, future research could attempt to develop mental health related prescribing safety indicators specific for younger populations exclusively with experts specialising in child and adolescent mental health.

Furthermore, as the identified prescribing indicator lists (Table 4.7 and Appendix (3)) in Chapter 4 contain medications licensed in different countries across the globe, these might therefore be used as a foundation for other international research/clinical groups to achieve this goal by selecting relevant indicators for validation for their specific countries and health settings, whether in specialist mental health hospitals/institutions or in primary care settings, as have been accomplished is this programme of work.

7.6.5 Quality assessment of consensus-based studies

Chapter 4 indicated that, as far as we know, there are no formal tools to assess the quality of consensus-based studies. Similar tools can be found for other type of studies (e.g. observational and randomised control trials).[511,512] In addition, there was a lack of standardisation in defining, using and reporting of consensus methods.[277] Therefore, efforts should be made to develop a specific tool or a checklist to assess the quality of design and reporting of consensus-based studies. The tool could help minimise biases, and increase the reliability of the study and its contribution to the scientific knowledge

7.7 Overall conclusion

The nature of psychotropic medications, coupled with the complexity of healthcare for those with mental illness places them at an increased risk of being associated with errors in medication use. This thesis has developed and implemented the first suite of prescribing safety indicators related to mental health disorders and medications that originated from the published literature and was agreed among an expert panel, with a subset of indicators identified as having high or extreme risk of patient harm. These prescribing safety indicators are essential to better understand, monitor and improve medication related harm in this population.

Primary care is the first point of contact for the majority of people with mental illness and this thesis has found that potentially hazardous prescribing and inadequate medication monitoring are common in those with mental illness in primary care with marked variation between practices for some of the indicators indicating potential for improvement. This work also found that the prevalence of some of the prescribing safety indicators has increased over time making them a target for remedial intervention.

This programme of work has identified several contextual recommendations to support the development of medication safety improvement efforts that align with current national priorities and reflect the unique characteristics of patients with mental illness and the structure of the health services designed to support them. It also identified a subset of indicators and composite indicators with good reliability that may be used to compare improvement between practices as part of these efforts. To conclude, the finding of this thesis provides a foundation for future medication safety improvement efforts for people with mental illness.

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Appendices

Appendix (1) Search strategy

Database(s): **Embase**

Search Strategy:

#	Searches
1	medication safety.mp.
2	medication error*.mp. or exp medication error/
3	prescribing error*.mp.
4	prescription error*.mp.
5	prescribing fault*.mp.
6	monitoring error*.mp.
7	inappropriate prescribing.mp. or exp inappropriate prescribing/
8	inappropriate medication*.mp. or exp potentially inappropriate medication/
9	irrational prescribing.mp.
10	prescribing appropriateness.mp.
11	appropriate prescribing.mp.
12	hazardous prescribing.mp.
13	drug-related morbidity.mp.
14	(prescribing adj3 safety).mp.
15	(prescribing adj3 quality).mp.
16	(inappropriate adj3 prescribing).mp.
17	high risk prescribing.mp.
18	high risk medication*.mp.
19	prescription error*.mp.
20	Medication related problem*.mp.
21	Drug related problem*.mp.
22	Guideline*.mp.
23	quality assurance.mp.
24	tool*.mp.
25	toolkit*.mp.
26	criteri*.mp.
27	instrument*.mp.
28	scale*.mp.
29	screen*.mp.
30	indicator*.mp.
31	measur*.mp.
32	list.mp.
33	outcome assessment*.mp.

34	patient reported outcome*.mp.
46	exp indicator/ or exp outcome assessment/ or exp patient reported outcome/
35	creat*.mp.
36	updat*.mp.
37	develop*.mp.
38	valid*.mp.
39	design*.mp.
40	consensus*.mp.
41	Delphi.mp.
42	rand appropriate*.mp.
43	revis*.mp.
44	Amend*.mp.
45	nominal group technique.mp.
47	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 46
48	35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45
49	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 or 19 or 20 or 21
50	47 and 48 and 49
51	limit 50 to yr="1990 -Current"

Appendix (2) Data extraction sheet

Data Extraction form

Name of reviewer:
Date of date extraction:

Study basic info.	Title	
	First Author	
	Year of Publication	
	Aim of the study	
	Country of origin	
	Publication details	

Study design	Targeted Setting	
	Targeted Population	
	Indicators sources	
	Validation method	
	No. of the participants in the consensus	
	Criteria for selecting the experts	
	Definition of consensus	
	Participants were allowed to add indicators	Yes/No
	Indicators were rated based on	
	Number of rounds	
	Type of indicators	

Results	Final No. of Indicators	
	No. of mental health related indicators	
	List of mental health related indicators	1.
		2.
		3.
		4.
		5.

Appendix (3) List of prescribing quality and safety indicators related to mental health medications and conditions

PIM: Independent of Diagnoses or Conditions

Table A.0.1: PIM: Independent of Diagnoses or Conditions (Antipsychotics)

Class/Medication	Age	References
Antipsychotics	≥ 65	303,304,321,324,325
	≥ 70	369
	0–5	345
	NH	366
Atypical antipsychotics	≥ 65	316,317
Aripiprazole	≥ 65	328
Chlorpromazine	≥ 65	328,329,342,389
	≥ 70	370
	≥ 75	361
Chlorprothixen	≥ 65	328
	≥ 70	370
Clozapine	≥ 65	327-329,342,351,364,389
Cyamemazine	≥ 65	328
	≥ 75	361
Droperidol	≥ 65	328
Flupentixol	≥ 65	328
Fluphenazine	≥ 65	327,328,364
	≥ 75	361
Haloperidol	≥ 65	364,389
Levomepromazine	≥ 65	328,329,342
	≥ 70	370
	≥ 75	361
Loxapine	≥ 65	328,342
Olanzapine	≥ 65	364,389
Perphenazine	≥ 65	327,328,364
	≥ 75	361
Pimozide	≥ 65	328
Pipotiazine	≥ 65	328
	≥ 75	361
Prochlorperazine	≥ 65	328
	≥ 70	370
Propericiazine (*periciazine*)	≥ 65	328
	≥ 75	361
Prothipendyl	≥ 65	364
Risperidone	≥ 65	389
Reserpine	≥ 65	323,328,342,391
	≥ 75	361
Sertindole	≥ 65	328
Sulpiride	≥ 75	359
Thioridazine	≥ 65	328,342,389
Trifluoperazine	≥ 65	328
Ziprasidone	≥ 65	328
Zuclopenthixol	≥ 65	328

Table A.0.2: PIM: Independent of Diagnoses or Conditions (Antidepressants)

Class/Medication	Age	References
Antidepressants	≥ 65	324
	0–5	345
	NH	366
TCA	≥ 65	303,317,321,341
	≥ 70	369
	≥ 75	173,359
	≤ 18	377
Amitriptyline	≥ 65	303,316,323,327-329,342,351,364,367,380,382,389,391
	≥ 70	370
	≥ 75	361
Amoxapine	≥ 65	303,328
	≥ 75	361
Clomipramine	≥ 65	303,327-329,342,351,364
	≥ 70	370
	≥ 75	361
Desipramine	≥ 65	303,328
Dosulepin	≥ 65	328,329,342
	≥ 75	361
Doxepin	≥ 65	323,327,328,342,351,364,380,382,389,391
	≥ 70	370
	≥ 75	361
Imipramine	≥ 65	303,327-329,342,351,367,389
	≥ 75	361
Maprotiline	≥ 65	327,328,351,364
	≥ 75	361
Melitracen	≥ 65	342
Nortriptyline	≥ 65	303,328
Protriptyline	≥ 65	303
Trimipramine	≥ 65	303,327,328,351
	≥ 70	370
	≥ 75	361
SSRI/SNRI	≥ 65	303
SSRI other than fluoxetine	≤ 18	173,377
Fluvoxamine	≥ 65	328,364
Fluoxetine	≥ 65	316,327-329,351
	≤ 18	173
Paroxetine	≥ 65	303,328
Venlafaxine	≥ 65	328
***NDRI** (Bupropion)*	≥ 65	328
***NRI** (Reboxetine)*	≥ 65	328
***MAOi** (Tranylcypromine)*	≥ 65	327,328,351

Table A.0.3: PIM: Independent of Diagnoses or Conditions (Sedative, hypnotics and anxiolytics)

Class/Medication	Age	References
Long acting Hypnotics or anxiolytic	≥ 65	321,341
Benzodiazepine	≥ 65	304,324,325,344
	≥ 75	359
	NH	366
long acting benzodiazepine	≥ 65	173,323,330,349,381,382,385
	≥ 75	361
short acting benzodiazepine	≥ 65	330
	≥ 75	173
Other than Temazepam or Zolpidem.	≥ 65	366
Alprazolam	≥ 65	303,327,328,389
Brotizolam	≥ 65	364
Bromazepam	≥ 65	327,328,364
Chlordiazepoxide	≥ 65	303,308,327-329,342,364,380,389,391
Clobazam	≥ 65	327-329,342,364
Clonazepam	≥ 65	303,328,342,364
Clorazepate	≥ 65	303,327,328,342,364
Diazepam	≥ 65	303,308,327-329,342,364,380,389,391
	≥ 70	369,370
Estazolam	≥ 65	303
Fludiazepam	≥ 65	342
Flunitrazepam	≥ 65	327,328,342,364
	≥ 70	369,370
Flurazepam	≥ 65	303,308,323,327,328,342,380,389,391
Halazepam	≥ 65	328
Loflazepate	≥ 65	328
Lorazepam	≥ 65	303,364,389
Medazepam	≥ 65	327-329
Midazolam	≥ 65	328,329
Nitrazepam	≥ 65	327,328,342,364
	≥ 70	369,370
Nordazepam	≥ 65	328,342
Oxazepam	≥ 65	303,364
Oxazolam	≥ 65	342
Prazepam	≥ 65	327,328,364
Quazepam	≥ 65	303,328
Temazepam	≥ 65	303,327,328
Triazolam	≥ 65	303,327,328,364,389
Z-drugs	≥ 65	304,324
	≥ 75	173,359
Eszopiclone	≥ 65	303
Zaleplon	≥ 65	303
Zolpidem	≥ 65	303
Barbiturates	≥ 65	308,391
Amobarbital	≥ 65	342
Butabarbital	≥ 65	303
Butalbital	≥ 65	303
Mephobarbital	≥ 65	303
Pentobarbital	≥ 65	303,327,342
Phenobarbital	≥ 65	303,323,328,330,364,389
Secobarbital	≥ 65	303,323,342
Chloral hydrate	≥ 65	323,327,328
Clomethiazole	≥ 65	328
	≥ 70	369
Meprobamate	≥ 65	303,308,323,328,342,391
First-generation antihistamines	≥ 65	304,324,325
	≥ 70	369
any sedating antihistamine	≥ 65	330

Alimemazine	≥ 75	361
	≥ 70	370
	≥ 65	328,342,382
Azatadine	≥ 65	342
Brompheniramine	≥ 65	303,328,342
	≥ 75	361
Buclizine	≥ 65	328,342
	≥ 75	361
Carbinoxamine	≥ 65	303,328,342
	≥ 75	361
Chlorcyclizine	≥ 65	342
Chlorpheniramine	≥ 65	303,328,342,391
	≥ 75	359,361
Chlorphenoxamine	≥ 65	342
Clemastine	≥ 65	303,328,329,342
Cyclizine	≥ 65	328,342
Cyproheptadine	≥ 65	303,328,329,342,391
	≥ 75	361
Dexbrompheniramine	≥ 65	303
Dexchlorpheniramine	≥ 65	303,328,342
	≥ 70	370
	≥ 75	361
Dimenhydrinate	≥ 65	303,328,329
	≥ 75	361
Dimetindene	≥ 65	328
Diphenhydramine	≥ 65	303,327,328,342,391
	≥ 75	359,361
Diphenylpyraline	≥ 65	342
Doxylamine	≥ 65	303,327,328,342
	≥ 75	361
Ebastine	≥ 65	328
Homochlorcyclizine	≥ 65	342
Hydroxyzine	≥ 65	303,328,329,351,391
	≥ 70	370
	≥ 75	361
Ketotifen	≥ 65	342
Mebhydrolin	≥ 65	342
Meclizine	≥ 65	303,328,342
Mepyramine	≥ 65	342
Mequitazine	≥ 65	328,342
	≥ 75	361
Oxomemazine	≥ 65	328
Oxatomide	≥ 65	342
Phenindamine	≥ 65	342
Pheniramine	≥ 65	342
	≥ 75	361
Pimethixene	≥ 65	328
Promethazine	≥ 65	303,328,329,342,382,391
	≥ 70	370
	≥ 75	361
Propiomazine	≥ 65	328
Terfenadine	≥ 65	328
Tripelennamine	≥ 65	328,342
Triprolidine	≥ 65	303,328,342
	≥ 75	359
Aceprometazine	≥ 65	328
	≥ 75	361
Phenothiazine	≤ 20	173
	≥ 65	317
Propranolol	≥ 65	323,328

Table A.0.4: PIM: Independent of Diagnoses or Conditions (Anti-dementia)

Class/Medication	Age	References
Anticholinesterase inhibitors	≥ 70	369
Cyclandelate	≥ 65	323,328
Dihydroergocristine	≥ 65	328,329,351
	≥ 75	361
Dihydroergocryptine	≥ 75	361
Dihydroergotoxine	≥ 65	303,323,328,329,389
	≥ 75	361
Ginkgo biloba	≥ 65	328-330,351
	≥ 75	361
Isoxsuprine	≥ 65	303,323
Moxisylyte	≥ 65	328
Naftidrofuryl	≥ 65	327-329
	≥ 75	361
Nicergoline,	≥ 65	327-329,351
	≥ 75	361
Pentoxifylline	≥ 65	327-329,351
	≥ 75	361
Piracetam	≥ 65	327-329,351
	≥ 75	361
Piribedil	≥ 75	361
Vinburnine	≥ 65	328,351
	≥ 75	361
Vincamine	≥ 65	328,351
	≥ 75	361

Table A.0.5: PIM: Independent of Diagnoses or Conditions (ADHD medications)

Class/Medication	Age	References
All ADHD Meds	< 6	377
Atomoxetine	0–4	345
Clonidine	≥ 65	303,316,328,330,342,389
	≥ 75	361
Guanfacine	≥ 65	303,328
	≥ 75	361
Methylphenidate	≥ 65	328
Stimulants	0–4	345

Table A.0.6: PIM: Independent of Diagnoses or Conditions (Mood stabilisers)

Class/Medication	Age	References
Carbamazepine	≥ 65	303,328
Lithium	≥ 65	328

Table A.0.7: PIM: Independent of Diagnoses or Conditions (Anticholinergics)

Class/Medication	Age	References
Anticholinergics	≥ 65	321
	≥ 75	361
	NH	366
High anticholinergic Meds	≥ 65	340,381
Atropine (excludes ophthalmic) [a]	≥ 65	303
Belladonna [a]	≥ 65	303,323,328,342,389,391
	≥ 75	361
Benzatropine [a]	≥ 65	303,328
Biperiden [a]	≥ 65	328,364
	≥ 75	359
Bornaprine [a]	≥ 65	364
Clidinium-chlordiazepoxide [a]	≥ 65	303,328
	≥ 75	361
Dicyclomine (Dicyclomine) [a]	≥ 65	303,391
Dihexyverine [a]	≥ 75	361
Diphenoxylate-atropine [a]	≥ 75	361
Hyoscine [a]	≥ 65	303,323,328,389
	≥ 75	361
Hyoscyamine [a]	≥ 65	303,323,328,342,391
Orphenadrine [a]	≥ 65	303,316,323,328,342,389
Propantheline [a]	≥ 65	303,391
Tiemonium [a]	≥ 75	361
Trihexyphenidyl [a]	≥ 65	303,328
	≥ 75	359
Tropatepine [a]	≥ 65	328

[a]. These medications were included because they can be used to treat some of the side effects caused by mental health medications.

PIM: considering diagnoses or conditions

Table A.0.8: PIM: considering diagnoses or conditions (Antipsychotics)

CONDITION	CLASS/MEDICATION	AGE	REFERENCE
Dementia or Cognitive Impairment	*Antipsychotics*	≥ 75	43,359
	Antipsychotics	≥ 65	303
	Perphenazine	≥ 65	357
	Clozapine	≥ 65	357
	Haloperidol	≥ 65	357
	Olanzapine	≥ 65	357
	Antipsychotic other than risperidone and olanzapine	≥ 75	361
Dementia but Not Psychosis	*Antipsychotics*	≥ 65	173
	Risperidone		30
	Olanzapine		30
Dementia and Psychosis	*Antipsychotic other than risperidone*	≥ 65	173
BPSD	*Antipsychotics*	≥ 65	303,304
	Antipsychotics	≥ 70	369
	Antipsychotic other than risperidone	NS	35
BPSD: Paranoia, Hallucination	*Olanzapine*	≥ 65	318
Advanced dementia	*Antipsychotics*	NS	360
Advanced dementia (palliative)	*Antipsychotics*	NS	354
Seizures or Epilepsy	*Antipsychotics*	≥ 65	389
	Chlorpromazine	≥ 65	303
	Phenothiazines	NS	347
		≥ 65	325,329
	Haloperidol	NS	347
	Clozapine	≥ 65	303
	Thioridazine	≥ 65	303
	Thiothixene	≥ 65	303
	Olanzapine	≥ 65	303
Parkinson's Disease	*Antipsychotics*	≥ 65	324
	Antipsychotics other than quetiapine or clozapine	≥ 65	173,304,317,330,366
	Antipsychotics other than aripiprazole, quetiapine, clozapine	≥ 65	303
	Prochlorperazine	NS	35
		≥ 65	303,304,317,325
	Haloperidol	≥ 65	349,357,389
	Droperidol	≥ 65	349
	Perphenazine	≥ 65	357
	Clozapine	≥ 65	357
	Olanzapine	≥ 65	357
History of prostatism or previous urinary retention of BPH	*Antipsychotics*	NS	347
	Chlorpromazine	≥ 65	304
	Clozapine		304
	Flupenthixol		304
	Fluphenazine		304
	Pipothiazine		304
	Promazine		304
	Zuclopenthixol		304
Glaucoma	*Fluphenazine*	NS	347
	Perphenazine		347
	Trifluoperazine		347
Syncope	*Chlorpromazine*	≥ 65	303
	Thioridazine		303
	Olanzapine		303,357
	Haloperidol		357

	Clozapine		357
	Perphenazine		357
Postural Hypotension	*Thioridazine*	≥ 65	362
	Chlorpromazine		367
History of Falls	*Antipsychotics*	≥ 65	303,329
	Conventional antipsychotics		362
	Perphenazine		357
	Clozapine		357
	Haloperidol		357
	Olanzapine		357
Delirium	*Antipsychotics*	≥ 65	303
	Chlorpromazine		303
	Perphenazine		357
	Clozapine		357
	Haloperidol		357
	Olanzapine		357
Depression	*Quetiapine*	≥ 65	318
	Olanzapine		318
ADHD without Hyperactivity	*Antipsychotics*	Children	377
Arrhythmia	*Antipsychotics*	≥ 65	389
HTN	*Clozapine*	NS	347
Swallowing Problems	*Antipsychotics*	≥ 65	324
Lewy Body Disease	*Antipsychotics other than quetiapine or clozapine*	≥ 65	304,317
Insomnia / Sleep Disorders	*Pipamperone*	≥ 65	318
	Melperone		318
DM	*Antipsychotics*	NS	347
Frail Adults with Limited Life Expectancy	*Antipsychotics*	NS	352
Chronic constipation	*Perphenazine*	≥ 65	357
	Clozapine		357
	Haloperidol		357
	Olanzapine		357

Table A.0.9: PIM: Considering Diagnoses or Conditions (Antidepressants)

CONDITION	CLASS/MEDICATION	AGE	REFERENCE
Heart block	*TCA*	≥ 65	362,367,389
	Amitriptyline at dose >75mg	NS	29
Cardiac conduction abnormalities	*TCA*	≥ 65	304,325,344
	Amitriptyline		357
	Clomipramine		357
	Imipramine		357
Cardiovascular risk factors or CVD	*TCA*	≥ 65	366
Heart failure	*Amitriptyline at dose >75mg*	NS	29
	TCA	NS	30,173,347
	TCA	≥ 65	329
Arrhythmia	*Amitriptyline at dose >75mg*	NS	29
HTN	*Venlafaxine*	NS	347
	Duloxetine		347
	MAOIs		347
Postural hypotension	*Amitriptyline at dose >75mg*	NS	29
	TCA	≥ 65	362,366,367
Syncope	*TCA*	≥ 65	329,389
	Tertiary TCAs		303
	Amitriptyline		357
	Clomipramine		357
	Imipramine		357
History of falls	*SSRI*	≥ 65	303,329,362

