Clozapine in Treatment-Resistant Schizophrenia (TRS): improving access and utilisation

A thesis submitted to Middlesex University in partial fulfilment of the requirements for the degree of Doctor of Philosophy

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Abstract

Schizophrenia is the most severe mental illness affecting humans. When the illness does not respond to treatment, it is even more devastating. When a patient fails to respond to two adequate, consecutive antipsychotic treatments, the illness is termed *treatment-refractory schizophrenia* (TRS). Clozapine is the only licensed and recognised effective treatment in TRS. Interestingly, rather than its current position as a third-line treatment, there are rather robust and convincing arguments for clozapine to be used as a second line. Sadly, in clinical practice there is widespread underuse of clozapine, with significant delays before it is prescribed in individuals with TRS, being relegated to the fifth or sixth line. Instead, non-evidence-based use of high-dose antipsychotics and the use of antipsychotics in combination is common practice, contributing to even longer delays.

This is a compilation of 33 of my publications and public works (PWs) spanning over two decades, from 1999 to 2021. In these, I explore why clozapine is underused, when it should be used and how it should be used, employing different methodologies. This is a combination of my reviews of the literature and my practical recommendations on how to overcome difficulties in specific situations using case reports and case series. I have collaborated with colleagues from a wide variety of disciplines including psychiatrists, pharmacologists, cardiologists, haematologists and data experts to advance knowledge in the management of TRS through these works. I have investigated various databases and been involved in the design and conduct of randomised controlled trials in schizophrenia.

My work has demonstrated that in the United Kingdom and probably in most other countries, significant variation exists in the rate of clozapine prescribing in patients with TRS. There is thus inequity in patient access to the most effective treatment in refractory schizophrenia. This has an enormous impact on patients and families and may be the difference between long-term institutional care and fulfilling, independent living in the community with freedom and liberty.

The delay and underutilisation of clozapine are centred around four principal factors. These are related to the drug itself, factors that relate to the patient, clinician-related factors and finally, those that pertain to licensing and regulatory control of the drug. Clozapine is a life-prolonging drug, and concerted efforts to overcome these well-recognised barriers would go a long way in improving outcomes in patients with TRS.

I believe that long-term solutions to the underuse of clozapine lie in education. Clinicians treating patients with schizophrenia need to identify patients with TRS as quickly as possible. Health systems to educate, support and encourage clinicians would provide much-needed confidence in evaluating risks and benefit to increase clozapine uptake. The stringent regulatory controls of clozapine should be thoroughly examined. The United States Food and Drugs

Administration (FDA) has gone some way by lowering the haematological threshold for clozapine continuation, but more needs to be done.

How can we be confident of overcoming all these seemingly impossible barriers? The answer, I believe, is in developing a national clozapine strategy. The United Kingdom is the centre of research in psychopharmacology. It houses the world-renowned Institute of Psychiatry, Psychology and Neurosciences (IoPPN) with expertise in the management of schizophrenia. A comprehensive national strategy that identifies all the barriers and a systematic approach to addressing the multifaceted problem would address these issues. This approach is not new. It has been successfully applied in countries such as the Netherlands. My PWs have shown that we can not only overcome these barriers, but substantially increase clozapine uptake.

The negative prognostic implications of delay and underuse of clozapine are now becoming glaringly apparent. The outcome for patients where clozapine use is substantially delayed is not as good as in patients where it is initiated as soon as treatment refractoriness is ascertained. When we can fully utilise clozapine in patients with TRS, then we can turn our attention to the 40-50% of patients who have less than satisfactory response to clozapine, or those patients deemed as ultra treatment refractory.

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CHAPTER 1: Introduction

1.1. Clinical Pharmacy in Psychiatry

Clinical pharmacy, the specialism within the pharmacy profession that pertains to the patient-centred, rational, evidence-based, cost-effective use of medicines (Cotter et al., 1994; Calvert, 1999), was already well developed in the United Kingdom (UK) in many specialist areas of medicine in the 70s and 80s. However, it was only beginning to evolve in mental health services in the early 90s. This coincided with my journey in mental health pharmacy, which began serendipitously. It was an exciting time to be involved in psychiatric pharmacy. At the time, it seemed like the dawn of a new era. It was the age of atypical antipsychotics, treatments that were meant to transform the lives of individuals living with the stigma of schizophrenia. Clozapine had only recently been re-introduced in the UK in 1990 after spending almost 20 years in psychopharmacological exile. This spurred the race to develop antipsychotics that did not possess the debilitating motoric side effects of the conventional antipsychotics. Risperidone was the first of this generation, launched in the UK in December 1992. The next to follow was olanzapine, which was launched in September 1996. Then came quetiapine in 2000. Almost parallel to the development of the new generation antipsychotic drugs was the change happening with antidepressant treatments. Fluoxetine, the first selective serotonin reuptake inhibitor (SSRI), entered the UK market in 1988, becoming a blockbuster drug. Other SSRIs such as sertraline, citalopram, fluvoxamine followed. These drugs began to gradually replace the tricyclic antidepressants and the monoamine oxidase inhibitors which had hitherto been the standard treatments for depression and anxiety disorders.

It was against this backdrop that I entered psychiatric pharmacy. Many psychiatrists had never worked with this new species of clinical pharmacists. These were pharmacists leaving the confines of the dispensary to go into the wards and become integrated with the multidisciplinary team caring for the patient. Unsurprisingly, the initial attitude of psychiatrists varied from an enthusiastic welcome and support to downright opposition. With the introduction of new psychotropic medicines, the knowledge requirement increased astronomically. The clinical pharmacist was there to fill that knowledge gap for the psychiatrist, the nurses and the patient themselves.

Some of my earliest works relate to the synthesis and provision of information to patients and clinicians. For example, in PW 1 'Evaluation of an antipsychotic information sheet for patients' (Whiskey and Taylor, 2005), I provide the patients and clinicians with a framework or tool to help guide the choice of antipsychotic based on the profile of side effects. In PW 2 (Taylor et al., 2002), published in 2002, my colleagues and I examine the implications of co-prescribing the newer atypical antipsychotics with the older conventional antipsychotics. We were at the forefront of drawing attention to the problem of polypharmacy and the hazards associated

with this pattern of prescribing in psychiatry and educating clinicians about the risks and side effects burden of such practice.

1.2. Medicines Information: Foundation to Psychiatric Research

My first post in psychiatric pharmacy was as a medicines information pharmacist at the Maudsley Hospital, London. This was a platform to integrate findings from research into everyday practice as a clinical pharmacist. In the early 1990s, medicines information services in the UK were structured into local, regional and national or specialist services. Across the country, there were specialist services for medicine use in pregnancy and lactation, use of drugs in liver disease, renal impairment, paediatrics and various other specialisms. The National Centre for Psychiatric Medicines Information was housed in my department at the Maudsley Hospital in London. This was a service dedicated to providing answers to a range of complex questions regarding the care of mental health patients. The enquiries came from psychiatrists, general practitioners, nurse specialists, hospital and community pharmacists and a host of other clinical specialists from all around the country and occasionally from abroad.

Questions form the basis of scientific enquiry, research and advancement. It was while I was in Medicines Information that I honed all the skills that would later help me on my research journey. My most cited research work, PW 3 (Whiskey et al., 2001), is a systematic review and meta-analysis of St John's wort in depression. This arose out of frequent and recurring questions on the efficacy, side effects, toxicity, and potential drug interactions of this herbal preparation.

Medicines Information provided a perfect route into research and publications. When clinicians asked for advice on how to manage the patients under their care, it was my responsibility together with my colleagues to synthesise and provide recommendations based on the best available evidence. Thus PW 4 (Whiskey and Taylor, 2004), for example, was work produced to explore the potential of pramipexole in affective illness and where it could sit in the hierarchy of evidence. It was also while in Medicines Information that I contributed my first book chapter, entitled 'Depression in cardiovascular disease' (PW 5). The book, titled *Case studies in psychopharmacology: the use of drugs in psychiatry*, was written especially by pharmacists for all grades of clinical staff, including doctors, pharmacists and nurses working in psychiatry.

Between 1999 and 2001, I served as a pharmacist editor (psychiatry) of the Royal Society of Medicine's publication *Current Medical Literature – International Hospital Pharmacy*. The journal aimed to provide its readers with the most important and exciting current developments in the field every quarter. While serving as editor, I developed analytical, evaluation and writing skills.

My interest in the treatment of refractory schizophrenia, the specific area to which I have dedicated my career, also developed while I was working in Medicines Information, a service which I went on to lead from 2005 to 2008. In 2003, I published PW 6 (Whiskey et al., 2003): 'Continuation of clozapine treatment: practice makes perfect' because I was interested in the pattern of clozapine prescribing and the experience of the clinician. The following year, in 2004, generic versions of clozapine became available in the UK market. I published an opinion piece in the *Pharmaceutical Journal* on generic clozapine PW 7 (Whiskey and Taylor, 2004). Since 2014, I have been part of the psychopharmacology expert panel of the National Psychosis Service, South London and Maudsley National Health Service (NHS) Foundation Trust that organise regular lectures on behalf of the Royal College of Psychiatrists. These lectures answer complex questions in the treatment of patients with TRS and serve to empower these clinicians.

The relationship between the triad of clinical pharmacy, medicines information and research is illustrated in Figure 1 below.