	Amitriptyline		357
	Clomipramine		357
	Imipramine		357
Seizures or epilepsy	*SSRI*	NS	35,347
	TCA	NS	347
	Bupropion	NS	29,308,347
	Bupropion	≥ 65	303,362
	Maprotiline	≥ 65	303
Dementia or cognitive impairment	*Antidepressants*	≥ 70	369
	TCA	≥ 65	173,304,325,329,344,362,389
	TCA	NS	35
	Amitriptyline	≥ 65	357
	Clomipramine	≥ 65	357
	Imipramine	≥ 65	357
Advanced dementia	*TCA*	NS	360
	Antidepressants other than TCA		360
Advanced dementia (Palliative)	*TCA*	NS	354
	Antidepressants other than TCA		354
BPSD: depression	*Citalopram*	≥ 65	318
	Escitalopram		318
	Sertraline		318
	Fluoxetine		318
	Venlafaxine		318
	Duloxetine		318
BPSD: sleep disorders	*Trazodone*	≥ 65	318
Glaucoma	*TCA*	≥ 65	304,325,329,344,366,367,389
	TCA	NS	347
	Amitriptyline	≥ 65	357
	Clomipramine	≥ 65	357
	Imipramine	≥ 65	357
	MAOI	NS	347
	Citalopram	NS	347
	Escitalopram	NS	347
	Fluoxetine	NS	347
	Fluvoxamine	NS	347
	Mianserin	NS	347
	Paroxetine	NS	347
Depression	*Nortriptyline*	≥ 65	318
	Mirtazapine		318
	Venlafaxine		318
	Duloxetine		318
	Moclobemide		318
	Bupropion		318
	Vortioxetine		318
	Agomelatine		318
	Reboxetine		318
	Trazodone		318
	St. John's Wort		318
Insomnia / sleep disorders	*Mirtazapine*	≥ 65	318
	Doxepin		318
	Opipramol		318
	Fluoxetine		329
	MAO		329
Prostatism or history of urinary retention or BPH	*TCA*	NS	347
	TCA	≥ 65	304,325,329,344,362,366,367
	Amitriptyline		357
	Clomipramine		357

	Imipramine		357
Urinary incontinence	*TCA*	≥ 65	329,389
Constipation	*TCA*	≥ 65	325,329,344,362,389
	Amitriptyline		357
	Clomipramine		357
	Imipramine		357
Current or recent significant hyponatraemia	*SSRI*	≥ 65	304,325,329,366
	SSRI	NS	35
Renal failure	*Paroxetine*	NS	347
Hepatic impairment or cirrhosis	*TCA*	NS	347
Gastrointestinal haemorrhage	*Paroxetine*	≥ 75	359
	Sertraline	≥ 75	359
	Fluvoxamine	≥ 75	359
	Escitalopram	≥ 75	359
Peptic ulcer disease	*SSRI*	NS	347
Bladder atony due to diabetes	*Imipramine*	≥ 65	321
Anorexia and malnutrition	*Fluoxetine*	≥ 65	329
Delirium	*Amitriptyline*	≥ 65	357
	Clomipramine		357
	Imipramine		357
Acute bipolar depression	*TCA*	Adults	331
Acute management of depressive bipolar disorder	*paroxetine*	Adults	331

Table A.0.10: PIM: Considering Diagnoses or Conditions (Sedative, hypnotics, and anxiolytics)

CONDITION	CLASS/MEDICATION	AGE	REFERENCE
Dementia or cognitive impairment	*Benzodiazepines*	≥ 75	361
	Benzodiazepines	≥ 65	303,342,362
	Alprazolam		357
	Clorazepam		357
	Triazolam		357
	Chlorazepate		357
	Chlordiazepoxide		357
	Diazepam		357
	Flurazepam		357
	Eszopiclone		303
	Zolpidem		303
	Zaleplon		303
	Barbiturates		362
History of falls or fractures	*Sedative-hypnotics*	≥ 65	362
	Benzodiazepines		303,329,362
	Alprazolam		357
	Clorazepam		357
	Triazolam		357
	Chlorazepate		357
	Chlordiazepoxide		357
	Diazepam		357
	Flurazepam		357
	Eszopiclone		303
	Zolpidem		303
	Zaleplon		303
	Chlorpheniramine		357
	Clemastine		357
	Doxylamine		357
	Triprolidine		357

Acute or chronic respiratory failure	*Benzodiazepines*	≥ 65	304
Asthma	*Benzodiazepines*	≥ 65	389
	Propranolol	≥ 65	359
COPD	*long-acting benzodiazepine*	≥ 65	329
	medium to long-acting benzodiazepine	≥ 65	321
	Benzodiazepines	≥ 65	340,342,389
	Benzodiazepines	NS	35
	Z-drugs	NS	35
	Propranolol	≥ 65	359
Sleep apnoea syndrome	*Benzodiazepines*	≥ 65	342,389
Delirium	*Benzodiazepines*	≥ 65	303
	Sedative- hypnotics		303
	Alprazolam		357
	Clorazepam		357
	Triazolam		357
	Chlorazepate		357
	Chlordiazepoxide		357
	Diazepam		357
	Flurazepam		357
Depression	*long-acting benzodiazepine*	≥ 65	318,321
	Barbiturates		321
	Benzodiazepines		318,329
	Short acting benzodiazepine		318
Insomnia / sleep disorders	*Zopiclone*	≥ 65	318
	Zolpidem		318
	Zaleplon		318
	Medium half-life Benzodiazepines		318
	Very short half-life Benzodiazepines		318
	Diphenhydramine		318
Urinary incontinence	*Benzodiazepines*	≥ 65	342
Urinary retention	*Benzodiazepines*	≥ 65	342
BPH	*Antihistamine*	≥ 65	389
Advanced dementia	*Antihistamine 1st generation*	NS	360
Parkinson disease	*Promethazine*	≥ 65	303
Hepatic impairment or cirrhosis	*Benzodiazepines*	NS	347
	Barbiturates		347
Chronic constipation	*Chlorpheniramine*	≥ 65	357
	Clemastine		357
	Doxylamine		357
	Triprolidine		357
	antihistamines		389

Table A.0.11: PIM: Considering Diagnoses or Conditions (Mood stabilisers)

CONDITION	CLASS/MEDICATION	AGE	REFERENCE
Heart failure	*Carbamazepine*	NS	347
HTN	*Carbamazepine*	NS	347
Bipolar disorder	*Carbamazepine*	≥ 65	318
	Valproic acid		318
	Lamotrigine		318
Renal failure	*Lithium*	NS	347
Rheumatoid arthritis	*Lithium*	NS	347
Thyroid disorders	*Lithium*	NS	347
Epilepsy	*Lithium*	NS	347

Table A.0.12: PIM: Considering Diagnoses or Conditions (Anti-dementia)

CONDITION	CLASS/MEDICATION	AGE	REFERENCE

Persistent bradycardia	*Acetylcholinesterase inhibitors*	≥ 65	304,324
Heart block	*Acetylcholinesterase inhibitors*	≥ 65	304
Recurrent unexplained syncope	*Acetylcholinesterase inhibitors*	≥ 65	303
Palliative care patients with advanced dementia	*Acetylcholinesterase inhibitors*	NS	354
	Memantine		354
Frail adults with limited life expectancy	*Memantine*	NS	352
Dementia	*Ginkgo biloba*	≥ 65	318
	Ergoline derivatives		318
	Piracetam		318
To treat dementia	*Nylidrin*	≥ 65	367
	Niacin		367
	Pentoxifylline		367

Table A.0.13: PIM: Considering Diagnoses or Conditions (Anticholinergics)

CONDITION	CLASS/MEDICATION	AGE	REFERENCE
Dementia or cognitive impairment	*Anticholinergics*	NS	308
	Anticholinergics	≥ 65	303,304,317,324,325,329,330,340,342,344,362,367
	Anticholinergics	≥ 75	361
	Trihexyphenidyl	≥ 75	361
	Tropatepine	≥ 75	361
	Biperiden	≥ 75	361
Delirium	*Anticholinergics*	≥ 65	303,304,317,324
Chronic constipation	*Anticholinergics*	≥ 65	304,324,330,342,362
	Anticholinergics	≥ 75	361
	Anticholinergics	NS	347
Glaucoma	*Anticholinergics*	≥ 75	361
	Anticholinergics	≥ 65	304,324,329,342,362
	Medication with high anticholinergic activity		381
	2 or more agents with low to moderate anticholinergic activity		381
	Orphenadrine [a]		347
	Hyoscine [a]		347
History of urinary retention of BPH	*Anticholinergics*	≥ 65	304,321,324,329,330,342,362
	Anticholinergics	≥ 75	361
	Anticholinergics	NS	307
	Strongly anticholinergic drugs, except antimuscarinics for urinary incontinence	≥ 65	303
To treat extra-pyramidal side-effects of neuroleptic medications	*Anticholinergics*	≥ 65	304,325,329,367

[a]. These medications were included because they can be used to treat some of the side effects caused by mental health medications.

Table A.0.14: PIM: Considering Diagnoses or Conditions (ADHD medications)

CONDITION	CLASS/MEDICATION	AGE	REFERENCE
Anorexia	*Cyproheptadine*	Children	377
	Clonidine		377
HTN	*Clonidine*	NS	347
	Atomoxetine		347

Palliative care patients with advanced dementia	*Clonidine*	NS	354
Advanced dementia	*Clonidine*	NS	360
Anorexia and malnutrition	*Methylphenidate*	≥ 65	329
to treat depression	*Methylphenidate*	≥ 65	329,367
Epilepsy	*Methylphenidate*	NS	347
Chronic constipation	*Clonidine*	≥ 75	361
	Guanfacine		361
Insomnia	*Amphetamine*	≥ 65	303
	Methylphenidate		303,329

Table A.0.15: PIM: Considering Diagnoses or Conditions (non-mental health medications with mental health conditions)

CONDITION	CLASS/MEDICATION	AGE	REFERENCE
Delirium	*Corticosteroids*	≥ 65	303
	Cimetidine		303
	Famotidine		303
	Nizatidine		303
	Ranitidine		303
	Meperidine (Pethidine)		303
Insomnia	*Pseudoephedrine*	≥ 65	303,329
	Phenylephrine		303,329
	Armodafinil		303
	Modafinil		303
	Theophylline		303
	Caffeine		303
	Phenylpropanolamine		329
	PPI		329
Depression	*Methyldopa*	≥ 65	389
	Sympatholytic antihypertensive		321
	Moderate to high lipophilic beta-adrenergic blocking agent (e.g., propranolol, pindolol)		321
Dementia	*Statins*	≥ 65	318
	Selegiline		318
	Nimodipine		318
	Pyritinol		318
	Antioxidants: vitamin e		318
	Antioxidants: vitamin c		318
	Antioxidants: selenium		318
	Phytotherapeutic agents, e.g. Ginseng		318
	Hormone preparations, e.g. DHEA (Dehydroepiandrosterone), testosterone		318
	Antiphlogistics, e.g. Indomethacin		318
	Desferrioxamine		318
	H2-receptor antagonists		303,389
	Antispasmodic		329,367,389
Advanced dementia	*Colchicine*	NS	360
	Digoxin		360
	Antiarrhythmics class I and III		360
	Hydralazine		360
	Bisphosphonates		360

	Antiplatelets excluding aspirin		360
	VKA		360
	Anticoagulants excluding VKA		360
	Appetite stimulants		360
	Bladder relaxants		360
	Antispasmodics		360
	Lipid-lowering medications		360
	Leukotriene receptor antagonists		360
	Antioestrogens		360
	Sex hormones		360
	Cytotoxic chemotherapy		360
	Hormone antagonists		360
	Immunomodulators		360
	NSAIDs		360
	Antidiarrheals		360
	Laxatives		360
	Antiemetics		360
	Proton pump inhibitors		360
	Beta-blockers		360
	Calcium channel blockers		360
	Diuretics		360
	Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers		360
	Nitrates/nitroglycerin		360
	Antibacterials		360
	Antivirals		360
	Antiparasitic agents		360
	Oral hypoglycaemics		360
	Thyroid hormones		360
	Antithyroid medications		360
	Corticosteroids		360
	Insulin		360
	Antihistamine second generation		360
	Electrolytes		360
	Antiglaucoma drops		360
	Anti-inflammatory eye drops		360
	Allopurinol		360
	Uroselective alpha blockers		360
	Aspirin		360
Advanced dementia (palliative)	*Bisphosphonates*	NS	354
	Hydralazine		354
	Antiarrhythmics		354
	Heparin and LMWH		354
	Antispasmodics		354
	Warfarin		354
	Hormone antagonists		354
	Immunomodulators		354
	Sex hormones		354
	Antioestrogens		354
	Lipid-lowering medications		354

	Antiplatelets excluding aspirin		354
	Leukotriene receptor antagonists		354
	Cytotoxic chemotherapy		354
	Mineralocorticoids		354
	Tamsulosin		354
	Digoxin		354
	Bladder relaxants		354
	Alpha blockers		354
	Antiandrogens		354
	Appetite stimulants		354
	Proton pump inhibitors		354
	Histamine-2 receptor blockers		354
	Beta-blockers		354
	Calcium channel blockers		354
	Diuretics		354
	Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers		354
	Nitroglycerin		354
	Mucolytics		354
	Inhaled corticosteroids		354
	Antibacterials		354
	Antivirals		354
	Antiparasitic agents		354
	Antifungal creams		354
	Oral hypoglycaemics		354
	Thyroid hormones		354
	Antithyroid medications		354
	Corticosteroids		354
	Insulin		354
	Antihistamines		354
	Decongestants		354
	Electrolytes		354
	Nutritional supplements		354
	Antiglaucoma drops		354
	Anti-inflammatory eye drops		354
	Capsaicin		354
	Allopurinol		354
	Colchicine		354
Dementia (non-palliative)	*Fentanyl*	≥ 65	329
	Morphine		329

Table A.0.16: PIM: Considering Diagnoses or Conditions (Non-specific psychotropics)

CONDITION	CLASS/MEDICATION	AGE	REFERENCE
History of falls	*psychotropics*	≥ 65	340

Drug-Drug Interactions

Table A.0.17: Drug-Drug Interactions (Non-specific psychotropics)

Medication/Class	Medication/Class	Age	References
More than one psychotropic drugs from the same class		≥ 75	361
3 or more psychotropics		≥ 70	369,370
Multiple psychotropics		≥ 65	381,382
≥2 CNS-active drugs	*Opioid receptor agonist*	≥ 65	303
Tranquilizer	*Tranquilizer*	≥ 65	385

Table A.0.18: Drug-Drug Interactions (Antipsychotics)

Medication/Class	Medication/Class	Age	References
3 or more antipsychotics		adults	345
Antipsychotics	*≥2 CNS-active drugs*	≥ 65	303
	Antipsychotic	≥ 65	317,323
		NS	278,347
	Antiparkinsonian agents	≥ 65	326
Atypical antipsychotic	*Atypical antipsychotic*	NS	278
Pimozide	*Macrolides antibiotics*		363
	Azole antifungal	NS	363
Phenothiazine antipsychotics	*Antiparkinsonian agents*	≥ 65	382
Aripiprazole	*Anti-HCV antivirals*	NS	347
Quetiapine			347
Iloperidone			347

Table A.0.19: Drug-Drug Interactions (Antidepressants)

Medication/Class	Medication/Class	Age	References
Antidepressants	*Antidepressants*	≥ 65	317
	≥2 other CNS-active drugs		303
TCA	*MAO*	NS	35
	Opiate	≥ 65	325,329,344
	Calcium channel blocker	≥ 65	325,329,344
	TCA	≥ 65	323,385
	Clonidine	≥ 65	323
		NS	384
	Cimetidine	≥ 65	389
		NS	384
	Fluoxetine	NS	384
		≥ 70	370
	Fluvoxamine	≥ 70	370
	Paroxetine	NS	384
	Selegiline	NS	376
SSRI	*Tramadol*	≥ 70	369
		NS	35
	Aspirin (no protection)	≥ 65	366
		NS	35
	medications that may contribute to serotonin toxicity	≥ 65	340
	SSRI's	≥ 65	304,325,344
	NSAID	≥ 65	330,344
	NSAID (no protection)	≥ 45	346
	Venlafaxine.	≥ 45	346
	VKA	NS	347
	Selegiline	NS	384
SSRIs/SNRIs	*NSAIDs*	≥ 70	369,370

	Warfarin		369,370
MAO	*Tramadol*	NS	35
	Dextromethorphan	NS	363
	Anorexiants	NS	363
	Amphetamine and derivatives	*NS*	376
	Fluoxetine	*NS*	376
	Narcotic analgesics	*NS*	376
	Triptans	*NS*	376
	Sympathomimetics	NS	363
	Meperidine	NS	363
	SSRIs	≥ 65	367
		NS	363
	Levodopa	≥ 65	323,385
	Meperidine	≥ 65	323,385
	Antidepressants	≥ 65	323,385
	MAOI	≥ 65	323,385
Amitriptyline	*Sertraline*	children	353
	Trazodone		353
	Psycholeptic	≥ 65	323
	opiate	≥ 65	357
	calcium channel blocker	≥ 65	357
Citalopram	*QT-prolonging drugs*	NS	35
Citalopram	*Linezolid*	children	353
Sertraline			353
Fluoxetine	*Alprazolam*	NS	384
Fluvoxamine	*Theophylines*	NS	363
	Ramelteon	NS	376
Paroxetine	*Metoprolol*	≥ 70	369
Fluoxetine			369
Bupropion			369
Trazodone	*anti-HCV antivirals*	NS	347
Escitalopram			347
Tranylcypromine	*Procarbazine*	NS	376
Clomipramine	*Opiate*	≥ 65	357
	Calcium channel blocker		357
Imipramine	*Opiate*	≥ 65	357
	Calcium channel blocker		357

Table A.0.20: Drug-Drug Interactions (Sedative, hypnotics and anxiolytics)

Medication/Class	Medication/Class	Age	References
Hypnotic or sedative	*Hypnotic or sedative*	≥ 65	317,323,385
Benzodiazepine	*Hypnotic or sedative*	≥ 65	323,385
	≥2 CNS-active drugs	≥ 65	303
	Azole antifungal agents	NS	363
	Cimetidine	≥ 65	389
	Benzodiazepines	≥ 45	346
		≥ 65	323,349,382,385,387
		NS	347
Alprazolam	*Strong CYP3A4 inhibitor*	≥ 65	330
Midazolam			330
Triazolam			330
Clonazepam	*Clonazepam*	≥ 65	385
	Benzodiazepines	≥ 65	323,385
Clorazepate	*Acepromazine*	≥ 65	328
Flurazepam	*Anti-HCV antivirals*	NS	347
Guazepam			347
Triazolam			347
Alprazolam			347

Z-drugs	*≥2 CNS-active drugs*	≥ 65	[303]
Zolpidem	*Strong CYP3A4 inhibitor*	≥ 65	[330]
Zopiclone			[330]
Zolpidem	*Anti-HCV antivirals*	NS	[347]
Barbiturates	*Hypnotic or sedative*	≥ 65	[323,385]
	Hormonal contraceptive or combination pills	NS	[384]
	Steroids	NS	[384]
	Barbiturates	≥ 65	[323,385]
	Warfarin	NS	[363,384]
	Opioids	≥ 65	[323,385]
	Antidepressants	≥ 65	[323,385]
Phenobarbital	*Rivaroxaban*	NS	[347]
	Voriconazole	children	[353]
Propranolol	*Insulin*	NS	[384]
	Rifampin		[384]
	Verapamil		[384]

Table A.0.21: Drug-Drug Interactions (mood stabilisers)

Medication/Class	Medication/Class	Age	References
Valproic acid	*Lamotrigine*	Children	[353]
	Meropenem	Children	[353]
	Barbiturates	NS	[384]
Carbamazepine	*Clarithromycin*	NS	[383]
		≥ 45	[346]
		≥ 70	[370]
	Erythromycin	≥ 45	[346]
		≥ 70	[370]
	Cimetidine	≥ 65	[389]
	oral or intravaginal contraceptives, patches or pure progestogen pills	NS	[347]
	Warfarin	NS	[384]
	Propoxyphene	NS	[363,384]
	Rivaroxaban	NS	[347]
Lithium	*ACEi*	≥ 65	[303]
	Loop diuretics	≥ 65	[303]
	thiazide diuretic	NS	[29,308,323,384]
	RAAS inhibitors	≥ 65	[330]
	NSAID	≥ 65	[330]
	Diuretics	≥ 65	[330]
		NS	[331]
Lamotrigine	*Hormonal contraceptive or combination pills*	NS	[347]

Table A.0.22: Drug-Drug Interactions (Anti-dementia)

Medication/Class	Medication/Class	Age	References
Anticholinesterase drugs	*Anticholinergic*	≥ 75	[361]
	Anticholinergic	≥ 65	[351]
	Anticholinesterase drugs	NS	[347]
	Beta-blockers	≥ 65	[304]
	Digoxin	≥ 65	[304]
	Diltiazem	≥ 65	[304]
	Verapamil	≥ 65	[304]

Table A.0.23: Drug-Drug Interactions (Anticholinergics)

Medication/Class	Medication/Class	Age	References
Two or more agents with low to moderate anticholinergic activity		≥ 65	381
Anticholinergic	*Anticholinergic*	≥ 65	303,304,317,330

Table A.0.24: Drug-Drug Interactions (ADHD medications)

Medication/Class	Medication/Class	Age	References
Clonidine	*Propranolol*	NS	384

Inappropriate Duration

Table A.0.25: Inappropriate Duration (Antipsychotics)

Class/Medication	Condition	Duration	Age	References
Antipsychotics	Dementia but not psychosis	>6 weeks	≥ 65	29
	Parkinsonism	>1 month	NS	35
			≥ 65	325,329
	as long-term hypnotics	>1 month	≥ 65	325,329,351
	non-psychotic indications	long term	≥ 65	382
	NS	>1 month	≥ 65	330
	NS	long term	≥ 65	324
More than one Antipsychotics	NS	>2 month	Adults	345
		45 days	6–17	345
Risperidone	NS	>6 weeks	≥ 65	328
	dementia and psychosis	≥ 12 weeks	≥ 65	173
Perphenazine	Parkinsonism	>1 month	≥ 65	357
	as long-term hypnotics	>1 month		357
Clozapine	Parkinsonism	>1 month	≥ 65	357
	as long-term hypnotics	>1 month		357
Haloperidol	Parkinsonism	>1 month	≥ 65	357
	as long-term hypnotics	>1 month		357
Olanzapine	Parkinsonism	>1 month	≥ 65	357
	as long-term hypnotics	>1 month		357

Table A.0.26: Inappropriate Duration (Antidepressants)

Class/Medication	Condition	Duration	Age	References
Antidepressants	NS	long term	≥ 65	324
		≥ 1 year	≥ 65	330
Three or more Antidepressants	NS	>3 month	adults	345
TCA	NS	>1 month	≥ 65	173
More than one TCA	NS	>1 month	adults	345
SSRI	NS	< 4 weeks (too short)	≥ 65	366
	single episode of depression	> 6 months	≥ 65	366
More than one SSRI	NS	>2 month	adults	345
SSRI and SNRI combination	NS	>2 month	adults	345

Table A.0.27: Inappropriate Duration (Sedative, hypnotics and anxiolytics)

Class/Medication	Condition	Duration	Age	References
Hypnotics	NS	long term	NS	347
			≥ 65	366
			≥ 70	369
		>1 month	NS	388
Benzodiazepine	not receiving on a long-term basis	≥21 days	≥ 65	29
	Depression	≥21 days	≥ 65	29
		>1 month	NS	35
	NS	>1 month	≥ 65	304,317,340,385
			NS	35,373
			≥ 45	346
		long term	≥ 65	324,366
		>6 month	≥ 65	350
Long-acting Benzodiazepine	NS	>1 month	≥ 65	325,344,351
	Agitation in dementia	long term	≥ 65	367
	Anxiety		≥ 65	367

	Insomnia		≥ 65	[367]
Intermediate acting benzodiazepine	NS	>1 month	≥ 65	[330]
Short acting benzodiazepine	NS	>1 month	≥ 65	[173,323]
Alprazolam	NS	>1 month	≥ 65	[323]
Oxazepam	NS	>1 month	≥ 65	[323,329]
Triazolam	NS	>1 month	≥ 65	[323]
Triazolam	to treat insomnia	long term	≥ 65	[367]
Chlorazepate	NS	>1 month	≥ 65	[357]
Chlordiazepoxide	NS	>1 month	≥ 65	[357]
Diazepam	NS	>1 month	≥ 65	[357]
Flurazepam	NS	>1 month	≥ 65	[357]
Z-drugs	not receiving on a long-term basis	≥21 days	≥ 65	[29]
	Depression	≥21 days	≥ 65	[29]
		>1 month	NS	[35]
	NS	>1 month	NS	[35]
			≥ 45	[346]
			≥ 65	[173,330]
		long term	≥ 65	[324]
Barbiturates	to treat insomnia	long term	≥ 65	[367]
Phenobarbital	NS	long term	≥ 65	[329]
First-generation antihistamine	NS	> 1 week	≥ 65	[325,329]
Chlorpheniramine	NS	> 1 week	≥ 65	[357]
Clemastine	NS	> 1 week	≥ 65	[357]
Doxylamine	NS	> 1 week	≥ 65	[357]
Triprolidine	NS	> 1 week	≥ 65	[357]

Table A.0.28: Inappropriate Duration (Non-specific psychotropics)

Class/Medication	Condition	Duration	Age	References
Four or more Psychotropics	NS	>3 months	6–17	[345]

Table A.0.29: Inappropriate Duration (non-mental health medication with mental health condition)

Class/Medication	Condition	Duration	Age	References
Opioids	Dementia (non-palliative)	long term	≥ 65	[325]

Table A.0.30: Inappropriate Duration (Anticholinergics)

Class/Medication	Condition	Duration	Age	References
Belladonna alkaloids [a]	NS	>3 months	≥ 65	[323]
Clidinium-chlordiazepoxide [a]	NS	>3 months	≥ 65	[323]
Dicyclomine [a]	NS	>3 months	≥ 65	[323]
Propantheline [a]	NS	>3 months	≥ 65	[323]

[a]. These medications were included because they can be used to treat some of the side effects caused by mental health medications.

Inappropriate dose

Table A.0.31: Inappropriate dose (Antipsychotics)

Medication (dose)	Condition	Age	References
Aripiprazole (2-15 mg/day)	BPSD: paranoia, hallucination	≥ 65	318
Citalopram (10-30mg)	BPSD: restlessness, agitation	≥ 65	318
Clozapine (10-50 mg/day)	BPSD: paranoia, hallucination	≥ 65	318
Haloperidol (>2 mg)		≥ 65	327-329
Haloperidol (>3 mg/day)		≥ 65	323
Haloperidol (>5 mg/day)		≥ 65	328
Haloperidol (initially 0.5 mg/day, max. 3 mg/day)	BPSD: paranoia, hallucination	≥ 65	318
Melperone (25-150 mg/day)	BPSD: paranoia, hallucination	≥ 65	318
Melperone (25-150 mg/day)	BPSD: restlessness, agitation	≥ 65	318
Olanzapine (>10 mg)		≥ 65	327,328,351
Pipamperone (20-120 mg/day)	BPSD: restlessness, agitation	≥ 65	318
Quetiapine (25-200 mg/day)	BPSD: paranoia, hallucination	≥ 65	318
Quetiapine (25-200 mg/day)	BPSD: restlessness, agitation	≥ 65	318
Reserpine (>0.1 mg/day)		≥ 65	303
Risperidone (initially 0,5-1 mg/day)	BPSD: paranoia, hallucination	≥ 65	318
Risperidone (initially 0,5-1 mg/day, Maximum 3 mg/day)	BPSD: restlessness, agitation	≥ 65	318
Risperidone (1 mg BID)	Dementia and agitation	≥ 75	381
Thioridazine (>30mg/day)		≥ 65	323
High dose antipsychotics		NS	278

Table A.0.32: Inappropriate dose (Antidepressants)

Medication (dose)	Condition	Age	References
Doxepin (>6 mg/day)		≥ 65	303
Doxepin (25-50 mg)	BPSD: sleep disorders	≥ 65	318
Fluoxetine (>40 mg/day)		≥ 65	323
Imipramine (>100 mg/day)		≥ 65	323
Trazodone (50-200 mg/day)	BPSD: restlessness, agitation	≥ 65	318
Trimipramine (>100 mg/day)		≥ 65	323
Mirtazapine (15-45mg/day)	BPSD: depression	≥ 65	318
Mirtazapine (15-30mg/day)	BPSD: sleep disorders	≥ 65	318

Table A.0.33: Inappropriate dose (mood stabilisers)

Medication (dose)	Age	References
Valproate (<1 g/day)	NS	278

Carbamazepine (< 600 mg/day)	NS	[278]

Table A.0.34: Inappropriate dose (ADHD medications)

Medication (dose)	**Age**	**References**
SR Methylphenidate two doses per day, rather than one dose	Children	[377]

Table A.0.35: Inappropriate dose (Sedatives, hypnotics and anxiolytics)

Medication (dose)	**Condition**	**Age**	**References**
Alprazolam (2 mg/day)		≥ 65	[308,329,344]
Alprazolam (2 mg/day)		≥ 75	[361]
Alprazolam (>0.75 mg/day)		≥ 65	[323]
Bromazepam (> 1,5 mg)		≥ 65	[329]
Brotizolam (>0.125 mg/day)		≥ 65	[327,328]
Clomethiazole (5-15 mg/day)	BPSD: restlessness, agitation	≥ 65	[318]
Clotiazepam (>5 mg/day)		≥ 75	[361]
Clotiazepam (>5 mg/day)		≥ 65	[328]
Gabapentin (>1400mg/day)	CrCl 30-59 mL/min	NS	[348]
Gabapentin (>700mg/day)	CrCl 15-29 mL/min	NS	[348]
Gabapentin (>300mg/day)	CrCl 10-14 mL/min	NS	[348]
Gabapentin (>150mg/day)	CrCl < 10 mL/min	NS	[348]
Loprazolam (>0,5 mg/day)		≥ 75	[361]
Loprazolam (>0.5 mg/day)		≥ 65	[328]
Lorazepam (>1 mg/day)		≥ 65	[328]
Lorazepam (> 2 mg/day)		≥ 65	[327]
Lorazepam (>3 mg/day)		≥ 75	[361]
Lorazepam (>3 mg/day)		≥ 65	[308,323,344]
Lormetazepam (>0.5 mg/day)		≥ 75	[361]
Lormetazepam (>0.5 mg/day)		≥ 65	[327,328]
Melatonin SR (2-4 mg)	BPSD: sleep disorders	≥ 65	[318]
Oxazepam (>30 mg/day)		≥ 70	[369,370]
Oxazepam (>30 mg/day)		≥ 65	[329]
Oxazepam (>60 mg/day)		≥ 65	[308,327,328,344]
Oxazepam (>60 mg/day)		≥ 75	[361]
Oxazepam unit dose >30 mg		≥ 65	[323]
Pregabalin (>300mg/day)	CrCl 30-59 mL/min	NS	[348]
Pregabalin (>150mg/day)	CrCl 15-29 mL/min	NS	[348]
Pregabalin (>75mg/day)	CrCl < 15 mL/min	NS	[348]
Temazepam (>15 mg/day)		≥ 65	[308,344]
Temazepam (>15 mg/day)		≥ 75	[361]
Temazepam (>30 mg/day)		≥ 65	[323]
Triazolam (>0.25 mg/day)		≥ 65	[308,342,344]
Triazolam (>0.25 mg unit dose)		≥ 65	[323]
Triazolam (>0.25 mg/day)		≥ 75	[361]
Triazolam (>0.125 mg/day)		≥ 65	[323]
Zaleplon (>5 mg/day)		≥ 65	[327,328]
Zolpidem (>5 mg/day)		≥ 65	[327-329]
Zolpidem (>5 mg/day)		≥ 75	[361]
Zopiclone (>3.75 mg/day)		≥ 75	[361]
Zopiclone (>3.75 mg/day)		≥ 65	[327-329]
Zopiclone (>5 mg/day)		≥ 70	[369]
Zopiclone (>7.5mg/day)		≥ 70	[370]
Zopiclone (3,75-7,5 mg)	BPSD: sleep disorders	≥ 65	[318]

Monitoring

Table A.0.36: Monitoring (Antipsychotics)

Medication/Class	Test	Age	Frequency	References
Antipsychotics	Glucose	NS	Annual	308
			3-4 months after starting therapy	331
	Weight	NS	Annual	308
			3-4 months after starting therapy	331
	Lipid profile	NS	3 months after starting therapy	331
Clozapine	WBC	≥ 65	NR	366
		NS	NR	390

Table A.0.37: Monitoring (mood stabilisers)

Medication/Class	Test	Age	Frequency	References
Carbamazepine	AST, ALT	NS	Baseline and yearly	386
			Annual	379
	LFT	NS	Annual	355
	FBC	NS	Baseline, monthly for 3 months, and yearly	386
			Annual	355,379
			Baseline and periodically	307
		≥ 65	Weekly during the first month of therapy, at least monthly during the next 5 months of therapy, and at least every 6 months thereafter	321
	Carbamazepine level	NS	Annual	355,379
		≥ 65	Every 6 months	321
		NS	2-4 weeks after initiation, with changing clinical status, and yearly	386
		NS	Every 6 months	307
Valproate	LFT	NS	Every 3 months	339
			Annual	355
			First 6 months of therapy	331
	AST of ALT	NS	Baseline, every 2 months for 6 months, and yearly	386
	FBC	NS	Annual	355,386
			First 6 months of therapy	331
	Valproate level	NS	Annual	355
		NS	At 2-4 weeks After initiation, with changing clinical status, and yearly	386
		≥ 65	Every 6 months	321
		NS	Every 6 months	307,331
Lithium	lithium level	NS	Annual	355,379
		NS	Every 3 months	47,339
		NS	Every 6 months	29,307,331
		≥ 65	Every 3 months	321
		≥ 65	Every month	321
		≥ 65	NR	366
		NS	2-4 weeks after initiation, with changing clinical status, and yearly	386
	TFT	NS	Annual	339,355
		≥ 65	NR	366
		NS	Every 6 months	331

	TSH	NS	Baseline, 3 and 6 month and yearly	[386]
		≥ 65	Every 6 months	[321]
	Ca and Mg	≥ 65	NR	[366]
	Na and K^+	NS	Annually	[355]
	FBC	NS	Baseline, 1 month after stabilized, and yearly	[386]
			Annual	[379]
	Creatinine	NS	Baseline, 1 month after stabilized, and yearly	[386]
		NS	Annual	[355,379]
		≥ 65	Every 3 months	[321]
	Renal function	≥ 65	NR	[366]
	Urinalysis	NS	Annual	[355]

Table A.0.38: Monitoring (ADHD medications)

Medication/Class	Test	Age	Frequency	References
Methylphenidate	Growth chart (height and weight)	Children	NR	[377]

Table A.0.39: Monitoring (Sedative, hypnotics and anxiolytics)

Medication/Class	Test	Age	Frequency	References
Phenobarbital	AST of ALT	NS	at Baseline and every 6 months	[386]
	CBC	NS	at Baseline and every 6 months	[386]
	Phenobarbital Level	NS	at 2-4 wk After initiation, with changing clinical status, and yearly	[386]

Omission

Table A.0.40: Omission

Medication/Class	Condition	Age	References
Acetylcholinesterase inhibitor	Mild- moderate Alzheimer's dementia	≥ 65	304
	Lewy Body dementia	≥ 65	304
Antidepressants	Moderate/severe depressive symptoms lasting at least three months	≥ 65	325
Non-TCA Antidepressants	Major depressive symptoms.	≥ 65	304
SSRI	Persistent severe anxiety that interferes with independent functioning.	≥ 65	304
SSRI first line	Depression	NS	347
Mood stabilisers	on antidepressants for acute bipolar depression	Adult	331
Lithium OR Valproate OR Carbamazepine	on lamotrigine and SSRI in bipolar disorder	Adult	331

Other inappropriate prescribing indicators

Table A.0.41: Other inappropriate prescribing indicators

Class	Indicator	Age	References
Antidepressants	Tricyclic antidepressants as first-line treatment of depression.	≥ 65	304
	Tricyclic antidepressants as first-line treatment of depression.	≥ 45	346
	Continued treatment for depression in spite of lacking indication.	≥ 65	366
	Discontinuation of antidepressant, which leads to withdrawal symptoms	≥ 65	366
	Tricyclic agents in combination with anticholinergic agents in patient with Nocturnal Enuresis	children	377
	Tricyclic agents as a first-line treatment with NOCTURNAL ENURESIS	children	377
	Tricyclic antidepressants except in case of severe depression or in low dose for neuropathic pain	≥ 65	324
	Patient diagnosed with acute bipolar depression is prescribed antidepressant monotherapy	Adult	331
Antipsychotics	Risperidone continued following discharge without follow-up to a patient with dementia	≥ 75	381
	Phenothiazines as first-line treatment	≥ 65	304
	Neuroleptics as hypnotics, unless sleep disorder is due to psychosis or dementia	≥ 65	304
	Prescribing older antipsychotic to a patient with Parkinsonian and mild cognitive impairment and mild to moderate agitation in the evening	≥ 75	381
Mood stabilisers	Lithium dose not adjusted or omitted in a patient with a lithium concentration above the therapeutic range (>1. - mmol l-1)	NS	35
	Lithium prescribed in conjunction with newly prescribed nonsteroidal anti-inflammatory drugs without dose adjustment or increased monitoring	NS	35
	Lithium therapy prescribed in conjunction with newly prescribed loop or thiazide diuretics without dose adjustment or increased monitoring	NS	35
	Patient treated with Electro-convulsive therapy (ECT) in bipolar disorder and with lithium dose NOT stopped or reduced	Adult	331
	Patient treated with lithium in bipolar disorder does NOT have a serum level 0.8–1.1 mmol/L	Adult	331
	Patient on lithium in bipolar disorder and with lithium serum level [1.5 mmol/L) Has lithium NOT discontinued	Adult	331
	In bipolar disorder, Patient who has discontinued lithium, does NOT have a recorded gradual reduction of lithium dose over at least 4 weeks	Adult	331
	Patient treated with divalproex in bipolar disorder does NOT have a serum level of 400–700 mmol/L	Adult	331
Others	Patient on a monotherapy regimen for the Acute management of depressive bipolar disorder NOT taking Lithium OR Lamotrigine	Adult	331

	OR Quitiepine OR Divalproex OR Lurasidone OR Carbamazepine OR Olanzapine OR ECT		
	Patient on a monotherapy regimen for the Acute management of depressive bipolar disorder taking Gabapentin OR Aripiprazole OR Ziprasidone	Adult	[331]
	Patient on combination therapy for the Acute management of depressive bipolar disorder taking adjunctive Ziprasidone OR Levetiracetam	Adult	[331]
	Three or more psychotropic drugs on an as required (PRN) basis.	NS	[278]
	Patient treated with lamotrigine and a second agent in bipolar disorder Is NOT prescribed Lithium OR Quetiapine OR Divalproex	Adult	[331]
	Patient treated with lithium and a second agent in bipolar disorder Is NOT prescribed	Adult	[331]
	Lamotrigine OR Quetiapine OR SSRI OR Bupropion OR Divalproex OR Olanzapine OR Risperidone OR MAOI OR Aripiprazole OR Ziprasidone OR Lurasidone OR Pramipexole OR Venlafaxine OR TCA"	Adult	[331]
	Patient treated with quetiapine and treated with a second agent in bipolar disorder Is NOT prescribed Lamtorigine OR SSRI OR Lithium OR Divalproex	Adult	[331]

Appendix (4) Participation flyers

Appendix (5) Introductory email

MANCHESTER 1824
The University of Manchester

Development and validation of prescribing safety indicators related to mental health disorders and medications using the Delphi technique

MENTAL HEALTH EXPERTS NEEDED

We are recruiting participants to be part of an expert panel to agree a list of prescribing safety indicators related to mental health medications and conditions. These indicators can be described as statements of potentially hazardous prescribing and drug monitoring that may place patients at risk of harm. As an example of potential prescribing safety indicator "antipsychotic prescribed to a patient with dementia or BPSD but not serious mental illness (increased risk of stroke and mortality)".

Whilst prescribing safety indicators have been developed for use across primary care and hospital settings, and form part of national medicines optimisation strategies, as well as being used in a national medication safety dashboard to inform safer prescribing. No prescribing safety indicators have been developed specifically for patients with mental illness.

We are looking for qualified health care professionals with at least 5 years' experience, who also have experience and interest in prescribing and/or medication management and safety for patients with mental illness. If you think that you fit these criteria and would like to know more then please do get in touch as we would like to hear from you!

As an expert panel participant, you would be asked to complete a series of three online questionnaires to rate your level of agreement with a list of potential prescribing safety indicators. You can complete the questionnaires anywhere you wish and we expect the total amount of time you will spend in the study as no more than 45 minutes per questionnaire.

All participants will be compensated for their time.

The purpose of this email is to gather expressions of interest for this project, which forms part of a PhD programme. Once we have enough responses, we will contact those who expressed an interest in the project to supply more detailed information about the study and find out whether they would like to take part.

If you are interested in learning more please contact the Principal Investigator:
Wael Y. Khawagi (PhD student)
Tel: 0161 306 0629
Email: wael.khawagi@postgrad.manchester.ac.uk

Chief investigator and PhD project supervisor: Dr. Richard Keers

Appendix (6) Invitation email

Development and validation of prescribing safety indicators related to mental health disorders and medications using the Delphi technique

Dear #First name Surname#,

My name is Wael Khawagi, a PhD student in the University of Manchester, Division of Pharmacy. I would like to invite you to participate in a research study that I am completing as part of my PhD studies, which aims to develop and validate a suite of prescribing safety indicators related to mental health conditions and medications.

Prescribing safety indicators can be described as statements of potentially hazardous prescribing or drug monitoring practice that may place patients at risk of harm. As an example of potential prescribing safety indicator "antipsychotic prescribed to a patient with dementia or BPSD but not serious mental illness *(increased risk of stroke and mortality)".*

Whilst prescribing safety indicators have been developed for use across primary care and hospital settings, and form part of national medicines optimisation strategies, as well as being used in a national medication safety dashboard to inform safer prescribing. No prescribing safety indicators have been developed specifically for patients with mental illness.

To achieve the aim of this study, we are using the Delphi method, which is used to develop a consensus of opinion between a panel of experts using electronic surveys to indicate the extent to which each of these indicators would be considered appropriate to be used to asses prescribing safety in populations with mental illness.

We are specifically looking for qualified healthcare professionals with at least 5 years' experience, who also have experience in prescribing and/or medicines management and safety for patients with mental illness.

The study will involve a series of **three online questionnaires**:

- In the first-round questionnaire, you will be asked to comment on a set of indicators and rate your level of agreement with each indicator to assess prescribing and drug monitoring safety.
- In the second round which will happen later, you will receive feedback on the group ratings and comments from the first round before being asked to re-rate the indicators again, in light of the first-round group ratings and comments.
- In the third and final round you will be asked to rate the final list of the approved prescribing safety indicators, based on the severity of their consequences for patients if not addressed and the likelihood they will occur in clinical practice.

The first online questionnaire is likely to take approximately 45 minutes to complete. Please note that you can complete the questionnaire anywhere, and we ask that you complete and submit within 4 weeks of being sent the electronic link.

You will be compensated for your time after you complete the three survey rounds.

Your responses will be anonymous to the other expert panel participants; the identity of each member will be known only to the research team.

I invite you to go through the participant information sheet (attached) before making any decisions about whether you want to take part, to help you understand the purpose of the study and find out more about what you will be asked to do if you took part.

We hope that you will accept our invitation to take part in this study. You can respond to this invitation and indicate your willingness to take part directly by going to the link below, where you will be asked to complete a short consent form and complete the survey. The link is:

#Link#

If you would like any further information, please do not hesitate to contact me.

Thank you for your time and consideration.

Yours sincerely,

Wael Yahya A Khawagi
PhD Student
Division of Pharmacy and Optometry
School of Health Sciences
Faculty of Biology, Medicine and Health
The University of Manchester
Stopford Building, Oxford Road, Manchester, M13 9PT
Tel: 0161 306 0629
Email: wael.khawagi@postgrad.manchester.ac.uk

Chief investigator and PhD project supervisor: Dr. Richard Keers

Appendix (7) Participant Information Sheet

Development and validation of prescribing safety indicators related to mental health disorders and medications using Delphi technique

Participant Information Sheet (PIS)

This PIS should be read in conjunction with The University privacy notice

You are being invited to take part in a research study to develop and validate prescribing safety indicators related to mental health conditions and medications. Before you decide whether to take part, it is important for you to understand why the research is being conducted and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Please ask if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for taking the time to read this.