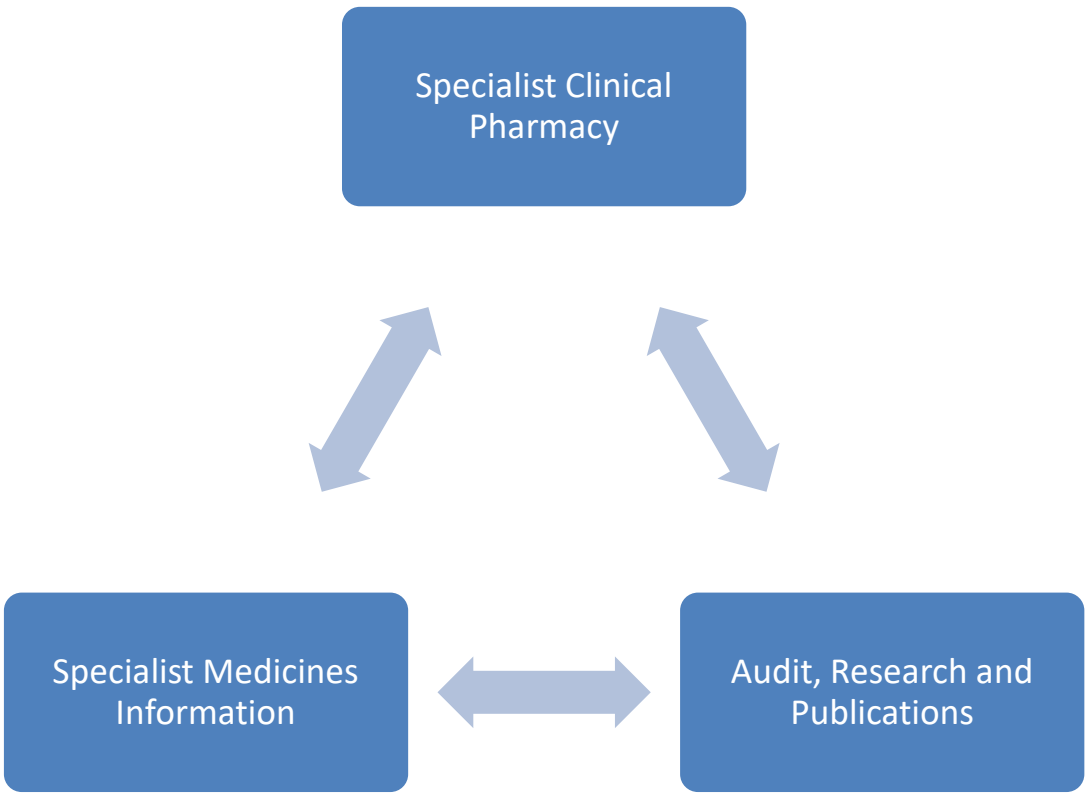


Figure 1: The triangle of my psychiatric pharmacy development

1.3. Overview of the context statement

This context statement covers my 33 PWs over the period 2003 to 2020 (Appendix 1). In 2010, I joined the National Psychosis Service of the South London and Maudsley NHS Foundation Trust, specialising in the treatment of refractory psychotic disorders. My PWs have focused mainly on addressing the underlying factors responsible for the underutilisation of clozapine, the only licensed, evidence-based treatment in patients with TRS. There are four pillars on which clozapine underutilisation rests. They represent the themes of my PWs. These are: factors relating to the drug, clozapine, a unique molecular entity; factors that pertain to the patient; issues related to the prescriber; and infrastructure and regulatory controls (see Figure 2 for details). My contribution as laid out in my PWs over the last one and a half decades has been to provide solutions that break down these pillars that form a formidable barrier in clozapine prescribing. It is without a doubt that these contributions have led directly to increased clozapine prescribing in the UK and worldwide. I have contributed to the understanding, evaluation and addressing of clozapine-related haematological adverse effects. I have been at the forefront of the use of granulocyte colony-stimulating factor (G-CSF) in clozapine rechallenge. I was the first to adopt the US monitoring parameters in the UK and call for a change in haematological monitoring in the UK. I have been involved in pioneering work with cardiologists educating psychiatrists about clozapine-related cardiac adverse effects.

Intramuscular clozapine is unlicensed in the UK. It was first used in the country on my unit at the National Psychosis Unit, a tertiary referral unit of the South London and Maudsley NHS Foundation Trust specialising in treating refractory schizophrenia. I authored the guideline for the use of intramuscular clozapine which has been widely adopted across NHS organisations in the UK. Our findings and experience have now been published and included in my PWs. Another important aspect of clozapine treatment is therapeutic drug monitoring (TDM), which is an important determinant of treatment outcomes. TDM is affected by drug formulation. My work in understanding clozapine pharmacokinetic changes based on pharmaceutical form has important clinical significance.

Factors that are related to the patient such as ethnicity, especially benign ethnic neutropenia (BEN) and the presence of medical comorbidity can severely limit clozapine prescribing. My work in this area has led to an increase in awareness and greater clozapine prescribing. I am still actively engaged in elucidating the genetic basis of BEN. The clinicians' knowledge and attitudes play a great part in prescribing. There is no place where this is of greater significance than in clozapine prescribing in TRS. Equally as important as increasing confidence in clozapine prescribing are efforts to develop viable alternatives. There is an urgent need for more effective as well as better tolerated treatments in refractory psychotic disorders.

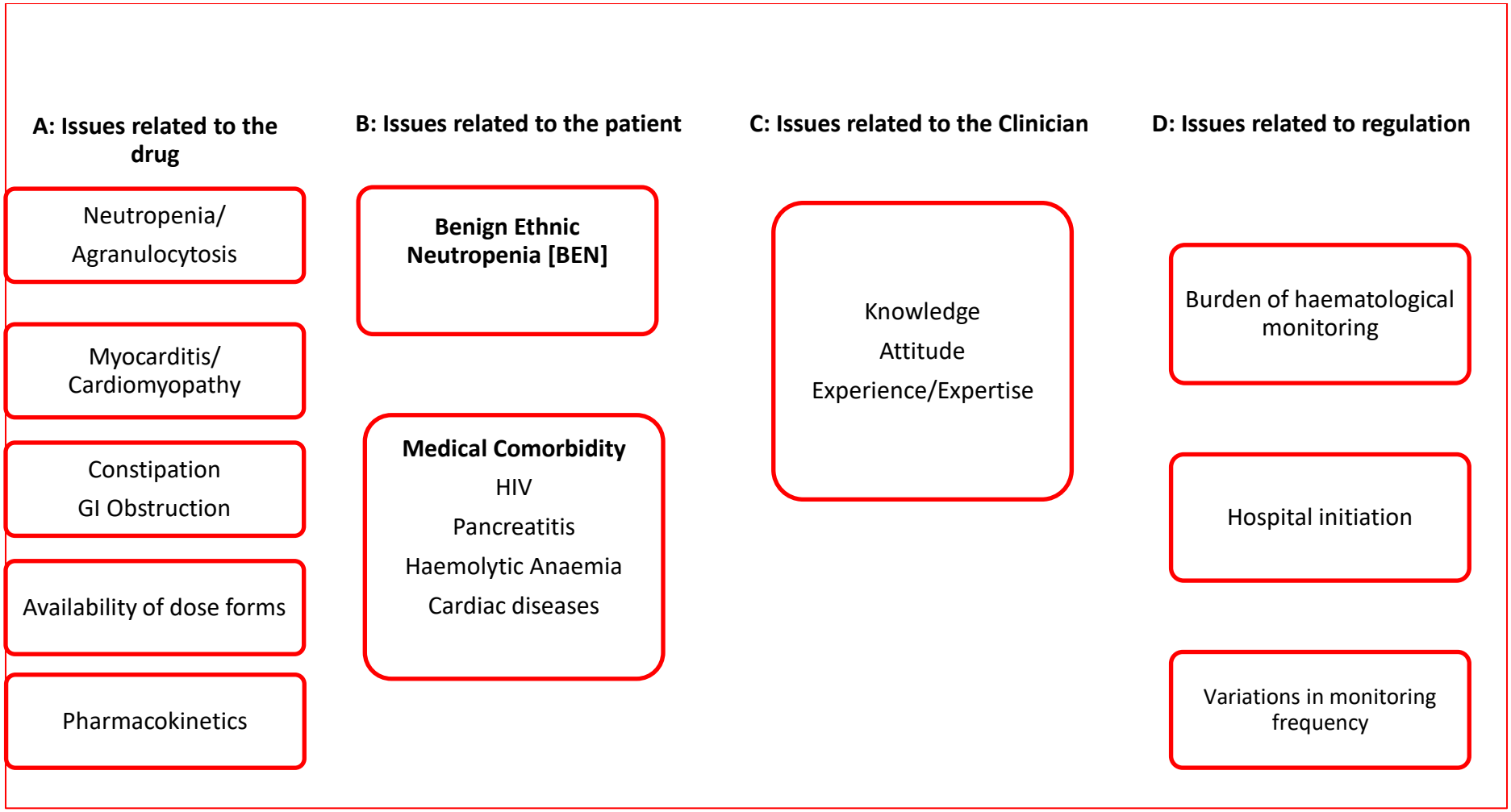


Figure 2: Themes - Barriers to clozapine utilisation

1.3.1. The context statement

This context statement will explore and critically discuss a range of papers representing my extended research over 20 years into the factors that underlie the underutilisation of clozapine in treatment-refractory schizophrenia and the strategies to deploy to overcome these barriers.

Specific issues will be explored throughout. These are:

- Haematological adverse effects of clozapine
- Benign ethnic neutropenia and clozapine use
- Cardiovascular adverse effects of clozapine
- Pharmacokinetics of clozapine
- Medical comorbidity as a limitation to clozapine use
- Intramuscular clozapine use to facilitate treatment
- Evaluation of the underuse of clozapine in the UK

1.3.2. Summary/Conclusion

"The biggest opportunity to improve patient outcomes is not discovering new therapies, but rather ensuring safe delivery of existing therapies" – Provonost, 2004.
Clozapine is the best opportunity in patients with TRS. This body of work will demonstrate strategies to optimise the most effective weapon in the pharmacotherapeutic armamentarium in TRS.

CHAPTER 2: Schizophrenia

2.1. Introduction

"So you shall be driven mad because of the sight which your eyes see". Deuteronomy 28:34

Schizophrenia is a complex illness indeed. There is such a wide variation in the illness presentation, features and prognosis that it is better conceptualised as a group of illnesses. We are only beginning to understand the neurobiology of the disease and why some patients do not respond to standard antipsychotic treatments. In this chapter, I discuss the illness, schizophrenia, the risk of developing the illness and the symptoms that patients present with. I include the range of antipsychotics used to treat the illness and discuss my work in relation to helping the patient choose antipsychotic treatment in early-phase schizophrenia (PW 1). I also critically discuss the algorithm for the treatment of schizophrenia. I look at the efficacy and tolerability of antipsychotic drugs and briefly look at some of the debilitating adverse effects of typical antipsychotic drugs and how these have now been replaced by the cardiometabolic side effects of the newer atypical agents. In addition, I introduce the concept of measurements in psychiatry, that is, the use of rating scales to determine outcomes such as response and remission, and the use of algorithms in the treatment of schizophrenia.

As a regular contributor to the Maudsley Prescribing Guidelines, I have been a strong and vocal advocate for rational pharmacotherapy. I have contributed to the systematic assessment and identification of patients in my NHS Trust who have been treated with multiple antipsychotics without adequate response, assessing the reasons for the delay in treatment and ensuring that they are offered clozapine treatment. I am a member of the expert drug panel of the National Psychosis Service at the South London and Maudsley NHS Foundation Trust. Also, the Royal College of Psychiatrists organise annual educational symposia where I deliver lectures on management strategies in the treatment of refractory schizophrenia.

2.2. Epidemiology of Schizophrenia

Schizophrenia is the most severe, chronic and disabling mental illness (Rössler et al., 2005; Knapp et al., 2004). It affects how individuals think, feel and behave. The burden of the illness on the patient, family, relatives and society is substantial. In 2013, schizophrenia was ranked in the top 25 leading causes of disability in the world (Chong et al., 2016). It has been recognised through the ages and it is present in all cultures (Bauer et al., 2011). There is no biological test for the diagnosis of schizophrenia. The diagnosis of schizophrenia is made when a patient presents with a set of psychological symptoms that cannot be explained by other conditions or disease processes.

The epidemiology of schizophrenia is complicated by the identification and precise definition of what the illness is as well as the methodological approach of the epidemiological studies.

Prevalence refers to the frequency, or how often an illness or condition is present in a population at a specific point in time. Incidence is a measure of the rate of occurrence of an illness or condition. The prevalence of the condition can be estimated at a given point, that is, point prevalence, over a given period, for example, a 12-month prevalence. Alternatively, it can be given in terms of the lifetime prevalence, which denotes the proportion of people in a population that will develop the illness or condition at some point over their lifetime. The most comprehensive reviews to date estimate the lifetime prevalence of schizophrenia at 0.4% (Saha et al., 2005; Simeone et al., 2015). This is considerably lower than the oft-cited figure of 1% (Bhugra, 2005). A systematic review estimates the incidence of schizophrenia at 15.2 cases per 100,000 population (McGrath et al., 2008).