Who is conducting the research?

The research is funded by the University of Manchester. The researchers involved in this study are:

- **Wael Khawagi,** (PhD Student/Principal investigator, The University of Manchester)
- **Dr. Richard Keers**, (Clinical Lecturer in Pharmacy/Chief investigator, The University of Manchester)
- **Dr. Douglas Steinke,** (Senior Lecturer in Pharmacoepidemiology, The University of Manchester)
- **Dr. Sarah Pontefract,** (Lecturer in Clinical Pharmacy and Therapeutics, University of Birmingham)
- **Joanne Nguyen,** (Honorary Clinical Lecturer, The University of Manchester)

What is the purpose of the research?

The overall aim of this study is to develop and validate a list of prescribing safety indicators specific for mental health conditions and medications. To achieve this aim, we are using the Delphi method, which is used to develop a consensus of opinion between a panel of experts using electronic surveys to indicate the extent to which each of these indicators would be considered appropriate to be used to asses prescribing safety in populations with mental illness.

Prescribing safety indicators can be described as statements of potentially hazardous prescribing and drug monitoring practice that may place patients at risk of harm. As an example of potential prescribing safety indicator "antipsychotic prescribed to a patient with dementia or BPSD but not serious mental illness *(increased risk of stroke and mortality)".* However, prescribing safety indicators are not always errors. Therefore, the role of a prescribing safety indicator is to prompt medication review to ensure the potentially hazardous prescribing is the best option for the patient and it is in their overall best interest.

Whilst prescribing safety indicators have been developed for use across primary care and hospital settings, and form part of national medicines optimisation strategies, as well as being used in a national medication safety dashboard to inform safer prescribing. No prescribing safety indicators have been developed specifically for patients with mental illness.

Why have I been invited to take part?

You have been selected as a potential participant because you are a qualified healthcare professional for a minimum of five years, with experience and interest in prescribing and/or medicines management and safety for patients with mental illness.

What would I be asked to do if I take part?

If you wish to participate, the study will involve a three-round online questionnaire (an optional paper questionnaire can be arranged and sent by post):

In the first round, you will be asked to rate your level of agreement to a list of prescribing safety indicators to be used to assess the safety of mental health prescribing and drug monitoring. Each indicator has 5 options, which range from 'strongly agree' to 'strongly disagree'. Use your clinical experience and judgement to rate the extent of your agreement that each indicator meets the criteria presented in the box below. If you feel that you do not have the expertise to rate a particular indicator, please record 'neutral'.

For each indicator, rate your level of agreement that they meet the following criteria:

A. The indicator describes a potentially hazardous prescribing or drug monitoring practice that may put patients at risk of harm.

B. The indicator describes a prescribing practice that is common in the UK.

You can add comments below each indicator if you wish. In addition, you are welcome to suggest new indicators at the end of each section of the questionnaire. The questionnaire is divided into sections, each section is for a specific therapeutic class (e.g. antipsychotics, antidepressants).

- **The second round** will follow approximately 1-2 months after round one, where you will then be asked to rate a revised set of prescribing safety indicators from round one in light of the first-round expert panel ratings and comments. You will not be invited to add new indicators at that stage.
- **The third and final round** will follow 1-2 months after the second round, and you will then be asked to rate a final set of prescribing safety indicators based on the likely severity of outcome if not resolved and the likelihood of indicator occurring in clinical practice.

What is the duration of the research?

For each questionnaire round you will have a maximum of 4 weeks to complete and submit the questionnaire upon receiving it. After questionnaires have been submitted for a single round, the next questionnaire will be prepared in 2 to 4 weeks and sent to you to start the next round.

The first online questionnaire is likely to take approximately 45 minutes to complete.

What will happen to my personal information?

In order to undertake the research project, we will need to collect the following personal information:

- Your Name
- Work email and telephone number
- Years of experience since qualification
- -Geographic region
- Profession and job title

Only the study team at the University of Manchester will have access to this information. Your name, telephone number and email address will be collected strictly for the purpose of sending questionnaires and reminders, and to inform you about the summary of findings if you wish. However, profession/job title, geographic area and years of experience will be published or reported anonymously.

We are collecting and storing this personal information in accordance with the General Data Protection Regulation (GDPR) and Data Protection Act 2018 which legislate to protect your personal information. The legal basis upon which we are using your personal information is "public interest task" and "for research purposes" if sensitive information is collected. For more information about the way we process your personal information and comply with data protection law please see our Privacy Notice for Research Participants.

The University of Manchester, as Data Controller for this project, takes responsibility for the protection of the personal information that this study is collecting about you. In order to comply with the legal obligations to protect your personal data the University has safeguards in place such as policies and procedures. All researchers are appropriately trained and your data will be looked after in the following way:

The study team at the University of Manchester will have access to your personal identifiable information, that is data which could identify you, and will be retained until the end of the study, or until you are informed about the study findings if you chose to. This information will be password protected and stored on the secure University of Manchester server. No personal data will be held or accessed in non-encrypted personal computers.

You have a number of rights under data protection law regarding your personal information. For example, you can request a copy of the information we hold about you. This is known as a Subject Access Request. If you would like to know more about your different rights, please consult our privacy notice for research and if you wish to contact us about your data protection rights, please email dataprotection@manchester.ac.uk or write to The Information Governance Office, Christie Building, University of Manchester, Oxford Road, M13 9PL. at the University and we will guide you through the process of exercising your rights. You also have a right to complain to the Information Commissioner's Office, Tel 0303 123 1113

What will happen to the research data?

All the generated research data will be exported from the encrypted Select Survey website into a Microsoft Excel sheet for analysis. This sheet will only be accessed by the study team at the University of Manchester since it will contain raw and personal data. It will be password protected and stored on the secure University of Manchester Research Data Storage, and it will only be accessed using university encrypted computers.

Aggregated and anonymous research data may be looked at by all the research team and will be stored on the secure University of Manchester personal data storage (P drive) and on a secure, cloud-based file sharing and synchronisation tool between internal and external members of the research team.

Findings from the analysis may be published in report(s), journal article(s) and/or conference presentation(s) which will not be identifiable to any particular participant.

Anonymised survey data will be retained for a minimum of 5 years as essential documents.

How will confidentiality be maintained?

Your identity and responses will be anonymous and no other panel member participants involved in this study will know your identity. Your identity will be known only to the research team to make sure that you are eligible for the study and for the purpose of follow up.

The study team at the University of Manchester will have access to your personal identifiable information, that is data which could identify you, and will be retained until the end of the study. This information will be password protected and stored on the secure University of Manchester server. No personal data will be held or accessed in non-encrypted personal computers.

What are the benefits and risks to me in taking part?

There are no direct benefits attributed to participants taking part in this project. However, it is anticipated that you may reflect on the survey exercise and identify important targets for improvement to local prescribing and drug monitoring practices, as well as benefiting from the satisfaction of knowing that you have contributed to the development of bespoke prescribing safety indicators for those with mental illness that may be applied on a wider scale in future.

It is highly unlikely that you will experience any dangers, discomfort or inconvenience from taking part in the research.

What happens if I do not want to take part or if I change my mind?

It is up to you to decide whether or not to take part. Taking part in the research is entirely voluntary; this means it is completely up to you to decide whether or not to join the study. If you do decide to take part you will be given this information sheet to keep and be asked to complete a consent form (which is embedded into the first page of the questionnaire). If you decide to take part you are still free to withdraw at any time without giving a reason and without detriment to yourself. However, it will not be possible to remove your data from the project once it has been anonymised and forms part of the dataset, one week after submission, as we will not be able to identify your specific data. This does not affect your data protection rights.

Will I be paid for participating in the research?

Yes, you will receive **£50** in shopping vouchers in the mail using recorded delivery as compensation for your time, once you have completed all three survey rounds.

Where will the research be conducted?

The online questionnaire was designed using the university approved and secure tool *SelectSurvey.net.* You can complete the questionnaire at any time or place convenient to you within 4 weeks of receiving this invitation. Once surveys are completed and submitted, data analysis will be conducted in the University of Manchester by the research team.

Will the outcomes of the research be published?

The results of the study will be analysed and used to contribute to one or more chapters of Wael Khawagi's PhD thesis. The results will be published in academic journals and presented at professional/academic conferences. You will not be identified from any reported/published data.

Who has reviewed the research project?

This project has been reviewed by the University of Manchester Proportionate Research Ethics Committee.

What if I want to make a complaint or if I have any inquiry?

If you have a minor complaint or if you have any inquiry then please contact the researcher(s) in the first instance.

- **Wael Y. Khawagi,** PhD Student/Principal investigator

Tel: 0161 306 0629

Email: wael.khawagi@postgrad.manchester.ac.uk

- **Dr. Richard Keers,** Clinical Lecturer in Pharmacy/Chief investigator

Email: richard.keers@manchester.ac.uk

- **Dr. Douglas Steinke,** Senior Lecturer in Pharmacoepidemiology

Email: douglas.steinke@manchester.ac.uk

Formal Complaints

If you wish to make a formal complaint or if you are not satisfied with the response you have gained from the researchers in the first instance then please contact
The Research Governance and Integrity Manager, Research Office, Christie Building, University of Manchester, Oxford Road, Manchester, M13 9PL, by emailing:
research.complaints@manchester.ac.uk or by telephoning 0161 275 2674.

What do I do now?

If you agree to take part in this research, then please respond to this invitation directly by going to the survey link provided in the email to complete the consent section before starting the questionnaire.

This Project Has Been Approved by the University of Manchester's Proportionate Research Ethics Committee

[Reference 2019-4632-9361]

Appendix (8) Proportionate UREC approval

Research Governance, Ethics and Integrity
2nd Floor Christie Building
The University of Manchester
Oxford Road
Manchester
M13 9PL
Tel: 0161 275 2206/2674
Email: research.ethics@manchester.ac.uk

Ref: 2019-4632-9361

22/02/2019

Dear Mr Wael Khawagi, Dr Richard Keers, Dr Douglas Steinke

Study Title: Mental health prescribing safety indicators

Proportionate UREC

I write to thank you for submitting the final version of your documents for your project to the Committee on 11/02/2019 15:24. I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form and supporting documentation as submitted and approved by the Committee.

Please see below for a table of the title, version numbers and dates of all the final approved documents for your project:

Document Type	File Name	Date	Version
Letters of Permission	invitation email (Supplementary 3)	21/01/2019	5
Additional docs	Protocol.V6	30/01/2019	6
Additional docs	Survey	30/01/2019	1
Letters of Permission	Introductory email (Supplementary 1)	30/01/2019	3
Advertisement	Flyer Portrait V5 (Supplementary2)	30/01/2019	5
Advertisement	Flyer Landscape V2 (Supplementary2)	30/01/2019	2
Data Management Plan	DMP V6	11/02/2019	6
Participant Information Sheet	PIS (Supplementary 4) V7	11/02/2019	7
Additional docs	UREC Comments	11/02/2019	1

This approval is effective for a period of five years however please note that it is only valid for the specifications of the research project as outlined in the approved documentation set. If the project continues beyond the 5 year period or if you wish to propose any changes to the methodology or any other specifics within the project, an application to seek an amendment must be submitted for review. Failure to do so could invalidate the insurance and constitute research misconduct.

You are reminded that, in accordance with University policy, any data carrying personal identifiers must be encrypted when not held on a secure university computer or kept securely as a hard copy in a location which is accessible only to those involved with the research.

Reporting Requirements:

You are required to report to us the following:

1. Amendments: Guidance on what constitutes an amendment
2. Amendments: How to submit an amendment in the ERM system
3. Ethics Breaches and adverse events
4. Data breaches
5. Notification of progress/end of the study

Feedback

It is our aim to provide a timely and efficient service that ensures transparent, professional and proportionate ethical review of research with consistent outcomes, which is supported by clear, accessible guidance and training for applicants and committees. In order to assist us with our aim, we would be grateful if you would give your view of the service that you have received from us by completing a **UREC Feedback Form**. Instructions for completing this can be found in your approval email.

We wish you every success with the research.

Yours sincerely,

Mrs Genevieve Pridham

Secretary to Proportionate UREC

Appendix (9) ISAC approval

ISAC EVALUATION OF PROTOCOLS FOR RESEARCH INVOLVING CPRD DATA

FEEDBACK TO APPLICANTS

CONFIDENTIAL			***by e-mail***
PROTOCOL NO:	19_234A		
PROTOCOL TITLE:	Examining variations in prescribing safety for patients with mental illness in UK primary care		
APPLICANT:	Dr Douglas Steinke University of Manchester Douglas.steinke@manchester.ac.uk		
APPROVED ☒	**APPROVED WITH COMMENTS (resubmission not required)** ☐	**REVISION/ RESUBMISSION REQUESTED** ☐	**REJECTED** ☐
INSTRUCTIONS: ***Protocols with an outcome of 'Approved' or 'Approved with comments' do not require resubmission to the ISAC.***			
DATE OF ISAC FEEDBACK:	10/02/2021		
DATE OF APPLICANT FEEDBACK:			

For protocols approved from 01 April 2014 onwards, applicants are required to include the ISAC protocol in their journal submission with a statement in the manuscript indicating that it had been approved by the ISAC (with the reference number) and made available to the journal reviewers. If the protocol was subject to any amendments, the last amended version should be the one submitted.

Guidance on resubmitting applications, or making amendments to approved protocols, can be found on the CPRD website at https://cprd.com/research-applications.

Appendix (10) Evidence-Based Summaries for each mental health related prescribing safety indicators (MH-PSIs)

Evidence-Based Summaries

Mental health related prescribing safety indicators (MH-PSIs)

(This is a draft version that needs to be reviewed by experts)

Indicator P1: Prescribing antipsychotic with a QT-prolonging drug

What is the risk to patients?

Most antipsychotics drugs are associated with ECG changes and some are causally linked to serious ventricular arrhythmia and sudden cardiac death. These medications block cardiac potassium channels and are linked to prolongation of the cardiac QT interval, a risk factor for the ventricular arrhythmia torsades de pointes, which is often fatal.[1] Many non-antipsychotics drugs are also linked to QT prolongation which pose an additional risk of torsades de pointes.[1]

What evidence is there that this pattern of prescribing is harmful?

Studies have suggested that the use of most antipsychotics is associated with increased risk ventricular arrhythmia and an increase in the rate of sudden cardiac death.[2-4] A UK based cohort study found that antipsychotic users had an increased risk of cardiac mortality, all-cause mortality, and sudden cardiac death compared to a psychiatric nonuser cohort.[2] Another case-crossover study using a nation-wide population-based sample obtained from Taiwan's National Health Insurance Research Database found that antipsychotic use was associated with a 1.53-fold increased risk of ventricular arrhythmia (VA) and/or sudden cardiac death.[3]

Many non-antipsychotics drugs are also linked to QT prolongation which pose an additional risk of torsades de pointes.[1] A study found that the risk of QT prolongation appeared to be additive when increasing number of medications with a known risk of QT prolongation.[5]

What evidence is there that correcting this pattern of prescribing leads to reduction in patient harm?

No studies evaluating the effects of stopping antipsychotics or another QT prolonging drugs to reduce the risk of QT prolongation were found in this review.

The British Heart Rhythm Society Clinical Practice Guidelines on the Management of Patients Developing QT Prolongation on Antipsychotic Medication suggest actions to be taken according to the QT interval, with one of the recommendations to stop the suspected medication if the QTc >500 ms.[6]

According to the Maudsley prescribing guidelines and the British Heart Rhythm Society, prescribers should prescribe the lowest dose possible and avoid polypharmacy/metabolic interactions, perform ECG on admission to in-patient unit, before discharge and at yearly check-up, and consider measuring QTc within a week of achieving a therapeutic dose of a moderate-/high-risk antipsychotic.[1,6]

NICE guideline recommends to offer ECG before starting antipsychotic medication if:[7]

- Specified in the summary of product characteristics (SPC)

- A physical examination has identified specific cardiovascular risk (such as diagnosis of high blood pressure)
- There is a personal history of cardiovascular disease or
- The service user is being admitted as an inpatient.

References

1. Taylor DM, Barnes TRE, Young AH. *The Maudsley Prescribing Guidelines in Psychiatry.* Hoboken, NJ: Wiley Blackwell; 2018.
2. Murray-Thomas T, Jones ME, Patel D, et al. Risk of mortality (including sudden cardiac death) and major cardiovascular events in atypical and typical antipsychotic users: a study with the general practice research database. *Cardiovasc Psychiatry Neurol.* 2013;2013:247486-247486.
3. Wu CS, Tsai YT, Tsai HJ. Antipsychotic drugs and the risk of ventricular arrhythmia and/or sudden cardiac death: a nation-wide case-crossover study. *Journal of the American Heart Association.* 2015;4(2):e001568.
4. Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Atypical antipsychotic drugs and the risk of sudden cardiac death. *New England Journal of Medicine.* 2009;360(3):225-235.
5. Meid AD, Bighelli I, Mächler S, et al. Combinations of QTc-prolonging drugs: towards disentangling pharmacokinetic and pharmacodynamic effects in their potentially additive nature. *Therapeutic Advances in Psychopharmacology.* 2017;7(12):251-264.
6. Lambiase PD, de Bono JP, Schilling RJ, et al. British Heart Rhythm Society Clinical Practice Guidelines on the Management of Patients Developing QT Prolongation on Antipsychotic Medication. *Arrhythm Electrophysiol Rev.* 2019;8(3):161-165.
7. National Institute for Health and Care Excellence. Psychosis and schizophrenia in adults: prevention and management: Clinical guideline [CG178]. National Institute for Health and Care Excellence Web site. https://www.nice.org.uk/guidance/cg178/resources/psychosis-and-schizophrenia-in-adults-prevention-and-management-pdf-35109758952133. Published 2014. Accessed April 27, 2021.

Indicator P2: Risperidone prescribed to a patient with dementia and without psychotic illness for more than 6 weeks

What is the risk to patients?

Antipsychotics are sometimes used to treat the behavioural and psychological symptoms of dementia (BPSD). However, there is an increased risk of cerebrovascular adverse events and death with antipsychotic medications when used to treat patients with dementia. Risperidone is licensed for this indication specifically for up to 6 weeks.

What evidence is there that this pattern of prescribing is harmful?

The Banerjee report published in 2009 estimated that there are 180,000 people with dementia treated with antipsychotic medication in England per year. Of these, 1,800 may die and an additional 1,620 suffer a cerebrovascular adverse event per year as result of the antipsychotics use.[1] For every 1,000 people living with dementia who have hallucinations, delusions or agitation and who take an antipsychotic for 6 to 12 weeks, 12 people will have a stroke because they take an antipsychotic, and 11 people will die because they take an antipsychotic.[2]

A retrospective case-controlled study published in 2015 found that the risk of death due to antipsychotic use in patients with dementia is higher than previously estimated. The study involved 46,008 patients and found that patients on haloperidol, risperidone, olanzapine and quetiapine had an increased mortality risk. Risperidone increased risk of death by 3.7%, with number needed to harm (NNH)= 27.[3]

The dementia treatment guideline from NICE states that antipsychotics should only be prescribed to patients experiencing agitation, hallucinations or delusions that are causing them severe distress, or at risk of harming themselves or others. Out of the available anti-psychotics, risperidone and haloperidol are the only ones licensed specifically for treatment of aggression in Alzheimer's disease. The marketing authorisation for risperidone only covers short-term treatment (up to 6 weeks) of persistent aggression in people with moderate to severe Alzheimer's disease unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others.[2,4]

What evidence is there that correcting this pattern of prescribing leads to reduction in patient harm?

A Cochrane systematic review of withdrawal versus continuation of chronic antipsychotic drugs for behavioural and psychological symptoms in older people with dementia suggested that withdrawal of antipsychotic medication can be completed successfully without worsening behaviour in patients with Alzheimer's dementia, and that withdrawal schedules should form part of clinical practice.[5]

NICE guidelines recommend that antipsychotics should be considered for non-cognitive symptoms in dementia only if the person is severely distressed or there is an immediate risk of harm to

themselves or others. If using antipsychotics if considered, it is recommended that the lowest effective dose is prescribed and they be used for the shortest possible time with reassessment of the person at least every 6 weeks to determine whether they still need medication.[2]

References

1. Banerjee S. The use of antipsychotic medication for people with dementia : time for action. An independent report commissioned and funded by the Department of Health. https://www.rcpsych.ac.uk/pdf/Antipsychotic%20Bannerjee%20Report.pdf Published 2009. Accessed July 4, 2018.
2. National Institute for Health and Care Excellence. Dementia: assessment, management and support for people living with dementia and their carers. NICE guideline Web site. www.nice.org.uk/guidance/ng97. Published 2018. Accessed January 18, 2021.
3. Maust DT, Kim HM, Seyfried LS, et al. Antipsychotics, Other Psychotropics, and the Risk of Death in Patients With Dementia: Number Needed to Harm. *JAMA Psychiatry.* 2015;72(5):438-445.
4. Joint Formulary Committee. British National Formulary (online). BMJ Group and Pharmaceutical Press. http://www.medicinescomplete.com. Accessed July 9, 2021.
5. Declercq T, Petrovic M, Azermai M, et al. Withdrawal versus continuation of chronic antipsychotic drugs for behavioural and psychological symptoms in older people with dementia. *Cochrane Database of Systematic Reviews.* 2013(3).

Indicator P3: Prescribing more than one regular antipsychotic for 3 months or more, excluding clozapine augmentation

What is the risk to patients?