Schizophrenia typically strikes at the prime of life, either in the late teens or early twenties. Onset of schizophrenia in men tends to be between the ages of 18 and 25 years. There appear to be gender differences in schizophrenia, but uncertainties remain. For women, the mean age of onset is between 25 and 35 years (Ochoa et al., 2012). Most studies indicate that onset of symptoms occurs earlier in males than females, although estimates of the difference vary considerably (Gogtay et al., 2011; Eranti et al., 2013). Whether men and women are equally likely to develop schizophrenia remains uncertain. The incidence of schizophrenia appears to be higher in men in comparison to women. The risk of men developing the illness is estimated to be about 1.4 times that of women (Aleman, Kahn and Selten, 2003; Abel, Drake and Goldstein, 2010). However, prevalence studies in the population have failed to reveal a gender difference (McGrath et al., 2008; Perälä et al., 2007). This gender difference in incidence and prevalence may be explained by higher mortality among men. This is especially true with respect to suicide. It could also be that men have better clinical outcomes than women. The neuroprotective effect of oestrogen in women has also been postulated as a mechanism that explains gender differences (Falkenburg and Tracy, 2014).

2.3. Symptoms of schizophrenia

The hallmark of schizophrenia is the presence of psychotic symptoms, namely auditory hallucinations (or the presence of voices) and delusions (fixed false beliefs). In Europe, the diagnosis of schizophrenia is based on the criteria outlined by the World Health Organization's International Statistical Classification of Diseases and Related Health Problems, currently in its tenth revision, ICD-10 (World Health Organization (2004). In the USA, the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, currently in its fifth edition, DSM-5 (American Psychiatric Association (2013).

Delusions are fixed false beliefs. They can be of a paranoid or persecutory nature, that is, a patient may believe that someone or something is out to do them harm, so they may not eat or drink because of a belief that the food or drink is poisoned. Delusions may be grandiose. Here a person may hold beliefs, contrary to evidence, of great wealth (e.g. of being a billionaire), of extraordinary power, ability and influence. A patient with schizophrenia, for example,

may claim to own the NHS, be able to heal various diseases, communicate with extra-terrestrials or have the ability to fly. Delusions can often have religious themes. A person with schizophrenia may believe that they or someone else is God, the son of God or the Virgin Mary. There may be delusions of reference, where an individual believes that something, an event or occurrence has a special reference or connection to them. There may be delusions of control, where a person believes that an external force can control their mind, body and movements.

A hallucination is a perception in the absence of a stimulus. A person with auditory hallucination perceives or "hears" voices. Thus, when an individual is "talking to himself", he is said to be responding to auditory hallucinations. These are the commonest type of hallucinations and they could be second-person auditory hallucinations, where the voice addresses the individual, or third-person hallucinations, where the voices discuss the patient. Hallucinatory experiences may be in other modalities. People may experience visual, tactile or olfactory hallucinations.

A person with schizophrenia will often present with a disorder of their thinking or thought processes. They may believe that something or someone can put thoughts into their head, withdraw their thoughts or can read their thoughts. The thinking may be muddled or illogical and the speech sometimes impossible to follow.

The symptoms described above are referred to as positive symptoms. Negative symptoms of the illness include features such as a lack of motivation, drive, poverty of speech and a blunted or flat affect.

Both the *International Classification of Diseases*, tenth edition (ICD-10) and the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5) emphasise the positive symptoms because they are easily observable. But the less dramatic cognitive and 'negative' symptoms can last for years and significantly impact people's quality of life, productivity and functionality. These are much more difficult to treat and less responsive to treatment. Between 80 and 90 per cent of people with schizophrenia experience persistent cognitive symptoms and approximately 40 per cent experience ongoing negative symptoms (Carbon and Correll, 2014; Green, 2006). Negative and cognitive symptoms make it difficult for people to function on an everyday basis, to interact socially, to sustain relationships, to live independently and to hold down a job. Negative symptoms include apathy, loss of motivation, loss of energy, and a loss of interest in people and activities, leading to social isolation. Cognitive symptoms affect memory and attention: people find it hard to concentrate and remember words, people and places; they process information slowly and find it difficult to plan and make decisions.

In patients with TRS, these negative and cognitive symptoms are magnified and contribute even more to the poor functional recovery in these patients. Thus, developing effective treatments is a high priority for patients, carers and clinicians.

2.4. Schizophrenia treatment algorithm

The drug treatment algorithm for schizophrenia needs considerable improvement. However, the requisite tools for an overhaul are still lacking. The choice of drug treatment is still based on a trial and error approach. Precision medicine is directed towards treatments that consider the whole person – the genetic variation of that individual, the environment in which he lives and the lifestyle choices he makes. This is still a long way from actualisation in the treatment of psychiatric disorders (van den Oord, Chan and Aberg, 2018; Fernandes et al., 2017).

There is no guideline on schizophrenia that recommends a specific antipsychotic to be used as first-line or second-line treatment in patients with first-episode schizophrenia. The National Institute for Health and Clinical Excellence (NICE) guidelines on schizophrenia recommend any oral antipsychotic medication for patients with first-episode psychosis. The choice of antipsychotic medication should be made jointly by the service user and the healthcare professional, considering the views of the carer if the service user agrees. Likewise, the Maudsley Prescribing Guidelines (MPG) make a similar recommendation, with the provision that if it is not possible to agree on the choice of the antipsychotic with the patient, a second-generation antipsychotic (SGA) should be prescribed.

The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines (Hasan et al., 2012) for the biological treatment of schizophrenia recommend that antipsychotics should be introduced with great caution. It recognises the high risk of extrapyramidal symptoms (EPS) in patients with first-episode psychosis. It recommends the use of the minimum effective dose of either a first-generation antipsychotic (FGA) or a second-generation antipsychotic (SGA) medication as possible treatments for a person experiencing a first episode of schizophrenia, but that SGAs should be favoured in first episode patients. This variability in recommendations was highlighted in a review of 24 schizophrenia treatment guidelines from 12 different countries (Gaebel et al., 2005). In the review, nine of the guidelines recommend SGAs as first-line treatment in multi-episode psychosis, 13 recommend either an FGA or SGA, and one recommends an FGA only.

What is consistent in most guidelines on schizophrenia is the almost universal recommendation of the use of clozapine in patients with TRS. That is, to use clozapine after the failure to respond to two different antipsychotics given at an adequate dose for an adequate period. At least one of the drugs should be a non-clozapine second-generation antipsychotic. The MPG also stipulates the use of clozapine after failure to respond to two different antipsychotics. We can therefore summarise the algorithm for the treatment of schizophrenia as follows in Figure 3.

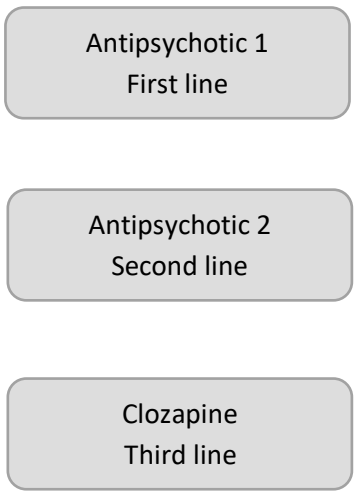


Figure 3: Algorithm for the treatment of schizophrenia

2.5. Helping to make the first-choice of an antipsychotic drug

One of the most life-impacting clinical decisions to make in the treatment of schizophrenia is the choice of which antipsychotic drug to use in a young person with a first-episode psychosis. Unfortunately, no specific antipsychotic is recommended as either the first or second line, and it is up to the clinician based on their experience and clinical judgement to determine which antipsychotic to use (Table 1). This is done in consultation with the patient and family/carer where possible. As schizophrenia is a condition in which long-term, often lifetime treatment is required, the choice of an antipsychotic drug is of paramount importance and must be based on efficacy and drug tolerability.

Table 1: Antipsychotic drugs

First-Generation Antipsychotics (FGA) oral	Second-Generation Antipsychotics (SGA) oral
• Chlorpromazine • Flupentixol • Haloperidol • Pericyazine • Perphenazine • Pimozide • Prochlorperazine • Sulpiride • Trifluoperazine • Zuclopenthixol	• Amisulpride • Aripiprazole • Asenapine • Cariprazine • **Clozapine[#]** • Lurasidone • Paliperidone • Quetiapine • Risperidone

First-Generation Antipsychotics (FGA) depot injections	Second-Generation Antipsychotics (SGA) depot injections
• Flupenthixol decanoate • Fluphenazine decanoate • Haloperidol decanoate • Zuclopenthixol decanoate	• Aripiprazole • Paliperidone palmitate • Olanzapine embonate • Risperidone

Recommended only in treatment-refractory schizophrenia

2.6. Efficacy of antipsychotic drugs

In the last decade, several meta-analyses and systematic reviews of the comparative efficacy of antipsychotics have been conducted (Huhn et al., 2019; Leucht et al., 2017; Leucht et al., 2013). The largest and the most recent of these is a network meta-analysis of placebo-controlled and head-to-head randomised controlled trials (RCTs) comparing 32 antipsychotics (Huhn et al., 2019). The study confirmed much of what is already known regarding the efficacy of antipsychotic drugs. First is the fact that the grouping of antipsychotics into two groups, FGAs and SGAs, is artificial and very misleading as these antipsychotics are not homogenous in any way. Secondly, there appear to be modest but significant differences in efficacy among antipsychotic drugs. The SGA olanzapine, amisulpride and risperidone appear to be more effective compared to other SGAs such as aripiprazole, quetiapine and other FGAs. The findings consistently showed that clozapine is the most effective agent with the greatest effect size compared to other antipsychotics. There is only one notable exception. In a meta-analysis of 40 randomised controlled trials in treatment-refractory schizophrenia (Samara et al., 2016), clozapine was not found to be significantly better than other antipsychotics.

2.7. Tolerability of antipsychotic drugs

If there remains a degree of uncertainty in antipsychotic efficacy differences, there is no doubt about the substantial differences in adverse effect. FGAs cause significantly more extrapyramidal side effects (EPSEs) compared to SGAs (Correll et al., 2004; Leucht et al., 2009; Zhang et al., 2013; Carbon et al., 2017). Even among SGAs, there are significant differences in their propensity to cause EPSE, with risperidone and amisulpride more likely than quetiapine and olanzapine (Rummel-Kluge et al., 2012; Leucht et al., 2013). EPSEs including Parkinsonism, acute dystonias and akathisia can occur early in treatment, or tardive dyskinesia (TD), which occurs later in treatment. These side effects can be distressing, stigmatising and in the case of TD, potentially irreversible (Divac et al., 2014).

While SGAs may be associated with a lower risk of neurological adverse effects, they cause substantially more metabolic adverse effects including weight gain, dyslipidaemia, impaired

glucose tolerance and diabetes (Hirsch et al., 2017; Zhang et al., 2017). Olanzapine and clozapine appear to carry the greatest risk for weight gain and diabetes (Jin, Meyer and Jeste, 2004; Rummel-Kluge et al., 2010; Smith et al., 2008). The increased mortality in patients with schizophrenia has been attributed by some authors in part to these metabolic changes with antipsychotic drugs (De Hert, Correll and Cohen, 2010; Casey et al., 2004).

2.8. Defining treatment-refractory schizophrenia (TRS)

TRS is defined as an insufficient response to two antipsychotics, although what this means both in research and clinical practice is imprecise. One must take into account illness severity, the number of antipsychotic drugs tried, the dose and duration of the antipsychotic treatment and patient adherence to treatment. Consensus criteria for TRS were put forward by the Treatment Response and Resistance in Psychosis (TRRIP) Working Group using these variables (Howes et al., 2017).