Prescribing multiple antipsychotics may increase the risk of adverse effects and increase mortality.[1]

What evidence is there that this pattern of prescribing is harmful?

There are a number of published reports of clinically significant adverse effects associated with use of combination antipsychotics, such as an increased prevalence of extrapyramidal symptoms, severe extrapyramidal symptoms, increased metabolic adverse effects and diabetes, sexual dysfunction, increased risk of hip fracture, paralytic ileus, grand mal seizures, prolonged QTc interval and arrhythmias.[1]

A cohort study of patients with schizophrenia followed patients prospectively over a 10-year period and found that receiving more than one antipsychotic concurrently was associated with substantially increased mortality. This risk was attributed to the co-prescription of antipsychotic medication rather than the more severe or refractory illness for which the combined antipsychotics may have been prescribed.[2] Another study, which involved follow-up of 99 patients with schizophrenia for 17-year period, found that those prescribed three antipsychotics simultaneously were twice as likely to die as those who had been prescribed only one.[3]

There is a lack of robust evidence confirming whether treatment with multiple antipsychotics is superior to a single antipsychotic.[1] The British Association for Psychopharmacology (BAP) guidelines for the treatment of schizophrenia recommend that regular combined antipsychotic medication should not be prescribed routinely, except for short periods when switching from one antipsychotic to another. However, clozapine augmentation strategies often involve combining antipsychotics and this approach is considered by BAP guidelines if an adequate trial of clozapine monotherapy proves to be of limited efficacy. ECG monitoring is recommended when a trial of combined antipsychotics is undertaken.[4]

What evidence is there that correcting this pattern of prescribing leads to reduction in patient harm?

One study found that in patients with schizophrenia receiving multiple antipsychotics, switching to monotherapy resulted in improvements in attention, daily living and work skills.[5] In addition, another study reported that changing patients' regimens from two or more antipsychotics to a single antipsychotic can be successful, where the majority (77.2%) of the patients showed improvement or remained stable.[6]

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Indicator P4: Antipsychotic other than quetiapine, aripiprazole or clozapine prescribed to a patient with Parkinson's disease or with Lewy Body Disease

What is the risk to patients?

Use of an antipsychotic other than quetiapine, aripiprazole or clozapine in patients with Parkinson's or Lewy Body disease increases the risk of severe extrapyramidal symptoms.

What evidence is there that this pattern of prescribing is harmful?

Parkinson's disease (PD) and dementia with Lewy bodies (DLB) share clinical and pathological similarities. The defining features are motor parkinsonism and cognitive impairment, often accompanied by visual hallucinations, fluctuating consciousness, autonomic and sleep disturbances, and a number of other non-motor symptoms.[1] Together they can be referred to as Lewy body disease. The neuropsychiatric manifestations may respond to treatment with antipsychotic medication. However, most antipsychotics are dopamine antagonists and therefore may worsen motor functioning and may be associated with increased mortality.[2] Quetiapine, aripiprazole and clozapine appear to be less likely to induce parkinsonism.[3-6]

NICE guidelines recommended the use of quetiapine and clozapine to treat hallucinations and delusions in people with Parkinson's disease.[7]

What evidence is there that correcting this pattern of prescribing leads to reduction in patient harm?

In has been reported that drug-induced parkinsonism usually resolves within weeks to months after stopping the offending drug. However, it may persist or progress in 10-50% of patients.[8] The Maudsley Prescribing Guidelines indicates that there are several options to manage parkinsonism in people on antipsychotics. Including reducing the dose, changing to an antipsychotics with a lower propensity for parkinsonism (such as quetiapine, aripiprazole and clozapine), or prescribe an anticholinergic.[6]

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Indicator P5: Selective serotonin reuptake inhibitor (SSRI) or serotonin and norepinephrine reuptake inhibitor (SNRI) prescribed with an NSAID or antiplatelet agent to a patient without gastrointestinal protection

What is the risk to patients?

The use of SSRIs and SNRIs with concomitant NSAIDs or antiplatelet agents has been found to increase the risk of upper gastrointestinal bleeding.[1-5] While adding gastrointestinal protection did not increase the risk.[2,5,6]

What evidence is there that this pattern of prescribing is harmful?

Serotonin is released from platelets in reaction to vascular trauma and stimulates vasoconstriction and a change in the shape of the platelets that leads to aggregation. SSRIs and SNRIs inhibit the serotonin transporter, which is responsible for the uptake of serotonin into platelets. Therefore, the use of SSRIs and SNRIs diminish platelet serotonin, causing lower capability to procedure clots and consequently increase the risk of bleeding.[7,8] They may also increase gastric acid secretion and consequently irritate the gastric mucosa and increase the risk of bleeding.[8]

Three meta-analyses published between 2007 and 2015 of case-control and cohort studies showed that SSRI use, alone and in combination with NSAIDs, substantially increases the risk of upper gastrointestinal bleeding, and the risk is significantly elevated when SSRIs are used in combination with NSAIDs.[3-5] A meta-analysis of 16 case-control studies and six cohort studies (over a million patients) reported that the risk of upper GI bleeding to be 55% higher in patients on SSRIs compared with non-users (OR 1.55; 95% CI: 1.35-1.78). The risk of upper GI bleeding was even higher in patients on both SSRIs and NSAIDs (OR 3.72; 95% CI: 3.01-4.67) or SSRIs and antiplatelet drugs (OR 2.48; 95% CI: 1.70-3.61).[5] However it has been reported that in patients receiving acid suppressing drugs along with SSRIs and NSAIDs, no significant increase in the risk of developing upper gastrointestinal bleeding was observed. (OR 0.98; 95% CI: 0.51-1.88).[5]

In addition, a nested control study reported that the use of SSRIs and SNRIs with NSAIDs among patients not using acid-suppressing medications to increase risk of bleeding 9 folds (OR, 9.1; 95% CI, 4.8-17.3) compared with patients on acid-suppressing medications (OR, 1.3; 95% CI, 0.5-3.3). In addition, the use of SSRIs and SNRIs with antiplatelet drugs among patients not on acid-suppressing agents increase risk of bleeding 4.7 folds (OR, 4.7; 95% CI, 2.6-8.3) compared with patients on acid-suppressing medications (OR, 0.8; 95% CI, 0.3-2.5).[6]

Several other risk factors increase the risk of bleeding for people using SSRIs and SNRIs. These include older age, alcohol misuse, coronary artery disease, drug misuse, hypertension, history of gastrointestinal bleed history of stroke, history of major bleeding or predisposition to bleeding, liver disease, peptic ulcer, renal disease and smoking.[8]

What evidence is there that correcting this pattern of prescribing leads to reduction in patient harm?

If an SSRI/SNRI is required in a patient at high risk of an upper GI bleed, consider the use of a gastro-protective agent.[8] Studies have shown that acid suppressing drugs, e.g. PPIs, protect against upper GI bleeds in patients receiving combined NSAID/antiplatelet and SSRI/SNRI treatment, as described above.[2,5,6]

NICE guideline on depression indicates that SSRIs increases the risk of bleeding, especially in older people or in people taking other drugs that have the potential to damage the gastrointestinal mucosa, such as NSAIDs and antiplatelets. NICE recommends considering prescribing a gastroprotective medication in those patients.[9]

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Indicator P6: SSRI or SNRI prescribed with a direct oral anticoagulant (DOAC) or warfarin

What is the risk to patients?

The use of SSRIs and SNRIs increase the risk of various types of bleeding. Their effect is exacerbated by co-prescription with anticoagulants.[1]

What evidence is there that this pattern of prescribing is harmful?

Serotonin is released from platelets in reaction to vascular trauma and stimulates vasoconstriction and a change in the shape of the platelets that leads to aggregation. SSRIs and SNRIs inhibit the serotonin transporter, which is responsible for the uptake of serotonin into platelets. Therefore, the use of SSRIs and SNRIs diminish platelet serotonin, causing lower capability to procedure clots and consequently increase the risk of bleeding.[1,2] They may also increase gastric acid secretion and consequently irritate the gastric mucosa and increase the risk of bleeding.[1]

Warfarin

Multiple studies showed that the use of SSRI was associated with higher risk of bleeding in patients concurrently prescribed warfarin.[3-7] One study also showed that concurrent use of warfarin with SSRI or SNRI relative to warfarin alone, increase the case fatality rate after primary intracerebral haemorrhage. Warfarin combined with SSRI/SNRI was a significant independent predictor of case fatality (adjusted HR 2.10, 95% CI 1.13-3.92).[8]

DOACs

A recent population-based nested case–control study found that among patients taking DOACs the concurrent use of SSRIs was associated with increased risk of major bleeding (adjusted OR 1.68; 95% CI, 1.10–2.59).[9]

The RE-LY trial compared dabigatran with warfarin showed that co-administration with SSRIs or SNRIs increased the risk of bleeding in all treatment groups.[10] The manufacturer of dabigatran warns that the bleeding risk may be significantly increased in patients concomitantly treated with SSRIs or SNRIs.[10] When SSRIs/SNRIs were concomitantly used with rivaroxaban, higher rates of major or non-major clinically relevant bleeding were observed in all treatment groups.[11]

Limited evidence suggests that SSRIs/SNRIs with weaker affinity for the serotonin transporter might have lower risk than others.[1]

What evidence is there that correcting this pattern of prescribing leads to reduction in patient harm?

No studies evaluating the effects of stopping an SSRI/SNRI in patients receiving warfarin or a DOAC were found in this review. The Maudsley prescribing guidelines suggest to try to avoid SSRIs in patients receiving anticoagulants.[1]

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Indicator P7: prescribing citalopram, escitalopram, TCA or trazadone with QT-prolonging drugs

What is the risk to patients?

Tricyclic antidepressants (TCAs), citalopram, escitalopram, and trazodone have been reported to prolong the QTc interval. a risk factor for the ventricular arrhythmia torsades de pointes, which is often fatal.[1]

What evidence is there that this pattern of prescribing is harmful?

MHRA alert reported that citalopram and escitalopram may have an additive effect to other drugs that prolong the QT interval and that co-administration of citalopram and escitalopram with other medicines that prolong the QT interval is therefore contraindicated.[2] According to the manufacturers citalopram and escitalopram are contraindicated with other medicinal products that are known to prolong the QT-interval.[3,4]

A prospective population-based cohort study reported that starting tricyclic antidepressants as a class increased the QTc interval significantly, by 6.9 milliseconds (95% CI 3.1-10.7 milliseconds) in comparison with participants not on TCAs.[5] In addition, several case reports indicated prolonged QT and arrhythmia with the use of trazodone.[1]

What evidence is there that correcting this pattern of prescribing leads to reduction in patient harm?

No studies evaluating the effects of stopping antidepressants or another QT prolonging drugs to reduce the risk of QT prolongation were found in this review.

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Indicator P8: SSRI or SNRI prescribed to a patient with a history of peptic ulcer or bleeding disorders without gastroprotection

What is the risk to patients?

The use of SSRIs and SNRIs increase the risk of various types of bleeding including upper gastrointestinal bleeding. History of peptic ulcer or bleeding disorders increase the risk of bleeding for people using SSRIs and SNRIs.[1]

What evidence is there that this pattern of prescribing is harmful?

Serotonin is released from platelets in reaction to vascular trauma and stimulates vasoconstriction and a change in the shape of the platelets that leads to aggregation. SSRIs and SNRIs inhibit the serotonin transporter, which is responsible for the uptake of serotonin into platelets. Therefore, the use of SSRIs and SNRIs diminish platelet serotonin, causing lower capability to procedure clots and consequently increase the risk of bleeding.[1,2] They may also increase gastric acid secretion and consequently irritate the gastric mucosa and increase the risk of bleeding.[1]

Three meta-analyses published between 2007 and 2015 of case-control and cohort studies showed that SSRI use alone substantially increases the risk of upper gastrointestinal bleeding,[3-5] and that having a previous history of GI bleeding adds to the risk of upper GI bleeding (relative risk 5.0 ; 95% CI 4.1 to 6.1).[6] Manufacturers of SSRIs and SNRIs advise caution using these agents in patients with a history of bleeding disorders.[7] Clinical Knowledge Summaries (CKS) from NICE provides guidance to prescribe SSRIs and SNRIs with caution to people with a history of bleeding disorders.[8,9]

What evidence is there that correcting this pattern of prescribing leads to reduction in patient harm?

If an SSRI or SNRI is required in a patient at high risk of an upper GI bleed (e.g. history of bleeding), consider the use of a gastro-protective agent.[1] Studies have shown that acid suppressing drugs, e.g. proton pump inhibitors, help protect against upper GI bleeds in patients receiving SSRIs.[5,10]

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Indicator P9: Any sedative-hypnotic prescribed to a patient with a history of falls.

What is the risk to patients?

Sedative-hypnotics increase risk of falls, and having history of falls is also a major risk factor.[1,2] Therefore the use of sedative-hypnotics should be avoided for patients with a history of falls.

What evidence is there that this pattern of prescribing is harmful?

A meta-analysis of 22 studies from 1996 to 2007 found that the use of sedatives and hypnotics demonstrated a significant association with falls in elderly individuals with an OR=1.47 (95% CrI, 1.35-1.62).[3] A meta-analysis of 14 studies reported 1.4-fold increase the risk of hip fractures in users of any benzodiazepine (RR = 1.40, 95 % CI 1.24–1.58).[4]

Another meta-analysis of nine studies reported a pooled estimate of 92% excess risk of fractures in zolpidem users.[5] In addition, a meta-analysis of five studies showed that the use of first-generation antihistamine was significantly associated with the risk falls or fracture (OR 2.03, 95% CI 1.49–2.76).[6] The BNF recognises that the use of benzodiazepines is inappropriate in patients prone to falls.[7]

What evidence is there that correcting this pattern of prescribing leads to reduction in patient harm?

A randomized controlled trial showed that withdrawal of psychotropic medication can significantly reduce the risk of falls.[8] NICE guidance on falls recommends that patients who have had a fall or are at increased risk of falling should have their medication reviewed as part of a multifactorial risk assessment; and if possible discontinued to reduce their risk of falling.[9]

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Indicator P10: Benzodiazepine, Z-drug or sedating antihistamine prescribed to a patient with dementia or cognitive impairment.

What is the risk to patients?

Benzodiazepine and Z-drugs use is associated with an increased risk of developing Alzheimer's disease,[1] worsening cognitive functions [2,3] and was also associated with increased risk of developing pneumonia among adults with Alzheimer disease.[4]

First-generation (sedating) antihistamines have strong anticholinergic properties, and it has suggested that long-term use of these medications could increase the risk for developing dementia.[5] In addition, the use of first-generation antihistamine to patient with dementia or cognitive impairment may lead to agitation and delirium.[6]

Patients with dementia are associated with increased risk of fall. Benzodiazepine, Z-drug and sedating antihistamine could contribute to this risk.[7]

What evidence is there that this pattern of prescribing is harmful?

A meta-analysis of five studies that involved 45,391 participants concluded that patients on long-term benzodiazepine had an increased risk of dementia by 22% compared with non-users (risk ratio 1:22, 95% CI 1.18–1.25).[8]

A case-control study found that benzodiazepine 'ever' use was associated with an increased risk of Alzheimer's disease (adjusted OR 1.51, 95% CI 1.36 to 1.69). The strength of association increased with exposure density (aOR 1.32, 95% CI 1.01 to 1.74) for 91-180 prescribed daily doses and (aOR 1.84, 95% CI 1.62 to 2.08) for >180 prescribed daily doses. The stronger association observed for long term exposures supports the notion of a possible direct association.[1]

A case-control examined the association between benzodiazepine and Z-drugs consumption and dementia in a large population over 60 years. The study found that the regular use of benzodiazepine and Z-drugs was associated with a significant increased risk of incident dementia for patients aged≥60 years (aOR 1.21, 95% CI 1.13–1.29).[9]

A systematic review of clinical trials on the effect of benzodiazepines on cognitive functions and disease progression reported that five studies noticed accelerated cognitive deterioration in association with benzodiazepine use.[3]

A cohort study reported that the use of benzodiazepines and Z-drugs was associated with an increased risk of pneumonia (a hazard ratio 1.22, 95% CI 1.05-1.42).[10]

First-generation antihistamines have anticholinergic activity and can readily penetrate the blood brain barrier and therefore cause significant cognitive impairment and unwanted cognitive adverse effects.[11] Patients with dementia, are vulnerable to first-generation H1-antihistamine medication because of its sedative effects, and because these medications may lead to agitation and delirium.[12]

First-generation antihistamines were among a list of medications to be avoided in dementia in the Maudsley prescribing guidelines. The BNF indicated that the use of antihistamines is associated with increased anticholinergic burden and cognitive impairment, therefore their use should be minimised.[13] A population-based cohort study reported that cumulative anticholinergic medication use is associated with an increased risk for dementia and Alzheimer's disease.[14]

A meta-analysis of 14 studies reported a pooled relative increased risk of 24–58% in benzodiazepine users over non-users for hip fracture.[15] Another meta-analysis of nine studies reported a pooled estimate of 92% excess risk of fractures in zolpidem users.[16] In addition, a meta-analysis of five studies showed that the use of first-generation antihistamine was significantly associated with the risk falls or fracture (OR 2.03, 95% CI 1.49–2.76).[17] The BNF recognises that the use of benzodiazepines is inappropriate in patients prone to falls.[13]

What evidence is there that correcting this pattern of prescribing leads to reduction in patient harm?

No studies evaluating the effects of stopping Benzodiazepine, Z-drug or sedating antihistamine to reduce the risk of cognitive impairment were found in this review.

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Indicator P11: Benzodiazepine or Z-drug prescribed to a patient aged ≥ 65 years.

What is the risk to patients?

Benzodiazepine or Z-drug hypnotics can cause drowsiness, ataxia and confusion. Therefore, they are associated with an increased risk falls, fractures, traffic incidents, and delirium especially in the elderly. [1-4] In addition, benzodiazepines have been associated with cognitive decline, risk of dementia, risk of pneumonia, and an increase in all-cause mortality.[5]

What evidence is there that this pattern of prescribing is harmful?

A meta-analysis of 22 studies found that the use of benzodiazepines demonstrated a significant association with falls in elderly individuals with an OR=1.57 (95% CrI, 1.43-1.72).[3]

The BNF recognises that the use of benzodiazepines is inappropriate in patients prone to falls.[1]

A systematic review and meta-analysis reported that there is strong evidence that both benzodiazepines and Z-drugs are associated with an increased risk of hip fracture in the elderly. The use of benzodiazepines and Z-drugs has been associated with at least a 50% increase in the risk of hip fracture in the elderly, with newly users having even greater risk after short-term use.[6]

A meta-analysis of 14 studies reported a pooled relative increased risk of 24–58% in benzodiazepine users over non-users for hip fracture.[7] Another meta-analysis of nine studies reported a pooled estimate of 92% excess risk of fractures in zolpidem users.[8]

A Case-control study found that benzodiazepine ever use was associated with an increased risk of Alzheimer's disease (adjusted odds ratio 1.51, 95% confidence interval 1.36 to 1.69). The strength of association increased with exposure density (1.32 (1.01 to 1.74) for 91-180 prescribed daily doses and 1.84 (1.62 to 2.08) for >180 prescribed daily doses). The stronger association observed for long term exposures reinforces the suspicion of a possible direct association.[9]

What evidence is there that correcting this pattern of prescribing leads to reduction in patient harm?

Stopping long-term benzodiazepines in elderly people has been found to improve their working memory and reaction times, increase levels of alertness, and improve concentration.[10] In addition, as long as benzodiazepines are tapered gradually, their discontinuation may be safe, and many patients can achieve benzodiazepine abstinence.[11] NICE guidance on falls in older people recommends that patients who are at increased risk of falling should have their medication reviewed as part of a multifactorial risk assessment and if possible discontinued to reduce their risk.[12] Information on specific withdrawal schedules available on CKS: Benzodiazepine and z-drug withdrawal.[13]

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Indicator P12: Benzodiazepine or Z-drug prescribed to a patient with asthma, COPD or sleep apnoea.

What is the risk to patients?

The use of Benzodiazepine or Z-drug to patients with asthma, chronic obstructive pulmonary disease (COPD) or sleep apnoea increases the risk of respiratory failure and risk of exacerbation of the condition.

What evidence is there that this pattern of prescribing is harmful?

Benzodiazepine receptors are expressed in the plasma membrane of neurons throughout the central nervous system (CNS) and peripheral nervous system. By binding to these receptors, CNS function is suppressed and sedation is achieved. However, the main problem associated with the use of Benzodiazepine or Z-drug is respiratory depression, which may worsen sleep-related hypoventilation, especially in patients with underlying pulmonary diseases.

A nationwide population-based case-control study in Taiwan reported that the use of Benzodiazepines and Z-drugs was associated with an increased risk of respiratory failure in COPD patients (adjusted OR 1.56, 95% CI 1.14–2.13).[1]

A matched case-control and survival analysis using the United Kingdom Clinical Practice Research Datalink reported that benzodiazepines and may increase the likelihood of asthma exacerbation (benzodiazepines adjusted matched OR 1.49; 95% CI 1.15, 1.93; zopiclone adjusted matched OR 1.59; 95% CI 1.37, 1.85). Benzodiazepines was also found to increase the likelihood of mortality following exacerbation (adjusted HR 2.78; 95% CI 1.26, 6.12).[2]

A retrospective case-control study reported that benzodiazepine use might increase the risk of acute respiratory failure in patients with obstructive sleep apnoea (OR = 28.6; 95% CI = 5.24-156).[3]

What evidence is there that correcting this pattern of prescribing leads to reduction in patient harm?

No studies evaluating the effects of stopping Benzodiazepine or Z-drug to patients with asthma, COPD or sleep apnoea were found in this review. The BNF indicates that all benzodiazepines are contraindicates in patients with sleep apnoea syndrome, and they should be used with caution in patients with any respiratory disease.[4]

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Indicator P13: Valproic acid prescribed to a woman of childbearing potential.