Most treatment guidelines endorse clozapine use when a patient meets the criteria for TRS. What is less clear is the definition of adequate response. Most clinical trials in schizophrenia define response as when there is a greater than 20% improvement in symptoms, as measured using a standardised rating scale such as the Brief Psychiatric Rating Scale (BPRS) or the Positive and Negative Syndrome Scale (PANSS). Unfortunately, this level of change does not translate into clinically meaningful improvement (Leucht et al., 2007). Furthermore, clinical rating scales do not usually constitute part of the routine clinical practice as they should. The implication of this is that only a minority of patients experience a good clinical response or achieve remission from symptoms (Leucht et al., 2017). In a study of patients with first-episode schizophrenia, haloperidol, an FGA, was compared with four SGAs, amisulpride, olanzapine, quetiapine and ziprasidone (Boter et al., 2009). Response, defined as ≥ 50% reduction in PANSS scores, was achieved in 37% for haloperidol, 67% for amisulpride, 67% for olanzapine, 46% for quetiapine, and 56% for ziprasidone patients at 12 months, whereas the corresponding figures for the proportion of patients who were in remission at 12 months were 17% for patients on haloperidol, 40% in amisulpride treated patients, 41% for olanzapine recipients, 24% for quetiapine, and 28% in ziprasidone treated patients.

2.9. When to start clozapine treatment in TRS

The overwhelming consensus is that there is a delay in clozapine initiation in TRS (Taylor et al., 2003; Howes et al., 2012; Bogers et al., 2016). In fact, recent studies suggest clozapine should be used as second line when patients fail to respond to the first agent prescribed. In a study of first-episode schizophrenia designed to examine an optimal drug treatment algorithm, patients were randomised to receive either olanzapine or risperidone (Agid et al., 2011). Patients who are classified as not meeting the predefined criteria for response were switched to receive the other antipsychotic. In the third phase, patients who failed to meet

the response criteria to the sequential trial of the two antipsychotics (olanzapine and risperidone) were switched to clozapine. In the first phase, 74.5% of patients responded, with a higher response rate for olanzapine (82.1%) compared with risperidone (66.3%). In the second phase, response rates dropped dramatically to 16.6%, with olanzapine being better than risperidone. In the third phase with clozapine, the response was once again 75%. This can be illustrated in Figure 4.

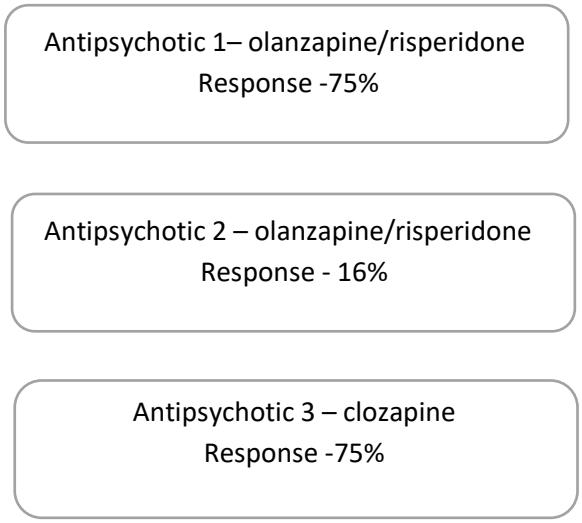


Figure 4: Algorithm in first-episode schizophrenia (adapted from Agid et al., 2011)

The results here indicate that response to first-line antipsychotic treatment in first-episode schizophrenia is reasonably good. However, for patients who do not achieve a satisfactory improvement with first-line agents, the probability of responding to the second-line antipsychotic is dramatically low. There is therefore sufficient reason to explore the rationale for the use of clozapine as a second-line agent after non-response to the first antipsychotic drug. A more recent three-phase switch study has been published (Kahn et al., 2018). In the first open-label phase, 18 first-episode schizophrenia patients received four weeks of treatment with amisulpride (800mg per day). Patients who did not meet the criteria for symptomatic remission entered phase two, a double-blind portion where patients were randomised to continue amisulpride or switch to olanzapine. Fifty-six per cent of patients achieved remission in the first phase after four weeks. In the second phase, 45% of amisulpride and 44% of olanzapine patients achieved symptomatic remission after six weeks. In the 12-week third phase of the trial on open-label clozapine treatment, 28 per cent of patients achieved remission (see Figure 5).

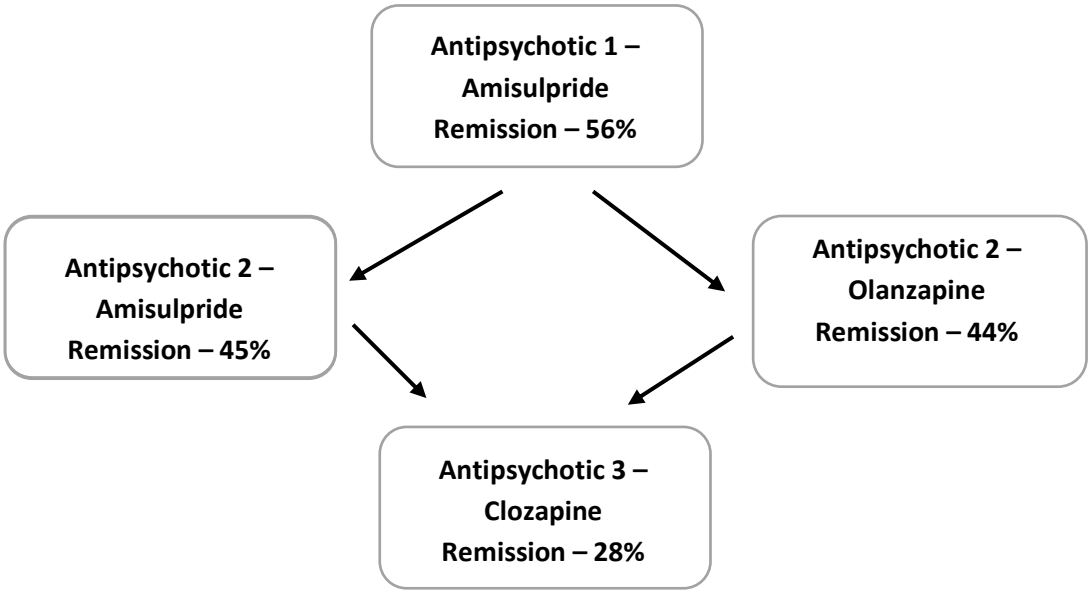


Figure 5: Algorithm in first-episode schizophrenia (adapted from Kahn et al., 2018)

The authors concluded that a switch from amisulpride to olanzapine did not improve the outcome for patients suffering from first-episode schizophrenia and that clozapine should be recommended when patients do not achieve remission after adequate treatment with a first-line agent. This is in contrast to current recommendations.

2.10. Place of Clozapine in TRS

About 30% of patients with schizophrenia are treatment refractory (Meltzer, 1997; Conley and Kelly, 2001). Clozapine is the most effective antipsychotic and the only drug licensed in the treatment of refractory schizophrenia (Mizuno et al., 2020; Siskind et al., 2016). It is more effective in improving the most meaningful and clinically significant outcomes in the management of schizophrenia. One such outcome measure is mortality, which is recognised to be greater in patients with schizophrenia (Hjorthøj et al., 2017). Treatment with clozapine is associated with reduced mortality compared with other antipsychotics (Tiihonen et al., 2009; Taipale et al., 2020). Many patients with schizophrenia die by suicide, a major cause of the increased mortality seen among patients with schizophrenia, and it is increased more than tenfold in patients with schizophrenia compared to the general population (Saha et al., 2007). Clozapine is proven to reduce suicide rates in schizophrenia, an indication for which it is specially licensed (Meltzer et al., 2003). Furthermore, not only is it demonstrated to be more effective in reducing rehospitalisation rates (Masuda et al., 2019; Taipale et al., 2018), it has greater efficacy in reducing hostility and aggression (Frogley et al., 2012) and is shown to reduce substance misuse among patients with schizophrenia better than other antipsychotics (Marcus and Snyder, 1995).

One sure way to improve outcomes is optimising clozapine prescribing, preventing unnecessary discontinuations and improving retention of patients in clozapine treatment programmes (see Figure 6 below). However, even with optimal clozapine prescribing, the work is only half done, as only about 40-50% of patients with refractory schizophrenia show a robust response to clozapine (Lieberman et al., 1994; Siskind et al., 2017). More urgent work is needed to find alternatives to clozapine in patients with TRS.

In the next chapter, I examine the peculiar characteristics of this unique drug that makes it so problematic for use by clinicians treating patients with schizophrenia.

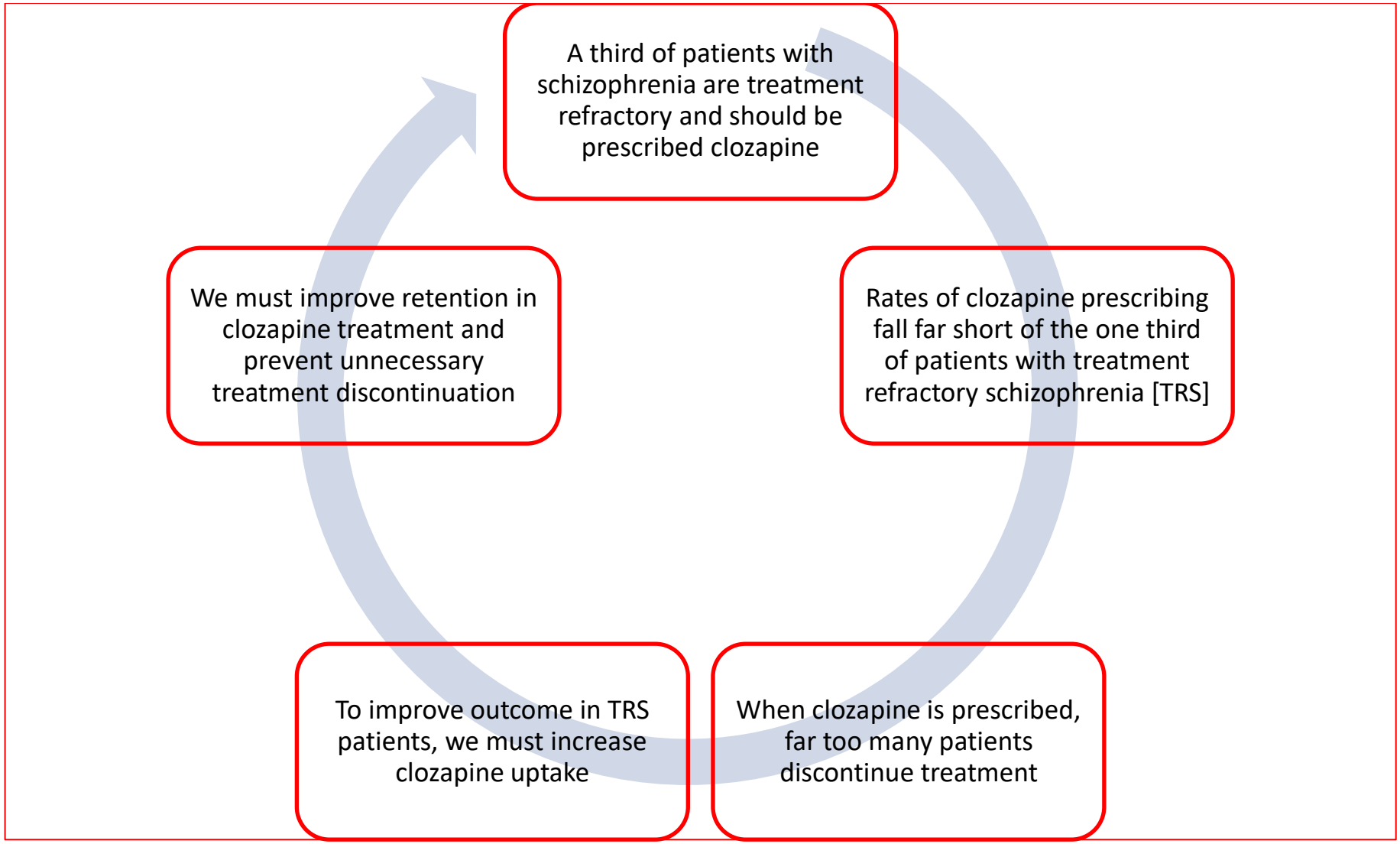


Figure 6: Optimising clozapine treatment in TRS

CHAPTER 3: Barriers related to clozapine

3.1. Introduction

The drug clozapine engenders intense fear both among clinicians and patient/family groups. After all, this is a drug that was considered too dangerous and was withdrawn from the market for almost 20 years before it was re-introduced. It is not helped by sensational headlines in the news media. An *Observer* headline in 2018 regarding clozapine was "She was unrecognisable – families warn of antipsychotic drug effects".