What is the risk to patients?

Valproate is known to be highly teratogenic and use in pregnancy leads congenital malformations and developmental disorders.

What evidence is there that this pattern of prescribing is harmful?

Valproate is highly teratogenic and evidence supports that use in pregnancy leads to physical birth defects in 10 in every 100 babies (compared with a background rate of 2 to 3 in 100) and neurodevelopmental disorders in approximately 30 to 40 in every 100 children born to mothers taking valproate.[1]

An MHRA alert has been published in 2018 stating that valproate must not be used in women and girls of childbearing potential due to the teratogenic risk, unless the conditions of the Pregnancy Prevention Programme are met.[1]

What evidence is there that correcting this pattern of prescribing leads to reduction in patient harm?

No studies evaluating the effects of stopping valproic acid to reduce the risk of congenital malformations and developmental disorders were found in this review. However, there are risks associated with discontinuing valproate in a patient whose bipolar disorder or epilepsy is well controlled. Therefore, whilst there are good reasons to minimise the use of sodium valproate in pregnancy, it is possible that in some individual cases, the risks of discontinuing the drug could outweigh the benefits.[2]

Valproate should not be prescribed to female children, female adolescents, women of childbearing potential or pregnant women unless other treatments are ineffective or not tolerate, and conditions of Pregnancy Prevention Programme are met.[1] All women and girls of childbearing potential being treated with valproate medicines must be supported on a Pregnancy Prevention Programme. These conditions are also applicable to female patients who are not sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.[1]

The Pregnancy Prevention Programme is a system of ensuring all female patients taking valproate medicines: have been told and understand the risks of use in pregnancy and have signed a Risk Acknowledgement Form, are on highly effective contraception if necessary and see their specialist at least every year.[1]

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Indicator P14: Prescribing lithium with an ACEi/ARB or a diuretic.

What is the risk to patients?

Prescribing ACEi/ARB or a diuretic to a patient in lithium increases the risk of lithium toxicity.

What evidence is there that this pattern of prescribing is harmful?

Lithium has a narrow therapeutic index, and toxicity can be fatal. Lithium is excreted primarily by the kidney, and any salt depletion or reduction in GFR will cause serum lithium concentrations to rise. ACE inhibitors can (i) reduce thirst, which can lead to mild dehydration, and (ii) increase renal sodium loss leading to increased sodium re-absorption by the kidney, resulting in an increase in lithium plasma levels.[1]

Diuretics can reduce the renal clearance of lithium. Lithium levels usually rise within 10 days of a thiazide diuretic being prescribed; the magnitude of the rise is unpredictable and can vary from an increase of 25 to 400%.[1]

A large nested case-control study in 2004 reported that a dramatically increased risk of lithium toxicity was seen within a month of initiating treatment with a loop diuretic (relative risk (RR)=5.5, 95% CI=1.9–16.1) or an ACE inhibitor (RR=7.6, 95% CI=2.6–22.0).[2] Angiotensin Receptor Blockers (ARBs) may be associated with similar risk.[3] Case reports describe lithium toxicity in patients on candesartan, losartan, valsartan, and irbesartan.[4]

What evidence is there that correcting this pattern of prescribing leads to reduction in patient harm?

The National Patient Safety Agency (NPSA) has issued a patient safety alert on safer lithium therapy in response to reports of harm and fatalities caused to patients involving lithium therapy. The alerts stressed that clinically significant alterations in lithium blood levels occur with commonly prescribed medications and that lithium levels are dependent on kidney function which can be affected the use of lithium. [5]

Starting or stopping this pattern of prescribing would require careful monitoring to lithium plasma level to avoid toxicity. If no suitable alternatives to ACE inhibitors or diuretics are available, this pattern of prescribing can be considered appropriate if the lithium levels are monitored and dose adjustments considered to avoid lithium toxicity.[6] There may also be occasions where lithium is initiated following prior use of ACE inhibitors and diuretics, and the dose of lithium can therefore be monitored and titrated accordingly.

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Indicator P15: A medication with medium/high anticholinergic activity prescribed to a patient with dementia or cognitive impairment.

What is the risk to patients?

These anticholinergic medications may further impair cognition in dementia and worsen behavioural symptoms.[1-5]

What evidence is there that this pattern of prescribing is harmful?

An increasing number of systematic reviews and meta-analyses report that drugs with anticholinergic effects are associated with an increased risk of cognitive impairment.[6,7] Patients with existing cognitive impairment and those with early stage dementia, age associated memory impairment, or mild cognitive impairment, can be especially vulnerable to these cognitive side effects.

An initial study in 2011, involving more than 13,000 men and women aged 65 years and over, from the UK, found that anticholinergic activity appears to increase the risks of both cognitive brain impairment and death in older people.[8] More recently, in 2018 a large case-control study of over 40000 patients aged 65-99 with dementia and 283 933 controls without dementia found a robust association between some classes of anticholinergic drugs and future dementia incidence.[9]

What evidence is there that correcting this pattern of prescribing leads to reduction in patient harm?

A study found that reducing anticholinergic burden reduce severity and frequency of BPSD.[10] Medications with a high anticholinergic activity should be avoided where possible in patients with dementia, and medications with a lower anticholinergic activity would be preferable. An NHS England dementia diagnosis and management resource for GPs recommends that drugs with strong anticholinergic activity should be stopped if possible or substituted for a drug with less anticholinergic activity.[11,12] The Department of Health dementia toolkit also recommends to consider stopping or reducing anticholinergic drugs.[12,13]

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Indicator P16: Mental health related medication with medium/high anticholinergic activity prescribed with another medication with medium/high anticholinergic activity.

What is the risk to patients?

Anticholinergics have been documented to cause dry mouth, constipation and urinary retention. They also have been linked to impaired cognition, physical decline, falls, and increased mortality and cardiovascular events.[1] Combining treatments with anticholinergic activity might have cumulative harmful effects, with evidence linking increased mortality with the number and potency of anticholinergic medications prescribed.[2]

What evidence is there that this pattern of prescribing is harmful?

Drugs with anticholinergic effects block the neurotransmitter acetylcholine and inhibit smooth muscle function in the lungs, gastrointestinal tract and urinary tract. Five distinct muscarinic receptor subtypes (M1–M5) are known to exist resulting in the potential for side effects. These include constipation, dry mouth, dry eyes, urinary retention and falls. Dizziness, sedation, confusion, agitation, delirium and even cognitive impairment have been reported as central adverse effects. In addition, the effect of multiple anticholinergic medications is accumulative.[2] Research suggests a link to increased hospitalisation and mortality with the number of anticholinergic agents prescribed.[2,3]

An increasing number of systematic reviews and meta-analyses report that drugs with anticholinergic effects are associated with an increased risk of cognitive impairment.[4,5] An initial study in 2011, involving more than 13,000 men and women aged 65 years and over, from the UK, found that anticholinergic activity appears to increase the risks of both cognitive brain impairment and death in older people.[6] More recently, in 2018 a large case-control study of over 40000 patients aged 65-99 with dementia and 283 933 controls without dementia found a robust association between some classes of anticholinergic drugs and future dementia incidence.[7]

What evidence is there that correcting this pattern of prescribing leads to reduction in patient harm?

Reducing the anticholinergic burden may result in improvements in short term memory, confusion, behaviours, delirium and quality of life.[1,8,9]

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Indicator P17: Mental health related medication with medium/high anticholinergic activity prescribed to a patient with a history of urinary retention or benign prostatic hyperplasia.

What is the risk to patients?

Using medications with anticholinergic activity (e.g. antipsychotic and antidepressant agents) increases the risk of developing urinary retention. The risk is higher for patients with a previous history of urinary retention or benign prostatic hyperplasia.[1]

What evidence is there that this pattern of prescribing is harmful?

The association between the use of certain medications with anticholinergic activity and the occurrence of acute urinary retention is well established.[1]

The risk of urinary retention due to medications is not exclusive for elderly patients, even children might experience this adverse effect. A study reviewed all records of cases of urinary retention in children over a 6-year period, and 13% of the reported urinary retention cases were attributed to the use of concomitant medication.[2]

What evidence is there that correcting this pattern of prescribing leads to reduction in patient harm?

No studies evaluating the effects of stopping anticholinergics in patients with a history of urinary retention or benign prostatic hyperplasia were found in this review.

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Indicator P18: Four or more psychotropics prescribed to a patient for more than 3 months.

What is the risk to patients?

The combination of several psychotropics does not have a robust evidence of positive impact on mental illness symptoms, and may increase the risk of interactions and side-effects.[1-3]

What evidence is there that this pattern of prescribing is harmful?

A Swedish nationwide case control study found that the number of prescribed psychotropics was associated with an increased risk of fall injuries, (4 psychotropics vs 0: adjusted OR: 1.53; 95% CI: 1.39–1.68), hospitalization (4 psychotropics vs 0: adjusted OR: 1.27; 95% CI: 1.22–1.33) and death (4 psychotropics vs 0: adjusted OR: 2.50; 95% CI: 2.33–2.69).[4]

What evidence is there that correcting this pattern of prescribing leads to reduction in patient harm?

Evidence suggest that withdrawal of psychotropics is effective in reducing rate of falls and it can result in an improvement of cognition.[5] A randomized controlled trial showed that withdrawal of psychotropic medication can significantly reduce the risk of falls.[6] In addition, a study reported that changing patients regimens from two or more antipsychotics to a single antipsychotic can be successful, where the majority of the patients showed improvement or remained stable.[7] NICE guidance suggests reviewing older patients on psychotropic medications to reduce their risk of falling.[8]

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Indicator M1: Antipsychotic prescribed for at least 12 months without monitoring glucose, weight, or lipid profile within the previous year

What is the risk to patients?

Antipsychotic medications contribute to the development of metabolic syndrome by causing weight gain, lipid disturbance, and glucose dysregulation.[1] Metabolic syndrome is a combination of diabetes, hypertension and obesity that increase the risk of coronary heart disease and stroke.

What evidence is there that this pattern of prescribing is harmful?

A systematic review and meta-analysis of 48 papers reported that the odds of developing metabolic syndrome is almost 5 timers higher in people treated with typical antipsychotics vs antipsychotic-naïve patients (OR 4.97; 95% CI 3.83-6.51). For Clozapine OR=7.81 (95% CI 6.02-10.22), Olanzapine OR=5.87 (95% CI 4.53-7.67), and Quetiapine OR=5.41 (95% CI 3.75-7.07).[2]

NICE guideline recommends that after starting antipsychotics fasting blood glucose, HbA1c and blood lipids should be monitored at 12 weeks, at 1 year and then annually, and to monitor weight weekly for the first 6 weeks, then at 12 weeks, at 1 year and then annually.[3]

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Indicator M2: Initiation of haloperidol without monitoring ECG at baseline

What is the risk to patients?

Haloperidol is linked to prolongation of the cardiac QT interval. A prolonged QT interval can increase the risk of ventricular tachyarrhythmia, and sudden death. Haloperidol is among the highest risk medications that causes prolonged QT interval.[1,2]

What evidence is there that this pattern of prescribing is harmful?

Haloperidol has been linked to QT prolongation and torsade de pointes. High doses and/or IV administration appear to increase risk.[2] The BNF advises that an ECG be performed before haloperidol initiation.[3] The Summaries of Product Characteristics (SmPC) for all haloperidol formulations (oral, intramuscular/intravenous immediate release injections & intramuscular long acting injections) advises that an ECG be performed before haloperidol initiation in all patients.[4]

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Indicator M3: Prescribing lithium without monitoring lithium plasma levels within the previous 6 months or within the last 3 months if the patient is aged ≥ 65 years, has a diagnosis of renal impairment or during the first year of treatment

What is the risk to patients?

Lithium has a narrow therapeutic index and most lithium adverse effects are dose and plasma level related. Lithium intoxication can cause seizures, cardiac arrhythmias, blood pressure changes, circulatory failure, renal failure, coma and sudden death.[1]

What evidence is there that this pattern of prescribing is harmful?

NICE guidelines recommend to test lithium plasma level every 3 months for the first year of therapy and then every 6 months, or every 3 months for people at higher risk of lithium toxicity. Such as older patients, patients with impaired renal function or during the first year of treatment.[2]

A patient safety alert related to the importance of monitoring lithium has been issued by the National Patient Safety Agency in 2009 after two fatal and 12 severe harm incidents involving lithium therapy.[3]

References

1. Joint Formulary Committee. British National Formulary (online). BMJ Group and Pharmaceutical Press. http://www.medicinescomplete.com. Accessed July 9, 2021.
2. National Institute for Health and Care Excellence. Bipolar disorder: assessment and management: Clinical guideline (CG185). National Institute for Health and Care Excellence. https://www.nice.org.uk/guidance/cg185/resources/bipolar-disorder-assessment-and-management-pdf-35109814379461. Published 2014. Accessed April 4, 2018.
3. NPSA. Safer lithium therapy 2009. *Patient Safety Alert.* 2009;NPSA/2009/PSA005.

Indicator M4: Lithium prescribed for at least 6 months without monitoring U&Es or thyroid function within the last 6 months

What is the risk to patients?

Lithium has a narrow therapeutic index and most lithium adverse effects are dose and plasma level related. Lithium intoxication can cause seizures, cardiac arrhythmias, blood pressure changes, circulatory failure, renal failure, coma and sudden death. Lithium plasma levels are dependent on kidney function and lithium has the potential to interfere with the renal and thyroid functions.[1]

Lithium can lead to reduction in the glomerular filtration rate, and higher lithium plasma levels and prolonged treatment are associated with higher risk of renal toxicity. In addition, long term lithium therapy increases the risk of hypothyroidism.[2]

What evidence is there that this pattern of prescribing is harmful?

NICE guidelines recommend to test urea and electrolytes including calcium, estimated glomerular filtration rate (eGFR) and thyroid function every 6 months, and more often if there is evidence of impaired renal or thyroid function for patients on lithium.[3]

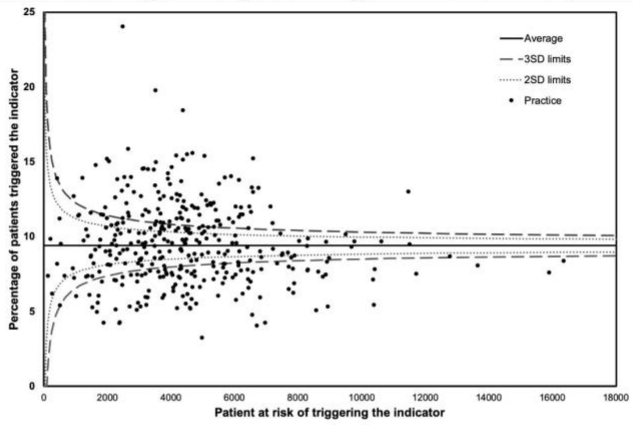
A patient safety alert related to the importance of biochemical monitoring in patients prescribed lithium has been issued by the National Patient Safety Agency in 2009 after two fatal and 12 severe harm incidents involving lithium therapy.[4]

References

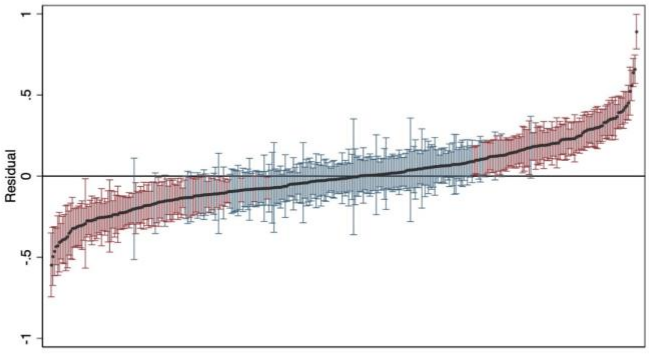
1. Joint Formulary Committee. British National Formulary (online). BMJ Group and Pharmaceutical Press. http://www.medicinescomplete.com. Accessed July 9, 2021.
2. Taylor DM, Barnes TRE, Young AH. The Maudsley Prescribing Guidelines in Psychiatry. Hoboken, NJ: Wiley Blackwell; 2018.
3. National Institute for Health and Care Excellence. Bipolar disorder: assessment and management: Clinical guideline (CG185). National Institute for Health and Care Excellence. https://www.nice.org.uk/guidance/cg185/resources/bipolar-disorder-assessment-and-management-pdf-35109814379461. Published 2014. Accessed April 4, 2018.
4. NPSA. Safer lithium therapy 2009. Patient Safety Alert. 2009;NPSA/2009/PSA005.

Appendix (11) The variation between practices for each prescribing safety indicators with adequate reliability before and after adjusting for patient characteristics and the quarterly changes in the indicator prevalence between 2009 and 2019.

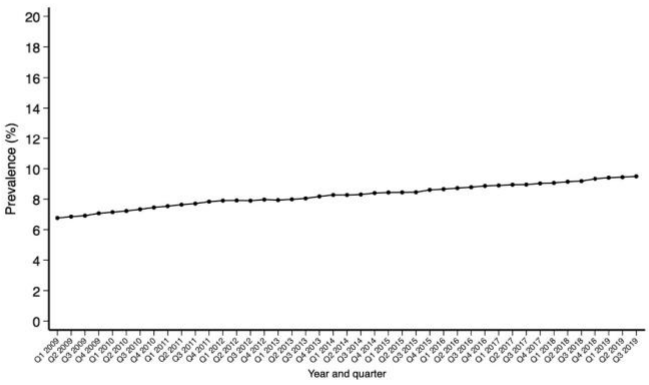
PSI Composite 1 (prescribing indicators P1-P18)



(a) Variations between practices in the proportion of patients triggering the indicator.



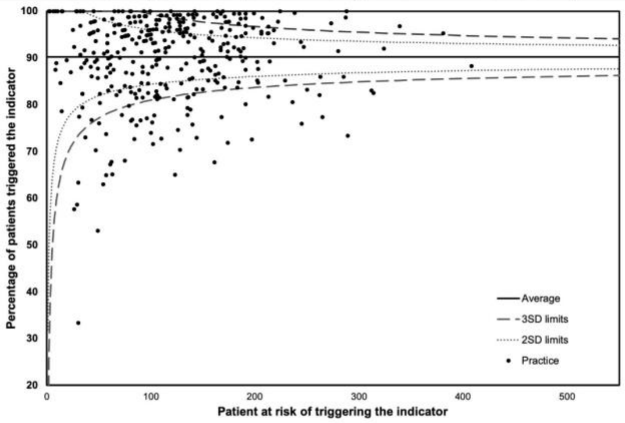
(b) Variation between practices, ranked, based on estimated practice-level residuals with 95% CIs after adjusting for patients characteristics.



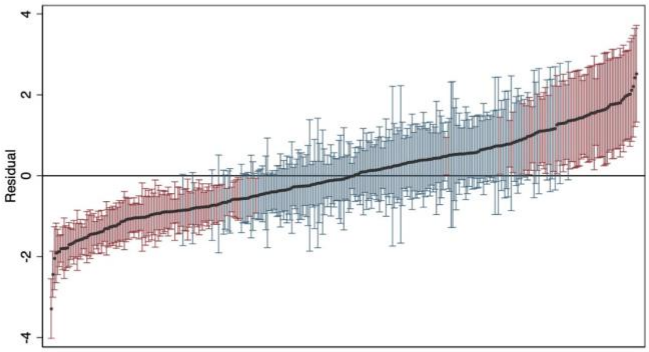
(c) Quarterly changes in the proportion of patients triggering the indicator.

1

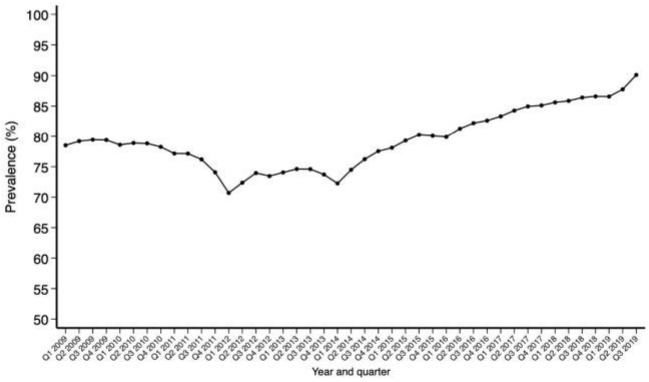
PSI Composite 2 (monitoring indicators M1-M4)



(a) Variations between practices in the proportion of patients triggering the indicator.

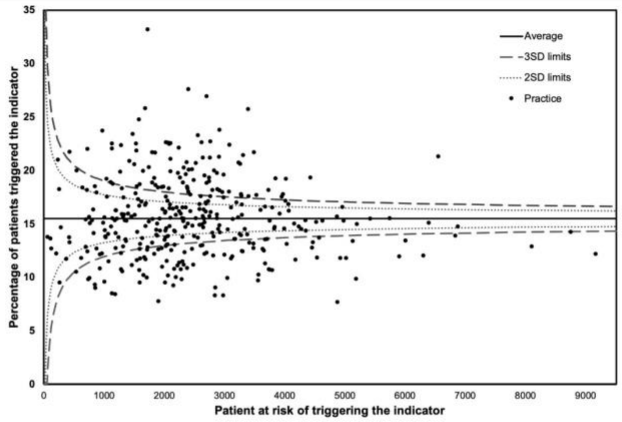


(b) Variation between practices, ranked, based on estimated practice-level residuals with 95% CIs after adjusting for patients characteristics.