From a psychopharmacological perspective, clozapine would be what is considered a "dirty" drug because of the great number of receptors that it interacts with. This affinity for numerous receptors accounts for a diverse range of adverse effects, some benign and others potentially life-threatening. Clozapine initiation is typically undertaken in hospitals, partly to mitigate the risk of side effects. Unfortunately, rather than a thorough evaluation of the benefits and risk of clozapine treatment, there is a much greater emphasis on the risk and less on the potential benefits. It is therefore fundamental to understand the nature of the risk of clozapine treatment and ways to reduce or eliminate them.

In this chapter, I focus on my PWs to examine clozapine adverse effects and how best to manage the risks.

3.2. Haematological adverse effects of clozapine

Monitoring haematological adverse effects of antipsychotics: from chlorpromazine to clozapine

All antipsychotics can cause haematological side effects including agranulocytosis but mandatory blood monitoring is required only for clozapine. Agranulocytosis is a life-threatening adverse effect of drugs in which, on exposure to the drug, individuals with previously normal haematologic values develop severe neutropenia in which the absolute neutrophil count (ANC) falls below 0.5×10^9/L (van der Klauw et al., 1999).

Clozapine is associated with well-recognised haematological adverse effects, including neutropenia, agranulocytosis, thrombocytopenia, anaemia and eosinophilia. Of these, agranulocytosis is the most feared for its potential lethality. The greatest barrier to increased clozapine use is the requirement for mandatory blood monitoring. Regular haematological monitoring was introduced almost universally as a requisite for clozapine treatment to mitigate this risk. Although this mandatory regular monitoring reduces risk, it greatly diminishes the widespread clinical utility of this important pharmacotherapeutic agent PW 10 (Whiskey et al., 2019).

As a consultant pharmacist at the South London and Maudsley NHS Foundation Trust, the largest provider of mental health and substance misuse services in the UK with its link to the world-renowned Kings College London Institute of Psychiatry Psychology and Neurosciences (IoPPN), my clinical and research interest is in the management of refractory psychotic disorders. A significant portion of my clinical time is spent in the evaluation of patients with possible clozapine-induced haematological adverse effects, assessing the probability of clozapine as the causative agent, the implication of concomitant medications, risk versus benefits of clozapine rechallenge, the details of the process of rechallenge and monitoring the outcome of clozapine rechallenge, PW 8-10 (Whiskey and Taylor, 2007; Meyer et al., 2015; Whiskey et al., 2019). PW 11 and 12 (Lally et al., 2017a, Lally et al., 2017b) examine the use of G-CSF in the context of clozapine-induced haematological adverse effects.

To fully appreciate the significance of the role of haematological monitoring in clozapine treatment, it is necessary to review the historical context. Chlorpromazine was the first antipsychotic employed in clinical use. It was introduced in France in 1952. Its introduction in psychiatric treatment was nothing short of revolutionary. It reduced the severity and intensity of psychotic symptoms, reduced agitation and behavioural disturbances, allowed many patients with chronic psychotic disorders to regain some functionality, and reduced the need for prolonged and often indefinite hospitalisations (Casey et al., 1960; Engelhardt et al., 1960). Not long after its introduction, along with other phenothiazines in the same class such as thioridazine, promazine and perphenazine, reports of haematological adverse effects began to emerge. The first report of agranulocytosis attributed to chlorpromazine was published in 1954 by Lomas, in which after two weeks of treatment a 69-year-old female developed fever and pallor. The drug was immediately stopped and blood investigation showed a total white cell count of 0.7 x 10^9/L. The episode lasted two weeks and the patient fully recovered. In 1958, Pisciotta et al. published a review of 16 cases of agranulocytosis following the use of phenothiazines, primarily chlorpromazine. The duration of treatment varied between ten days to 401 days, with an average of 55 days before onset symptoms. The risk of agranulocytosis with chlorpromazine appeared to be higher in women compared to men (Pretty et al., 1958; Pisciotta, 1958). There appeared to be a pattern to the occurrence of agranulocytosis with chlorpromazine. Upon initiation of drug treatment, there was a latency period of about three weeks, followed by a rapid fall in neutrophil counts over a period of a few days which reached a nadir in about five days. On drug discontinuation, the process is reversible and recovery occurs in about five to ten days. Where death has resulted from agranulocytosis, it has been secondary to infections, mainly of the respiratory tract (Pisciotta et al., 1958).

After about ten years of clinical use of chlorpromazine in more than 50 million patients worldwide, a review of its efficacy and adverse effects was published by Ayd (1963) in which he described 69 cases of chlorpromazine-induced agranulocytosis. The reaction was more likely to occur in women and the highest risk period was between day 20 and 60 of treatment initiation. According to Ayd, “often patients periodically have a temporary leukocytosis or a temporary leukopenia, or both, with a return to normal as treatment with this drug continues. Such variations in the blood picture seem unrelated to the taking of chlorpromazine". He further asserts that the risk is greatest within the first three months of treatment and diminishes

with treatment. He argues against routine haematological monitoring as this only provides a sense of “false security”.

Haematological monitoring of phenothiazine treatment was described by Pisciotta (1969). From 1960 to 1968, patients who were treated with phenothiazines had routine weekly blood monitoring for two months, considered the highest risk period for agranulocytosis. In a sample of 6,200 patients, they detected five new cases of agranulocytosis. Importantly, however, they also detected mild transient leukopenia in 10% of the patients in the sample (Pisciotta, 1978). Thus, although the risk of blood dyscrasias in early-phase treatment was recognised with chlorpromazine, the practice of routine blood monitoring did not become entrenched in the clinical treatment of patients with psychotic disorders.

The true incidence of agranulocytosis with chlorpromazine and other phenothiazines is unknown but there have been various estimates. The risk has been estimated to be 0.3% in treated patients (Korst, 1959). Huguley (1964) estimated the risk to be between 0.13% and 0.7% in chlorpromazine treated patients. In one large retrospective study of over 10,000 patients, the incidence of agranulocytosis was estimated to be 0.05% (Litvak and Kaelbling, 1971).

If the introduction of chlorpromazine was revolutionary, the advent of clozapine into psychiatric treatment was a revelation. The drug was synthesised in 1958 and entered clinical use in the early 1960s. Clozapine revealed that a drug could possess antipsychotic activity without the burden of extrapyramidal symptoms (Gerlach et al., 1974; Bürki et al., 1974). Soon after its introduction, it became clear that clozapine had superior efficacy in patients with schizophrenia compared to the phenothiazine derivatives chlorpromazine and haloperidol (Gerlach et al., 1974; Hemphill et al., 1975; Chiu et al., 1976; Shopsin et al., 1979; Povlsen et al., 1985). Importantly, there was no statistically significant difference in the occurrence of haematological adverse effects (Griffith and Saameli, 1975).

The course of psychopharmacological history was altered by the so-called “Finnish epidemic” of agranulocytosis that occurred in June and July 1975 (Amsler et al., 1977). Before this time, clozapine was already widely used in more than 20 countries around the world including Switzerland, Austria and West Germany (Griffith and Saameli, 1975). Clozapine was launched in Finland in February 1975. Between June and July 1975, 16 cases of agranulocytosis were reported, of which half (eight patients) died (Idänpään-Heikkilä et al., 1977; Senn et al., 1977). The uncharacteristically high rate of occurrence of agranulocytosis was 21 times that observed in other countries (Anderman and Griffith, 1977). Another unusual feature about this “outbreak” was that it was limited to the south and south-west of Finland and occurred in six out of 69 hospitals in the country (Idänpään-Heikkilä et al., 1975). The possibility of contributing genetic, local factors or adulterated drug batch were thoroughly examined, and no probable cause could be determined. This incident in Finland led to the withdrawal of clozapine from most countries.

A thorough and exhaustive review of the Finnish cases commissioned by the drug manufacturer and the Government of Finland recommended weekly blood monitoring for the first 18 weeks of clozapine treatment, the period during which 90% of cases of agranulocytosis occur while checking for any signs of infection (Amsler et al., 1977). It was further recommended that thereafter, blood tests should be performed for any patient showing any signs of infection. Indeed, this recommendation was almost identical to that previously made with regards to phenothiazine treatment, suggesting weekly blood counts for the first two months of treatment (Pisciotta et al., 1958, Pisciotta, 1959; Pisciotta, 1969). Thus, despite the withdrawal of clozapine from most markets, patients who were established on clozapine and others for whom there was no alternative could continue treatment in some European countries.

Notwithstanding the withdrawal of clozapine, interest in the drug continued to grow and the use on compassionate grounds increased for those whose illness was refractory to conventional antipsychotics. Towards the path of licensing, because of the risk of agranulocytosis, the efficacy bar that was set for clozapine far exceeded what was ever required for any other drug. It was required that clozapine be effective for those patients who had not responded to other antipsychotics and secondly, that it be more effective than other agents (Crilly, 2007). So, in 1984, the Sandoz Clozapine Study # 30 began, leading to the publication of the seminal work of Kane et al. (1984). This was a six-week comparison of clozapine and chlorpromazine in 286 patients with treatment-resistant schizophrenia. The results of the trial were extraordinary. 30% of clozapine-treated patients were classed as responders, compared to just 4% in the chlorpromazine group. This was the catalyst for the reintroduction of clozapine as a treatment in refractory schizophrenia, with the requirement for mandatory blood monitoring. Unfortunately, contrary to adopting the recommendations of weekly blood monitoring for only the first 18 weeks of treatment as was stipulated following the Finnish outbreak of 1975, the reintroduction of clozapine in 1990 mandated regular blood monitoring throughout the duration of treatment. Because there was no robust evidence for haematological monitoring of clozapine, different monitoring schedules were implemented in different parts of the world (Nielsen et al., 2016).

Prevention is the essence of clozapine haematological monitoring. The aim is to uncover agranulocytosis at the asymptomatic phase before the onset of infection so that the drug is promptly discontinued. If this takes place, bone marrow recovery usually follows within days of treatment cessation. It is now 30 years since the reintroduction of clozapine and it remains the gold standard in the treatment of refractory schizophrenia. There is substantial experience with its use and the associated risks. Epidemiological data indicates that the risk of agranulocytosis is about 0.8% and that the peak risk period is the first 18 weeks of treatment (Alvir et al., 1993; Atkin et al., 1996). After the first year of treatment, the risk decreases exponentially with an incidence of 0.07% (Atkin et al., 1996). Female gender and older age are risk factors for clozapine-induced agranulocytosis. The most recent meta-analysis indicates that the risk may have been overestimated, and puts the overall prevalence at 0.4% (Xiao-Hong et al., 2020). This is more in line with our own clinical experience of clozapine use

in our services at the National Psychosis Unit, a UK tertiary referral service at the South London and Maudsley NHS Foundation Trust that specialises in the treatment of patients with refractory schizophrenia.

Indefinite clozapine haematological monitoring is neither necessary nor evidence-based. Firstly, weekly blood monitoring with clozapine or indeed with chlorpromazine would detect agranulocytosis in the asymptomatic phase. However, longer intervals of monitoring have a very low probability of detecting agranulocytosis and only give a false sense of security (Ayd, 1963; Honigfield, 1996; Patel et al., 2002). The implications of monitoring regulations are discussed further in Chapter 7.

Furthermore, the cost of long-term clozapine haematological monitoring has also been examined and it has not been found to be cost-effective (Zhang et al, 1996; Girardin et al., 2014)

To summarise, the risk of clozapine-induced agranulocytosis is very low. The risk is highest in the first 18 weeks of treatment and the risk decreases exponentially thereafter. After one year of treatment, the risk is in the same order as other antipsychotics. Therefore, long-term haematological monitoring is not necessary, evidence-based nor is it cost-effective. Although there are cases of late-onset agranulocytosis, when monitoring occurs at less than weekly intervals, the capacity to detect agranulocytosis is dubious but rather, is more likely to detect benign neutropenia unrelated to clozapine treatment.

3.3. Cardiac side effects of clozapine

Like any other drug, continuation with clozapine treatment is based on the individual assessment of the balance of efficacy and tolerability. Regardless of how effective a drug is, patients will discontinue treatment if there are overwhelming tolerability issues. It is therefore important to understand the pharmacology of clozapine so that effective steps are taken to prevent side effects and to mitigate them when they do occur. The side effects of clozapine are readily understandable from its receptor action.

Among the common causes of frequent and unnecessary discontinuation in clozapine-treated patients are cardiac adverse effects. At the initiation of treatment, the dose of clozapine is gradually increased over a period of about one month. The principal reason for this gradual dose escalation is to minimise the risk of cardiac side effects, mainly tachycardia and postural hypotension. It is for this reason that the majority of cases of clozapine initiation occurs in inpatient settings, to allow for regular assessment of blood pressure, pulse and temperature in the first few weeks of treatment.

My PWs 13-17 (Patel et al., 2019; Sweeney et al., 2020; Joy et al., 2017; Whiskey et al., 2020) have furthered our understanding of the cardiac side effects of clozapine.

3.3.1 Postural hypotension:

Postural or orthostatic hypotension is a drop in blood pressure when rising from a sitting position. It is defined as a decrease in systolic blood pressure (SBP) of ≥20 mm Hg or diastolic blood pressure (DBP) of ≥10 mm Hg within three minutes of standing up (Leung et al., 2012). This can cause dizziness, light-headedness or syncope. The frequency and severity of clozapine-induced postural hypotension are determined by the speed and magnitude of dose increases. According to the manufacturer, circulatory collapse may occur because of postural hypotension when the dose is increased too quickly. In severe cases, this can lead to cardiac or pulmonary arrest (Mylan). Postural hypotension tends to occur in the first few weeks of initiating treatment. It occurs in about one in ten patients and tolerance to the effect gradually develops (Young et al., 1998). Assessment is done by taking lying and standing blood pressure, and patients are advised to take time when standing up. The effect is related to clozapine's potent α_1- adrenergic blocking properties. It has the highest affinity for this receptor compared to other antipsychotics and thus the greatest potential to induce orthostatic hypotension (Leung et al., 2012).

The mean elimination half-life of clozapine is 12 hours (Choc et al., 1987; Jann et al., 1993; Lin et al., 1994). This implies that if a patient stops taking clozapine, within two to three days, the drug is eliminated from the system. Tolerance to the cardiovascular effects is diminished and dosage re-titration from the beginning, at a low dose of 12.5mg daily, is required. Although clozapine initiation and re-titration can occur in the community, the perceived burden of physical health monitoring of blood pressure, pulse and temperature, makes community initiation unappealing. Therefore, patients with a history of non-compliance with treatment present a formidable challenge. Often clozapine treatment is abandoned because of short-term

difficulties, whereas evidence that clozapine reduces rehospitalisation is very robust (Pollack et al., 1998; Ahn et al., 2005; Taipale et al., 2018; Kesserwani et al., 2019).

The requirement for in-patient initiation and monitoring of clozapine for cardiac, haematological and other related side effects accounts in no small measure for the underutilisation of clozapine. Nowhere is this more evident than in Japan, which has one of the lowest usages of clozapine in the world (Bachmann et al., 2017), and where a patient is required to be in hospital for 18 weeks. In a survey of 144 clinical staff (Gee et al., 2014) the need for or refusal of hospital admission was identified as one of the top reasons for the delay in clozapine initiation.

3.3.2 Tachycardia:

Tachycardia, a condition in which the heart rate exceeds 100 beats per minute, commonly occurs with clozapine. Just as with postural hypertension, it tends to occur within the first four to six weeks of treatment. Between a quarter to a third of patients treated with clozapine will experience tachycardia (Safferman et al., 1991; Nilsson et al., 2017; Sweeney et al., 2020). Tolerance to clozapine-induced tachycardia usually develops (Marinkovic et al., 1994), but may be persistent in some patients (Nilsson et al., 2018; Adeyemo et al., 2020).

Clozapine-induced tachycardia is related to the potent anticholinergic property, causing vagal inhibition (Young et al., 1998; Fitzsimons et al., 2005; Ronaldson, 2017). In addition to the anticholinergic effects, clozapine's inhibition of presynaptic α2 adrenoceptors, and indirect activation of the β adrenoceptors in the heart, contribute to the increased heart rate (Leung et al., 2012). Sinus tachycardia in clozapine-treated patients is usually a benign and self-limiting process, but very rarely, it can be in the context of a more severe cardiac pathology such as myocarditis, leading to premature termination of treatment. As a specialist pharmacist working within a multidisciplinary team at the National Psychosis Service (NPS), we regularly receive referrals for patients with "suspected" myocarditis. The NPS is a tertiary referral facility within the South London and Maudsley NHS Foundation Trust, specialising in the treatment of patients with refractory schizophrenia. The service works closely in partnership with a variety of clinical specialists including cardiologists, neurologists, haematologists and oncologists at Kings College Hospital London, to ensure safe clozapine prescribing.

To better understand the nature of the cardiovascular side effects of clozapine, my colleagues and I undertook a retrospective study of all patients admitted to our NPS who were referred for cardiology review over a nine-year period (Joy et al., 2017). Of a total of 27 clozapine-treated patients, 16 (59%) were referred due to tachycardia. We found no significant relationship between the duration of clozapine treatment and heart rate. After a cardiology review, rate-controlling medications were started in seven of the 16 patients, five on beta-blockers and two on ivabradine. Interestingly, there was no difference in the heart rate between patients who were started on rate-controlling medications and those who were not (Joy et al., 2017). The cardio-selective β-blocker bisoprolol is the most commonly used agent in clozapine-induced tachycardia (Lally et al., 2014). A Cochrane systematic review of pharmacological interventions for clozapine-induced tachycardia (Lally et al., 2016) concluded that there was no evidence derived from well-controlled clinical trials to guide clinical practice.

Nevertheless, there is justification in the use of β-blockers or other rate-controlling treatments in persistent clozapine-induced tachycardia, given that cardiomyopathy may develop from prolonged tachycardia (Shinbane et al., 1997; Umana et al., 2003; Ronaldson 2017).

3.3.3 QTc interval prolongation

Antipsychotics to a varying extent, cause QT interval prolongation, which in turn can cause torsade de pointes and sudden cardiac death. The QT interval on the electrocardiogram is the time from the start of the Q wave to the end of the T wave. It is the time taken for the ventricles to completely depolarise and repolarise (Haddad and Anderson, 2002). An important determinant of the QT interval is the heart rate for which it should be corrected to give the corrected value or QTc (Postema and Wilde, 2014). The upper normal QTc interval is widely regarded as 440msec for men and 470msec for women (Johnson and Ackerman, 2009; Van Noord et al., 2009).

Despite the tremendous fear of the potential consequences of QTc prolongation and the frequent and ubiquitous electrocardiographic assessments of patients on antipsychotics, the interpretation of these ECG recordings is often imprecise and open to errors. For example, there are well over a dozen different formulas to correct for the QT, of which the most commonly used is Bazett's correction (Luo et al., 2004). Bazett's correction provides a value that represents the QT interval, normalised for a heart rate of 60 beats per minute (Indik et al., 2006) and thus tends to overcorrect when the heart rate exceeds this. As tachycardia is a relatively common occurrence in clozapine-treated patients, QTc interval prolongation may be inaccurately attributed and could erroneously lead to premature clozapine termination (Kim et al., 2018). Indeed, it is recommended that Bazett's correction not be used when the heart rate exceeds 80 beats per minute (Nielsen et al.,2013).

3.3.4. Myocarditis:

Myocarditis, defined as an inflammation of the heart muscles, is a recognised but rare side effect of clozapine. It is characterised by a non-specific set of symptoms including chest pain, tachycardia, fever, breathlessness and flu-like symptoms. There is controversy surrounding the true incidence of clozapine-induced myocarditis. Figures vary substantially from 0.01% to as high as 9% (Sweeney et al., 2020). The reason for such variability is unclear, although various explanations have been tendered. Perhaps the most commonly cited and valid explanation is the criteria used in the diagnosis of myocarditis.

Most cases of myocarditis occur within the first 30 days of clozapine initiation (Bellissima et al., 2018). As the symptoms can be quite variable and can range from mild non-specific symptoms to fulminant myocarditis resulting in death, termination of clozapine treatment is often the course of action at the first suggestion of possible myocarditis. Indeed, a significant proportion of patients are referred to the National Psychosis Service for clozapine rechallenge following suspected myocarditis, with most successfully rechallenged.

Unlike haematological monitoring, there is no widely acceptable monitoring protocol for myocarditis. A monitoring protocol involving the measurement of troponin and C-reactive protein, said to detect 100% of symptomatic cases, has been proposed by Ronaldson et al. (2011). Unfortunately, this monitoring rarely occurs in routine clinical practice, neither is it mandated by the clozapine manufacturers.

3.3.5. Cardiomyopathy:

Cardiovascular adverse effects associated with clozapine can be conceptualised as early occurring or late occurring, with the early-occurring symptoms potentially giving rise to the late-occurring, see PW 16 (Whiskey et al., 2020), PW 13 (Patel et al., 2019). While myocarditis tends to occur early in clozapine treatment, cardiomyopathy often manifests months or years after treatment. It is a condition characterised by left ventricular dilatation and hypertrophy leading to reduced ejection fraction. Diagnosis is by echocardiography and the most common symptom is breathlessness.