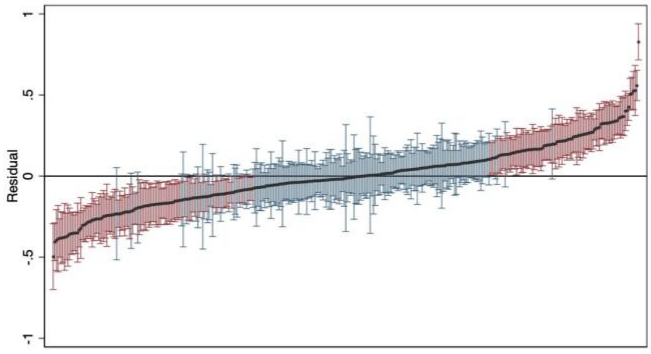


(c) Quarterly changes in the proportion of patients triggering the indicator.

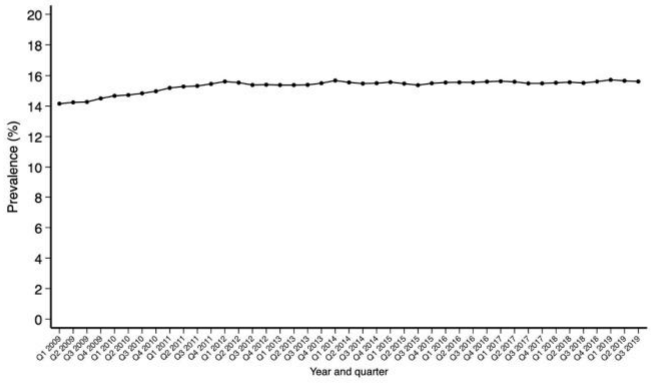
PSI Composite 3 (prescribing indicators excluding P11 and P13, specific for elderly or female)



(a) Variations between practices in the proportion of patients triggering the indicator.

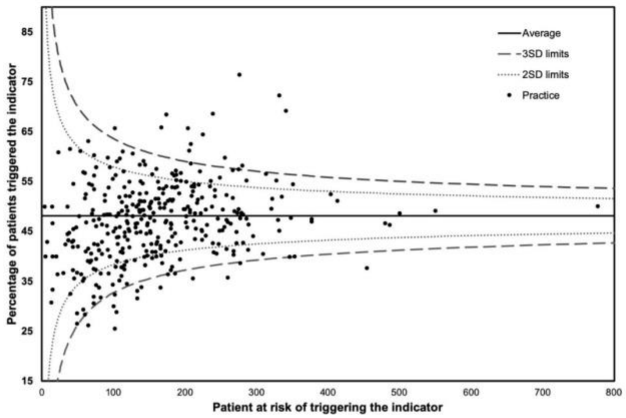


(b) Variation between practices, ranked, based on estimated practice-level residuals with 95% CIs after adjusting for patients characteristics.

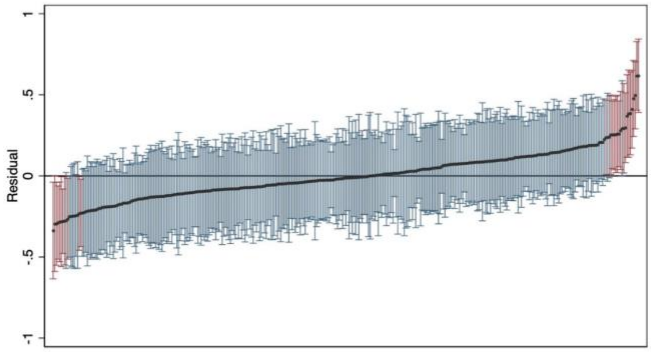


(c) Quarterly changes in the proportion of patients triggering the indicator.

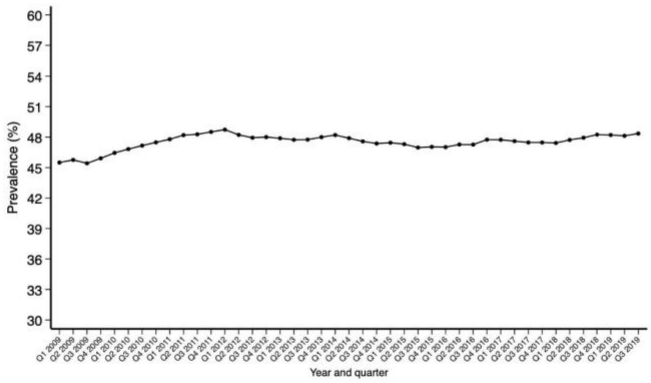
P1: Prescribing antipsychotic with a QT-prolonging drug



(a) Variations between practices in the proportion of patients triggering the indicator.

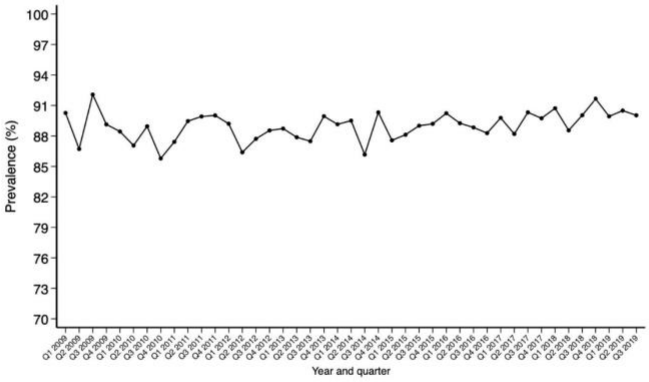


(b) Variation between practices, ranked, based on estimated practice-level residuals with 95% CIs after adjusting for patients characteristics.



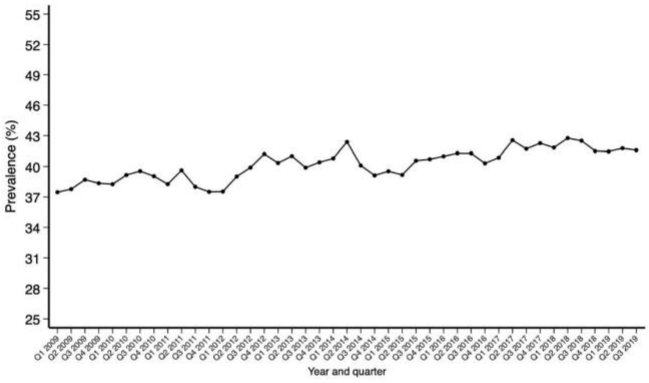
(c) Quarterly changes in the proportion of patients triggering the indicator.

P2: Risperidone prescribed to a patient with dementia and without psychotic illness for more than 6 weeks



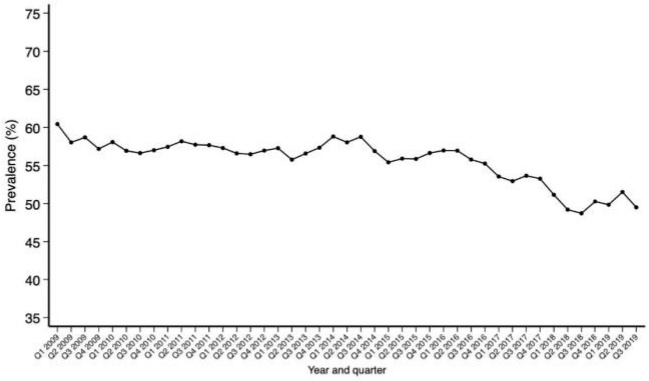
(a) Quarterly changes in the proportion of patients triggering the indicator.

P3: Prescribing more than one regular antipsychotic for 3 months or more, excluding clozapine augmentation



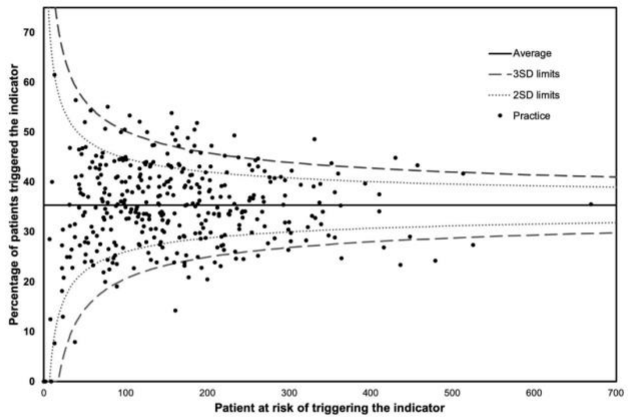
(a) Quarterly changes in the proportion of patients triggering the indicator.

P4: Antipsychotic other than quetiapine, aripiprazole or clozapine prescribed to a patient with Parkinson's disease or with Lewy Body Disease

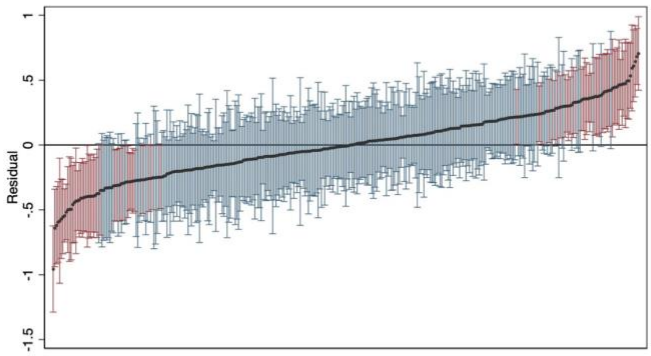


(a) Quarterly changes in the proportion of patients triggering the indicator.

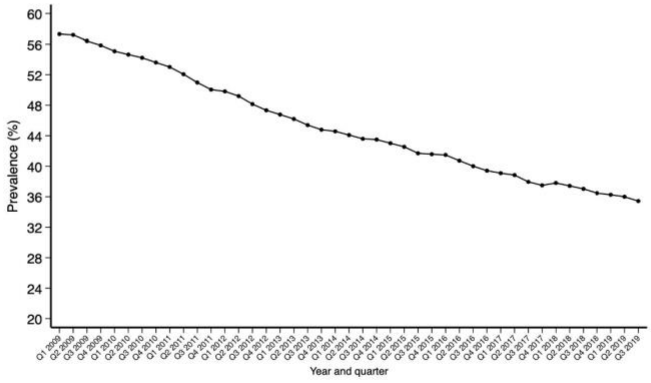
P5: Selective serotonin reuptake inhibitor (SSRI) or serotonin and norepinephrine reuptake inhibitor (SNRI) prescribed with an NSAID or antiplatelet agent to a patient without gastrointestinal protection



(a) Variations between practices in the proportion of patients triggering the indicator.

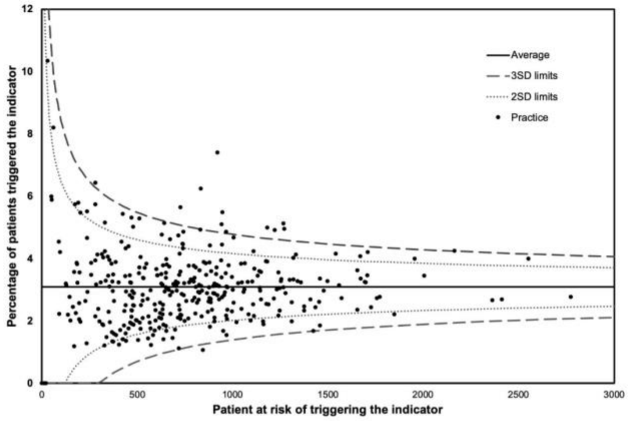


(b) Variation between practices, ranked, based on estimated practice-level residuals with 95% CIs after adjusting for patients characteristics.

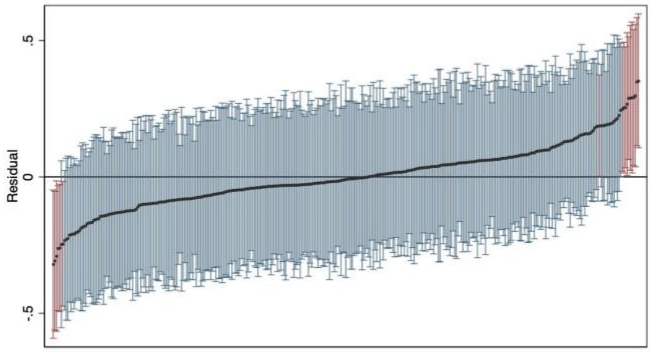


(c) Quarterly changes in the proportion of patients triggering the indicator.

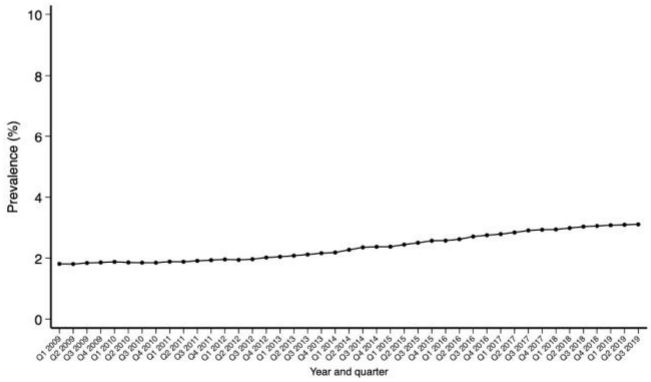
P6: SSRI or SNRI prescribed with a direct oral anticoagulant (DOAC) or warfarin



(a) Variations between practices in the proportion of patients triggering the indicator.

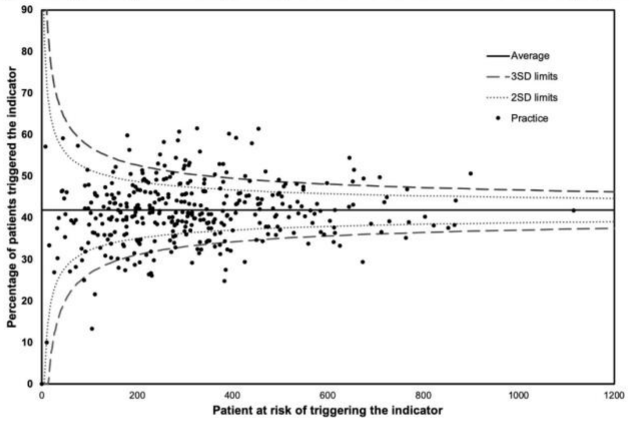


(b) Variation between practices, ranked, based on estimated practice-level residuals with 95% CIs after adjusting for patients characteristics.

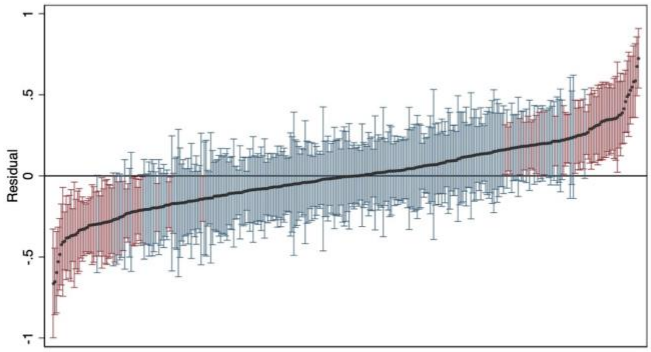


(c) Quarterly changes in the proportion of patients triggering the indicator.

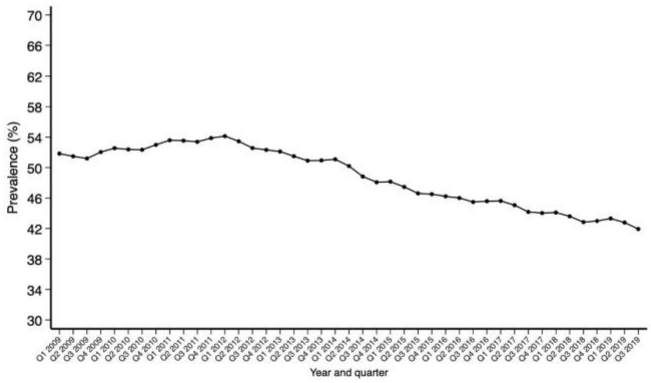
P7: Prescribing citalopram, escitalopram, TCA or trazadone with QT-prolonging drugs



(a) Variations between practices in the proportion of patients triggering the indicator.

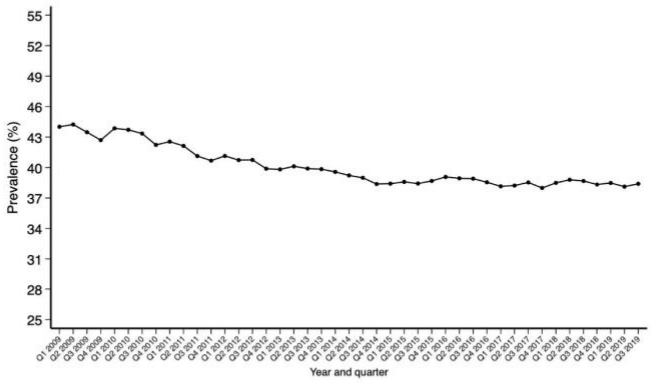


(b) Variation between practices, ranked, based on estimated practice-level residuals with 95% CIs after adjusting for patients characteristics.



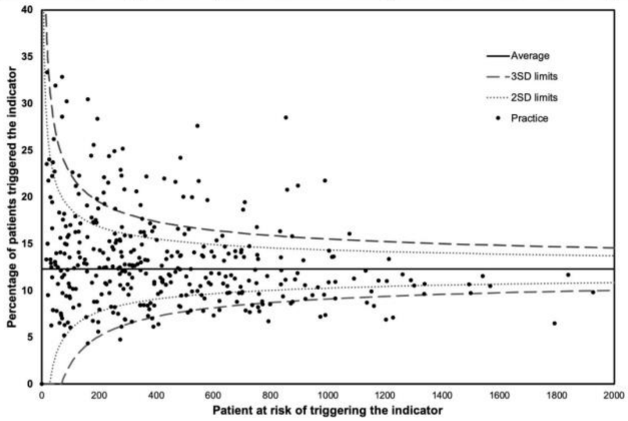
(c) Quarterly changes in the proportion of patients triggering the indicator.

P8: SSRI or SNRI prescribed to a patient with a history of peptic ulcer or bleeding disorders without gastroprotection

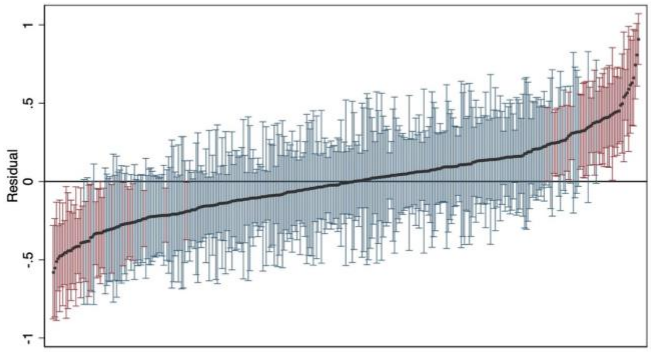


(a) Quarterly changes in the proportion of patients triggering the indicator.

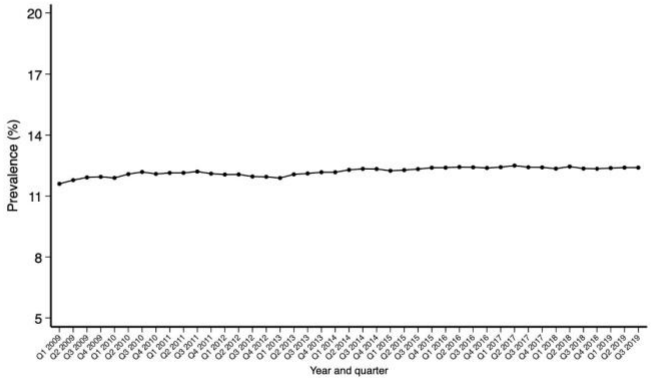
P9: Any sedative-hypnotic prescribed to a patient with a history of falls



(a) Variations between practices in the proportion of patients triggering the indicator.

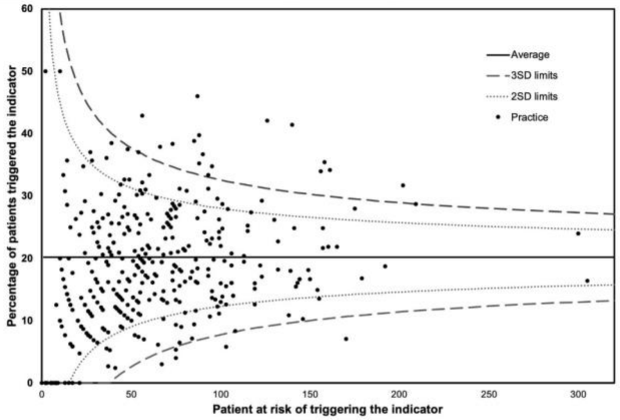


(b) Variation between practices, ranked, based on estimated practice-level residuals with 95% CIs after adjusting for patients characteristics.

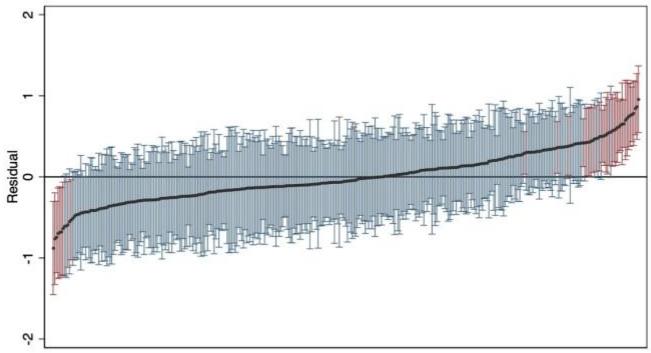


(c) Quarterly changes in the proportion of patients triggering the indicator.