Clozapine-associated cardiomyopathy usually leads to drug discontinuation. However, in our review PW 13 (Patel et al., 2019), we point out that although cessation of clozapine treatment may be necessary sometimes, it is not always mandatory. Treatments with cardio-supportive agents such as angiotensin-converting enzyme inhibitors (ACEi), beta-blockers may allow clozapine treatment to continue successfully PW 16 (Whiskey et al., 2020).

Joint working between psychiatry and cardiology prevents premature termination of clozapine treatment and promotes successful clozapine rechallenges where treatment was discontinued prematurely.

3.4. Clozapine dosage forms, plasma levels and therapeutic response

For a drug to be effective, it must be administered to the patient. In this section, I discuss PW 20 to 23 (Casetta et al., 2020; Oloyede et al., 2019; Keshavarzi et al., 2020). Licensed clozapine was only available as a tablet until 2012, when the first liquid preparation Denzapine® suspension was licensed by Britannia Pharmaceuticals Limited. My colleagues and I had realised the importance of the availability of different formulations of clozapine, and we had started to manufacture an unlicensed suspension of 100mg in 5ml as early as 1996. Since this was an unlicensed preparation, we were interested in finding if there were any clinical correlates of this practice. My colleagues published their findings showing that clozapine levels were lower when switched from the tablets to the unlicensed liquid preparation (Coker-Adeyemi and Taylor, 2002). This was of real clinical significance given the relationship between clozapine plasma levels and therapeutic response. Since then, my colleagues and I have undertaken further research, exploring changes in the pharmacokinetic parameters when patients are

switched between different clozapine preparations (Oloyede et al., 2019; Keshavarzi et al., 2020)

Perhaps of greatest clinical significance is the introduction of intramuscular clozapine into clinical practice in the UK. When a patient actively chooses not to comply with oral medication because of a lack of insight into their mental health, clinicians will usually resort to the use of treatment by other routes of administration, usually parenteral administration. Many antipsychotics are available both as oral and intramuscular forms. The intramuscular forms are further divided into short-acting forms and long-acting depot injections. The short-acting injections can be given to patients who are very agitated, verbally and physically aggressive, in the form of rapid tranquillisation when they refuse oral treatments. The long-acting depot injections are employed in patients known to be non-compliant with oral antipsychotic treatment, and may help to reduce relapse and rehospitalisation (Correll and Lauriello, 2020).

There is no licensed short-acting clozapine injection. Because of the potential haematological side effects, depot clozapine has not even been considered. This is because, in the event of a severe adverse reaction to a drug, it needs to be discontinued immediately. Long-acting depot injections persist in the body for several months.

At the National Psychosis Unit, one of the challenges we faced was a group of patients with treatment-refractory schizophrenia who refused to take any oral treatment. This is a surprisingly common feature in this group of patients and there was little that could be done to facilitate clozapine treatment. It was not until 2015 that we could finally obtain unlicensed intramuscular clozapine from the Netherlands. I was responsible for writing the protocol and guidelines for the use of intramuscular clozapine at the South London and Maudsley NHS Foundation Trust (see Appendix 2). We were able to administer intramuscular clozapine to the first patient at our unit in 2016. As the pioneers in the UK, we shared our protocol with other NHS organisations and it became the template on which clozapine injection was used in the country.

Our experience of the use of intramuscular clozapine is outlined in Casetta et al. (2020). Here, we describe the outcomes for the first cohort of patients in whom the drug was prescribed. We found that in half the cases, there was no need to administer the injection. The patients decided to take it orally when presented with the option of either the oral form or injection of clozapine. For those who received injections, the majority of patients received between 1-3 injections before transitioning to oral clozapine. The prescription of intramuscular clozapine thus allowed the initiation of clozapine for a cohort of patients in whom it would otherwise have been impossible. Importantly, the outcome for these patients was no different from those prescribed only oral clozapine.

In the next chapter, I examine some specific and peculiar characteristics of some groups of patients that make the use of clozapine unattractive to the treating clinicians. Here, much weight is given to treating the patient safely, and less emphasis is given to treating the patient effectively, thus skewing the risk-benefit ratio greatly in the direction of risk.

CHAPTER 4: Barriers related to the patient

4.1. Introduction

Unfortunately, clozapine cannot be prescribed for every patient with TRS. Every licensed medication has its contraindications, a list of conditions when the drug must not be prescribed. With clozapine, the contraindications include hypersensitivity to the active substance or any of the excipients, a history of agranulocytosis, impaired bone marrow function, uncontrolled epilepsy, severe renal or cardiac disease and active liver disease, among other conditions. There are also other situations requiring special care in the use of clozapine.

In this chapter, I discuss a specific patient characteristic, namely, black ethnicity as a limiting factor in clozapine use. In addition, I examine some of the medical comorbidities that I have had to overcome to establish patients on clozapine treatment.

This field is of special interest to me and I currently have several ongoing research projects. One such study is the development of a genetic test for BEN, and another is measuring improvement in the recognition of BEN in clinical practice. PW 18 and 19 describe some of my contributions in this field.

4.2. Benign ethnic neutropenia

When healthy individuals from other ethnic groups (non-Caucasians) have neutropenia, defined as recurrent absolute neutrophil count (ANC) of less than 1.5 x 10^9/L, this is termed benign ethnic neutropenia (BEN) or benign familial neutropenia (Haddy et al., 1999; Manu et al., 2016). In parallel to benign neutropenia, people of African ancestry have been recognised for decades to have lower total white cell count (WCC) and neutrophil count when compared to white populations (Bain et al., 1984; Cheng et al., 2004; Adetifa et al., 2009,). Both factors contribute in no small measure to the underutilisation of clozapine in black patients (Kelly et al., 2007).

In recognition of such variation, the International Federation of Clinical Chemistry (IFCC) recommends setting up country-specific reference intervals (Ichihara et al., 2017). Indeed, many researchers have advocated for the usage of racial/ethnic-specific reference intervals for laboratory tests (Lim et al., 2010; Lim et al., 2015), but there are enormous challenges with this approach because of a lack of consensus and large differences in reference intervals for different ethnicities. For example, in a study of 417 healthy volunteers comprising 115 Black Africans, 102 Afro-Caribbeans and 200 Caucasians, black patients had lower total white cell counts, neutrophil and platelet counts compared to Caucasian patients, but among black patients, counts were lower in Africans than in Afro-Caribbeans (Bain, 1996).

For 12 years after the reintroduction of clozapine in the UK in 1990, there was no consideration of the difference in haematological reference intervals between black and white patients.

The same Caucasian reference range was applied for all patients. Unsurprisingly, black patients were significantly more likely to have pre-treatment neutropenia, making them ineligible for starting treatment (Atkin et al., 1996) and more likely to discontinue treatment due to neutropenia during treatment. The recognition and introduction of BEN monitoring in 2002 was, therefore, a welcome first step in the right direction. It allowed clozapine haematological monitoring with a lowered threshold in patients of African ancestry diagnosed as having BEN by a haematologist (Rajagopal, 2005; PW 18 - Whiskey et al., 2011).

I did not fully appreciate the magnitude of the problem of BEN in relation to clozapine treatment until about 2007, when I was working at Lambeth Hospital, part of the South London and Maudsley NHS Foundation Trust. Lambeth Hospital is in Brixton, South London, an area with one of the highest percentages of Black and Minority Ethnic (BaME) populations in the country. The Borough of Lambeth is also associated with high levels of poverty and deprivation. It is among the 10% most deprived authorities in England (out of 326 districts) (Lambeth, *State of the borough,* 2016). At the same time, the higher risk of schizophrenia and other psychotic disorders has been consistently reported among black and ethnic minority groups for several years (Sharpley et al., 2001; Bhavsar et al., 2014; Tortelli et al., 2015). To worsen the prognosis even more, the prevalence of substance misuse was very high in this population (Phillips et al., 2003; Afuwape et al., 2006; Di Forti et al., 2019). Thus, no matter what metrics were used, the outcome for patients with schizophrenia in Lambeth was depressingly poor.

It was against this background that I was frustrated to observe, first, the inability of black patients with treatment-resistant illness to enrol on clozapine treatment because of low baseline neutrophil counts, and secondly, patients who were already on treatment were called in repeatedly for blood tests when neutrophil counts fell in the "amber" range, between 1.5 - 2.0 x 10^9/L in accordance with the Medicines and Healthcare products Regulatory Agency (MHRA) monitoring guidelines. When patients' blood results fall in the amber range, they are required to have twice-weekly blood monitoring until neutrophils are above 2 x 10^9/L. If neutrophils fall below 1.5 x 10^9/L, this is regarded as a red result and clozapine treatment is stopped immediately. It is therefore no wonder that black patients feel constricted and restrained by this rigid framework. The opportunities for a young black patient recovering from psychosis who is in part-time education or employment become very slim indeed with frequent and often clinically irrelevant blood tests to satisfy the regulatory requirements.

Many black patients, unfortunately, end up on the clozapine Central Non-Rechallenge Database (CNRD), a register of patients who have experienced haematological adverse effects related to clozapine. This is a centralised database to prevent inadvertent re-exposure of at-risk patients. Fortuitously, the introduction of monitoring per the BEN guidelines in 2002 provided some leeway for patients in that the threshold for treatment cessation was reduced. See Table 2 below:

	Current UK MHRA Guidelines	
Status	**General population Criteria**	**BEN criteria**
Green* WBC Neutrophils	 ≥ $3{\cdot}5x10^9$ ≥ $2{\cdot}0x10^9$	 ≥ $3{\cdot}0x10^9$ ≥ $1{\cdot}5x10^9$
Amber** WBC Neutrophils	 ≥ 3·0 and < $3{\cdot}5x10^9$ ≥ 1·5 and < $2{\cdot}0x10^9$	 ≥2·5 and < $3{\cdot}0x10^9$ ≥ 1·0 and < $1{\cdot}5x10^9$
Red*** WBC Neutrophils	 < $3{\cdot}0x10^9$ < $1{\cdot}5x10^9$	 < $2{\cdot}5x10^9$ < $1{\cdot}0x10^9$
Action in the UK: *Green – Continue clozapine **Amber – Continue clozapine with increased monitoring frequency (twice a week) until green result is obtained ***Red – Stop clozapine (interruption) and sample blood daily, monitoring for infection. Patient not re-exposed to clozapine until there have been two separate green results on two consecutive days. UK: United Kingdom MHRA: Medicines and Healthcare Products Regulatory Agency WBC: White Blood Cell BEN: Benign Ethnic Neutropenia		

Table 2: UK Medicines and Healthcare Products Regulatory Agency (MHRA) guidelines for clozapine monitoring.

Unfortunately, there was a lack of awareness on the part of psychiatrists and clinicians treating black patients with refractory schizophrenia. Black patients were inadvertently being denied the most effective treatment because of a lack of knowledge by clinicians. Thankfully, the risk of the more serious and potentially life-threatening agranulocytosis was not increased in black patients relative to Caucasians (Munro et al., 1999). Paradoxically, the risk of clozapine-induced agranulocytosis may in fact be lower in black patients, although this is yet to be determined. This assertion is based on drawing parallels between the observations of the similarities between chlorpromazine and clozapine-induced agranulocytosis. With either drug, the risk was highest in the first few months of treatment and decreased the longer the treatment duration; risk was increased in women and with increasing age (Korst, 1959; Ayd, 1963; Pisciotta, 1969). One of the epidemiological findings of extensive use of chlorpromazine and other phenothiazines is the reduced risk of agranulocytosis in black patients (Lambo, 1957; Pisciotta et al., 1958). There is therefore the possibility of a similar likelihood of reduced risk of clozapine-induced agranulocytosis among black patients. That the risk of clozapine-induced agranulocytosis may have a genetic basis is borne out by the fact that relative to Caucasian patients, Asian patients have 2.4 times the risk of agranulocytosis (Munro et al., 1999).