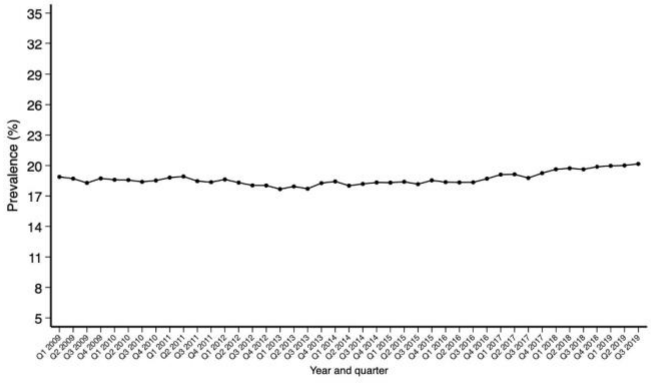
P10: Benzodiazepine, Z-drug or sedating antihistamine prescribed to a patient with dementia or cognitive impairment



(a) Variations between practices in the proportion of patients triggering the indicator.

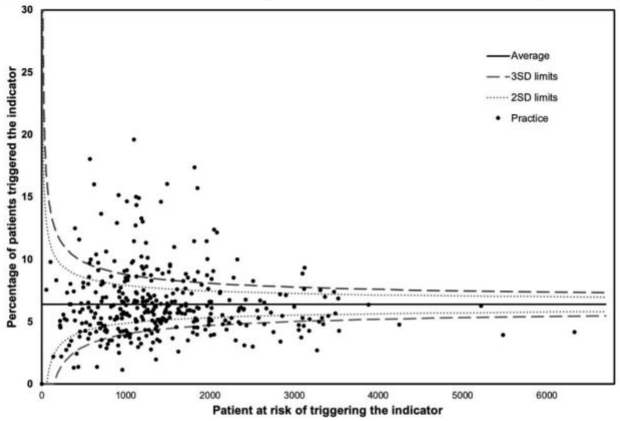


(b) Variation between practices, ranked, based on estimated practice-level residuals with 95% CIs after adjusting for patients characteristics.

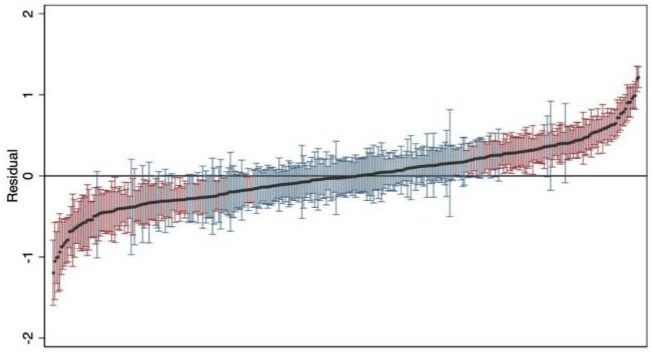


(c) Quarterly changes in the proportion of patients triggering the indicator.

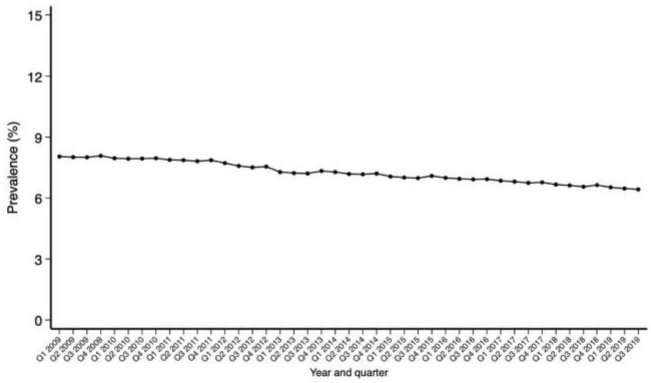
P11: Benzodiazepine or Z-drug prescribed to a patient aged ≥ 65 years



(a) Variations between practices in the proportion of patients triggering the indicator.

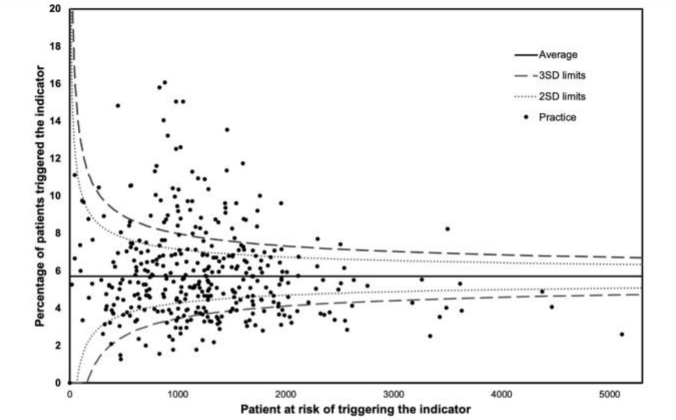


(b) Variation between practices, ranked, based on estimated practice-level residuals with 95% CIs after adjusting for patients characteristics.

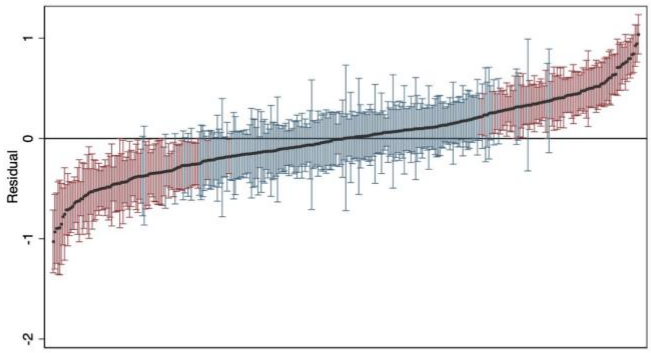


(c) Quarterly changes in the proportion of patients triggering the indicator.

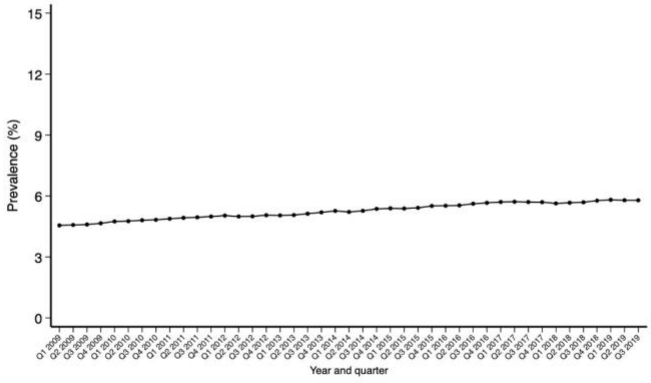
P12: Benzodiazepine or Z-drug prescribed to a patient with asthma, COPD or sleep apnoea



(a) Variations between practices in the proportion of patients triggering the indicator.

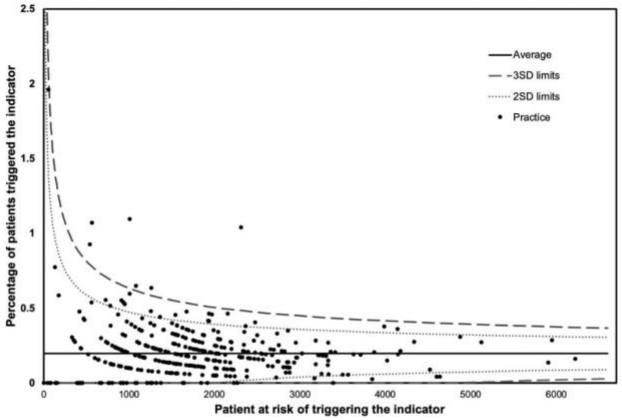


(b) Variation between practices, ranked, based on estimated practice-level residuals with 95% CIs after adjusting for patients characteristics.

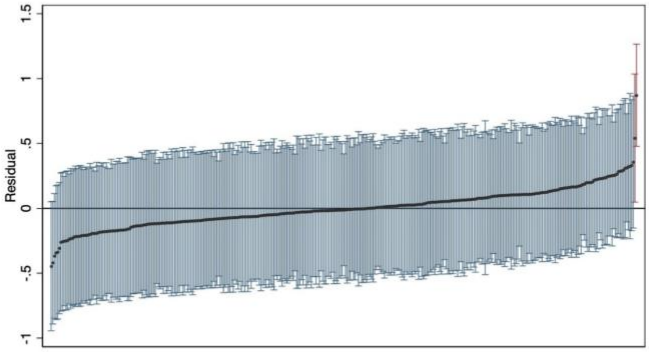


(c) Quarterly changes in the proportion of patients triggering the indicator.

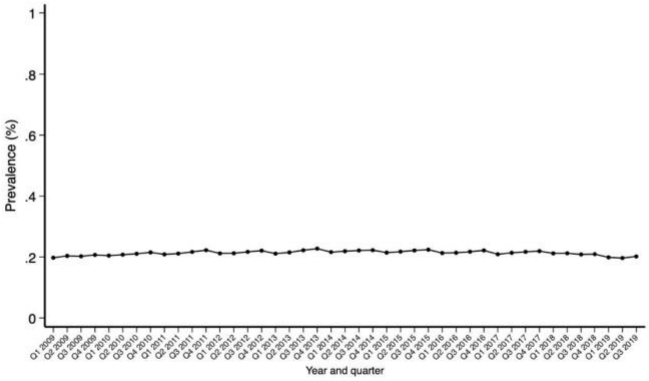
P13: Valproic acid prescribed to a woman of childbearing potential



(a) Variations between practices in the proportion of patients triggering the indicator.

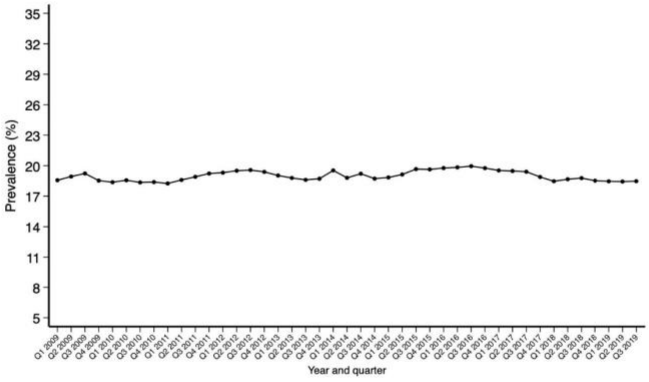


(b) Variation between practices, ranked, based on estimated practice-level residuals with 95% CIs after adjusting for patients characteristics.



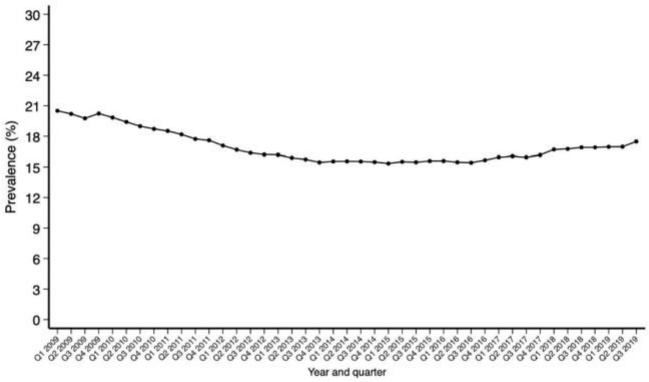
(c) Quarterly changes in the proportion of patients triggering the indicator.

P14: Prescribing lithium with an ACEi/ARB or a diuretic



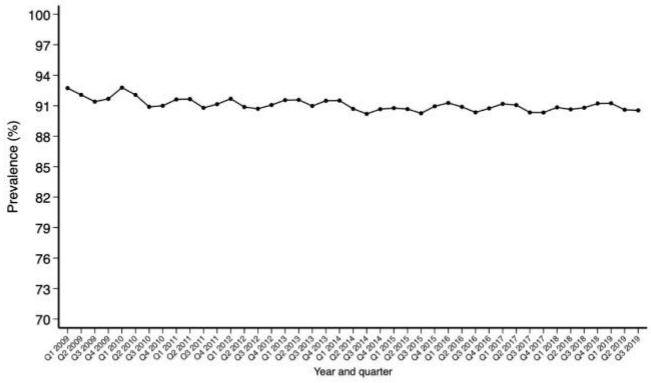
(a) Quarterly changes in the proportion of patients triggering the indicator.

P15: A medication with medium/high anticholinergic activity prescribed to a patient with dementia or cognitive impairment



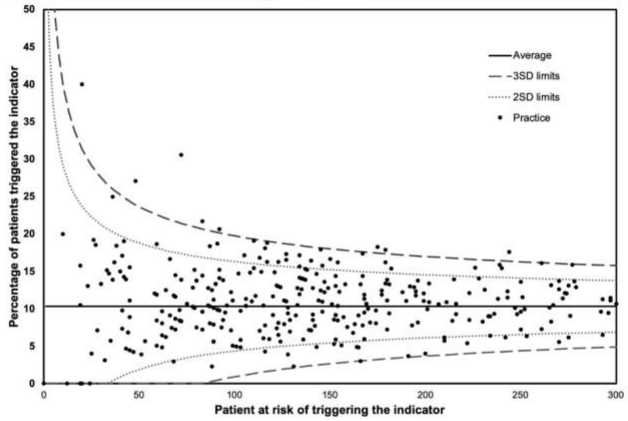
(a) Quarterly changes in the proportion of patients triggering the indicator.

P16: Mental health related medication with medium/high anticholinergic activity prescribed with another medication with medium/high anticholinergic activity

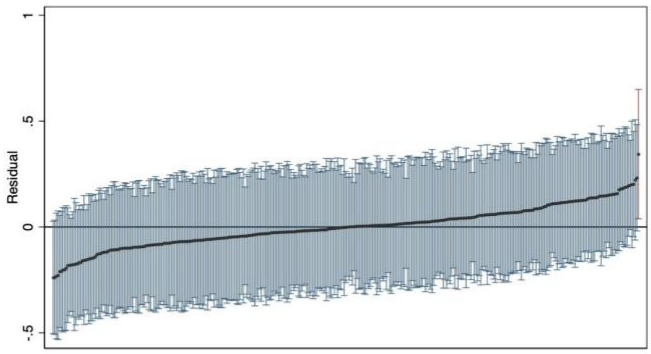


(a) Quarterly changes in the proportion of patients triggering the indicator.

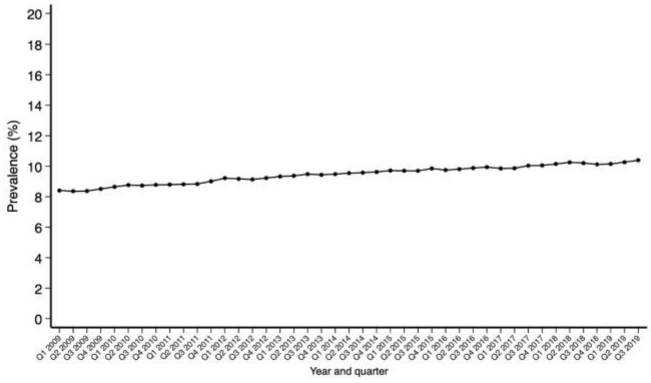
P17: Mental health related medication with medium/high anticholinergic activity prescribed to a patient with a history of urinary retention or benign prostatic hyperplasia



(a) Variations between practices in the proportion of patients triggering the indicator.

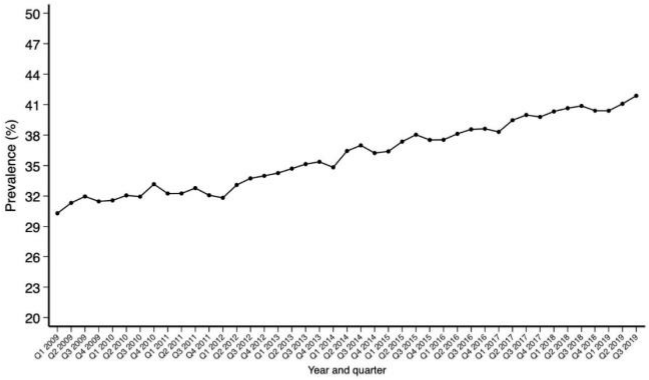


(b) Variation between practices, ranked, based on estimated practice-level residuals with 95% CIs after adjusting for patients characteristics.



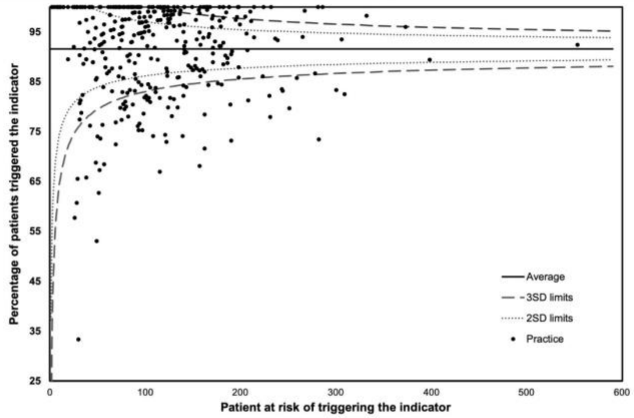
(c) Quarterly changes in the proportion of patients triggering the indicator.

P18: Four or more psychotropics prescribed to a patient for more than 3 months

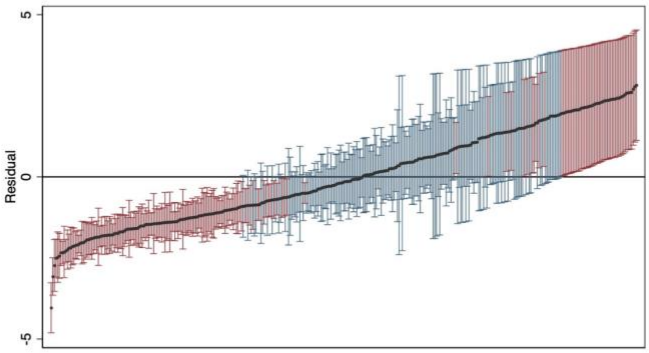


(a) Quarterly changes in the proportion of patients triggering the indicator.

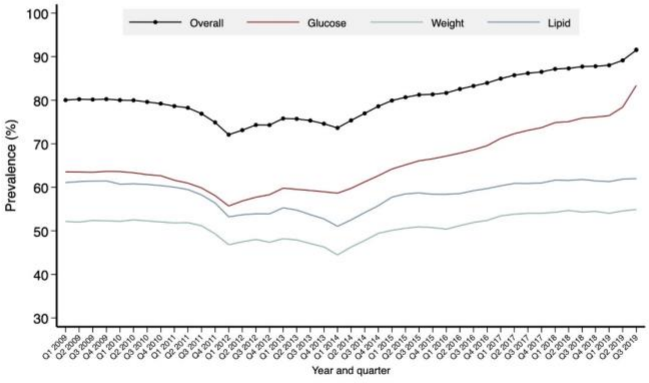
M1: Antipsychotic prescribed for at least 12 months without monitoring glucose, weight, or lipid profile within the previous year



(a) Variations between practices in the proportion of patients triggering the indicator.

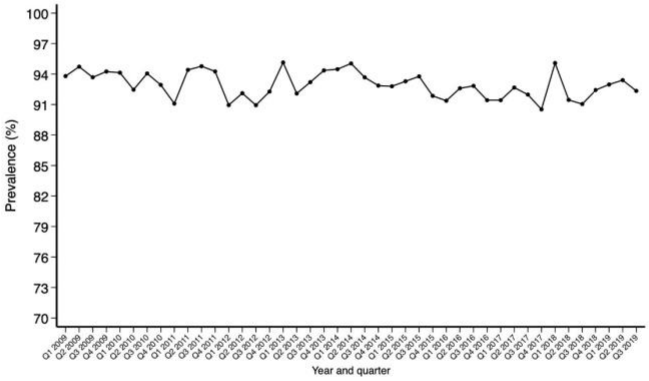


(b) Variation between practices, ranked, based on estimated practice-level residuals with 95% CIs after adjusting for patients characteristics.



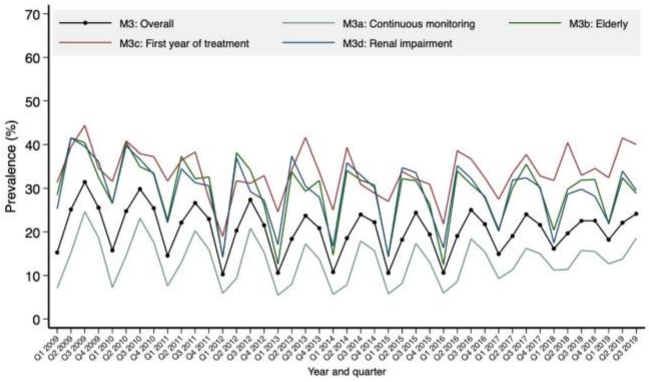
(c) Quarterly changes in the proportion of patients triggering the indicator.

M2: Initiation of haloperidol without monitoring ECG at baseline



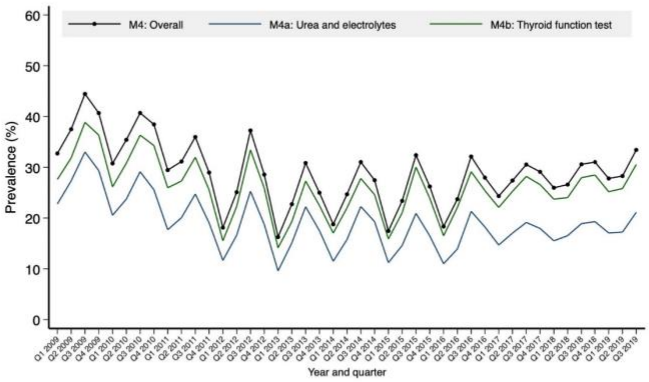
(a) Quarterly changes in the proportion of patients triggering the indicator.

M3: Prescribing lithium without monitoring lithium plasma levels within the previous 6 months or within the last 3 months if the patient is aged ≥ 65 years or have a diagnosis of renal impairment or during the first year of treatment



(a) Quarterly changes in the proportion of patients triggering the indicator.

M4: Lithium prescribed for at least 6 months without monitoring U&Es or thyroid function within the last 6 months



(a) Quarterly changes in the proportion of patients triggering the indicator.