As an African myself, the health inequality hit home when sometime in 2008, I had a blood test at my local GP as part of a routine check-up. I found that my neutrophil counts were below 1.5 x 10^9/L and that I would be ineligible for clozapine treatment if it were ever needed. This was the time I started to follow up on several of the cases of black patients with treatment-refractory illness who were having problems during treatment. I ached for every patient who was ineligible to start clozapine treatment or discontinued either directly or indirectly due to haematological reasons. This culminated in the publication of the paper "The importance of the recognition of benign ethnic neutropenia in black patients during treatment with clozapine: case reports and database study" (Whiskey et al., 2011).

4.2.1. Prevalence of benign ethnic Neutropenia

Benign ethnic neutropenia has been observed in Black African, Afro-Caribbean and Middle Eastern populations. The prevalence varies from about 10 – 50% (Haddy et al., 1999; Hsieh et al., 2007; Thobakgale and Ndung'u, 2014), depending on the population studied and the ANC that is used to define the condition. Although the threshold to define BEN is commonly accepted as ≤ 1.5 x 10^9/L as per the United States Cancer Institute threshold for neutrophil toxicity (Hsieh et al., 2010), other values are sometimes used. A neutrophil threshold of ≤ 2.0 x 10^9/L has been used by others to define the condition. For example, Shoenfeld et al. (1988) found a prevalence of BEN in 37.2% of Black Beduin and Falashah Jews using this parameter. In their systematic review, Manu et al. (2016) define BEN as persons in this group with neutrophil counts in the range of 1.0 – 1.8 x 10^9/L.

4.2.2. Diagnosis of benign ethnic neutropenia

BEN is a diagnosis of exclusion. This means that the diagnosis is made in people of African and Middle Eastern ancestry with low neutrophil counts without any known cause, who are not at increased risk of infections. For a patient to be monitored using BEN criteria, the diagnosis must be confirmed by a haematologist.

Having highlighted the nature and extent of the limitation that the lack of recognition of BEN imposes in initiating and maintaining black patients on clozapine, it was important to implement necessary changes. I undertook extensive and wide-ranging educational interventions, speaking to consultant psychiatrists, junior doctors and all clinical staff both in in-patient and out-patient settings. I highlighted the problem in lectures and symposia that I and colleagues from the National Psychosis Unit (NPU) deliver annually on behalf of the Royal College of Psychiatrists. The NPU is a tertiary referral facility at the South London and Maudsley NHS Foundation Trust that specialises in the treatment of patients with refractory psychotic disorders.

The next phase of addressing this lack of recognition was to identify a haematologist with a special interest in psychiatry and the care of mental health patients. Up till now, the diagnosis of BEN in a black patient was largely due to chance. It depended on the local hospital where the patient was assessed, and by which haematologist. It was not infrequent that a patient deemed not to have BEN was certified as having BEN by another haematologist. This is perhaps understandable in a condition identified only by the exclusion of other conditions. Furthermore, rather than being a categorical status of having BEN or not, it is most likely a continuum rather than absolute. For example, in a long-term follow-up of the natural history of

46 individuals with BEN, neutrophil counts were in the range 0.03 – 5.8 x 10^9/L with counts > 1.5 x 10^9/L in about half the tests (Lakhotia et al., 2019). There is also a natural variation in neutrophil counts with reports of morning pseudoneutropenia (Esposito et al., 2003) which may obfuscate a BEN diagnosis. It was in the process of writing our protocol for the use of granulocyte colony-stimulating factor (G-CSF) in clozapine challenge that I met with Dr Alec Mijovic, a consultant haematologist at King's College Hospital. Dr Mijovic eventually became our most important ally and together, we pushed back the boundaries of psychiatry and psychopharmacology and authored many peer-reviewed papers jointly.

In the meantime, I did all I could within my limitations as a non-prescribing pharmacist to increase the uptake of clozapine among black patients. I encouraged and educated psychiatrists who were more risk-averse to the availability of BEN monitoring, a useful tool in initiating clozapine in black patients. I became the referral point for my pharmacy colleagues who would ask my views about their patients. I would contact the clozapine registries, evaluate patients' haematological history frequently regarding clozapine rechallenges. We developed a systematic method of clozapine rechallenge based on my review published a few years earlier (Whiskey and Taylor, 2007). We used adjunctive lithium in BEN patients to increase neutrophil counts before the introduction of clozapine. My colleagues and I developed expertise in the use of G-CSF (Spencer et al., 2012; Lally et al., 2017). Unfortunately, one of the downsides to adjunctive treatment is the increase in the medication load for patients. The other is the risk of adverse effects and drug-drug interactions. The use of lithium with clozapine, for example, increases the risk of neurological adverse effects (Garcia et al., 1994; Small et al., 2003; Bender et al., 2004). Long-term lithium side effects such as impairments in renal and thyroid function (Gitlin et al., 1989; Shine et al., 2015) may make this unattractive for some patients. Indeed, in the case of one of our patients with severe treatment-refractory schizophrenia, after successful maintenance treatment with clozapine and G-CSF for six months, the patient declined continuation of treatment because of repeated weekly injections of G-CSF. Thus, the use of adjunctive medications solely for increasing the neutrophil count to maintain clozapine treatment should only be used as a last resort, and only where there is a robust clozapine clinical effect.

It was with great delight that I welcomed the new clozapine monitoring guidelines introduced in the United States in 2015. Under the new US clozapine monitoring guidelines, the neutrophil threshold for cessation of clozapine was lower both in the general population and in patients with BEN. The impact of this was that measures used previously solely to increase neutrophil counts such as lithium and G-CSF became less important. More and more patients could be treated with confidence without the fear of impromptu clozapine discontinuation. Our group was the first to use the US guidelines in the UK and call for regulatory alignment with the US (PW 10 - Whiskey et al, 2019).

My colleagues and I have recently completed a retrospective analysis of patients registered on the CNRD in our Trust. Of the 115 patients reviewed, only 7 (6%) met the equivalent US criteria. Patients' clinical status significantly worsened off clozapine. Of the 115 patients on the CNRD, 62 (54%) were rechallenged. 59 of them (95%) were successfully rechallenged on clozapine and remained off the CNRD at the end of the follow-up period. Adopting the US monitoring criteria would have a major impact in reducing clozapine discontinuations.

4.2.3. Genetics of benign ethnic neutropenia

Neutrophils constitute about two-thirds of all white blood cells. They help in the fight against infections. When neutrophils drop below 0.5 x 10^9/L, there is an increased risk of infections. People with BEN are at no greater risk of infections. Studies have shown the recurrence of BEN in families (Shoenfeld et al., 1988) and the genetic basis of BEN has been identified. Genetic studies have shown an association between individuals with a variant in the Duffy Antigen Receptor for Chemokines (DARC) gene or the Duffy-null variant and low neutrophil counts (Nalls et al., 2008; Reich et al., 2009; Reiner et al., 2011; Charles et al., 2018).

The association of the genetic basis of BEN in the context of clozapine treatment has been investigated (Legge et al., 2019). In a study of 552 individuals with treatment-resistant schizophrenia, they found that individuals homozygous for the C allele at rs2814778 were significantly more likely to develop neutropenia and 20 times more likely to stop clozapine treatment (Legge et al., 2019). This was a very exciting finding because it raised the hope of a genetic test for BEN. This was the premise for the Developmental Pathway Funding Scheme (DPFS) of the Biomedical Research Council grant application in 2019, of which I am named co-investigator.

It has been ten years since I published the paper on the importance of recognition of BEN. We have submitted a proposal for a follow-up study, evaluating the progress in addressing the problem.

Summary:
BEN is a common clinical finding in black patients but it is grossly underdiagnosed. It is a diagnosis of exclusion; unfortunately for many patients, it is arbitrary and down to chance. BEN is not a risk factor for the more severe agranulocytosis, but rather paradoxically, the risk may be lower in black patients. Yet, BEN is a critical factor in the underutilisation of clozapine in this group of patients. The new US monitoring guidelines go a long way to addressing some of the challenges of clozapine use in black patients, and UK regulatory alignment would be a welcome development.

4.3. Medical comorbidities as a barrier to clozapine use

Physical health comorbidity is common among patients with severe mental illness. On average, the life expectancy of patients with severe mental illness is reduced by 20 years compared to the general population (Hennekens et al., 2005; Laursen, 2011; Hjorthøj et al., 2017). The excess mortality seen in this group is largely due to physical diseases and medical conditions such as cardiovascular, endocrine and respiratory diseases (Brown et al., 2000; Saha et al., 2007; Reininghaus et al., 2015). Paradoxically, the presence of some of these physical health conditions can increase the hazards of clozapine use in some patients, thereby reducing its use in the medically ill. Under usual circumstances, clinicians are wary about starting clozapine in patients who are diabetic, have cardiovascular disease or are overweight. This is

because of the fear that instituting clozapine treatment may increase the risk of death in these patients. A review by Nielsen et al. (2013) describes medical conditions that warrant the discontinuation of clozapine.

Over the last two decades at the National Psychosis Service of the South London and Maudsley NHS Foundation Trust, we have treated a wide variety of patients with a multitude of clinical conditions that would constitute relative or absolute contraindications. Several patients have been referred to us for the initiation of clozapine because of their pre-existing medical conditions.

In the following PWs 24, 16 and 25 (Whiskey et al., 2018; Whiskey et al., 2020; Rodriguez et al., 2020), I describe the use of clozapine in a patient with HIV, heart failure and pancreatitis, respectively. In patients with HIV, the use of clozapine can be challenging. Haematological abnormalities are not uncommon in HIV patients. This can be misinterpreted as being due to clozapine leading to termination of treatment. Drug-drug interactions between antiretrovirals and clozapine can have significant clinical implications. The adverse cardiovascular effects of clozapine have already been discussed in detail in Chapter 4. In the patient with pancreatitis, a thorough longitudinal history of the patient, careful clinical assessment and a detailed risk-benefit assessment allowed for the successful reintroduction in the patient.

The use of clozapine in patients with significant medical comorbidities requires joint working with medical specialists including neurologists, haematologists, cardiac specialists, oncologists, renal and liver specialists. The question that we pose is not whether to use clozapine, but, how we can safely use clozapine in these patients.

In my next chapter, I explore the crucial factor of the clinician, ultimately the decision-maker on when, why and how to introduce clozapine in patients who have not responded adequately to treatment.

CHAPTER 5: Barriers related to the clinicians

5.1. Introduction

Prescriber knowledge, experience and attitudes constitute a significant barrier in clozapine use. Large variations in clozapine prescribing are mainly due to this factor. In this chapter, I show a few examples of some questions that clinicians have when treating patients using clozapine. As an extension of this knowledge and experience variation, I discuss my work looking at the extent of underuse and variation in the rates of clozapine prescribing across the UK. This is a hugely important factor because it reflects the inequity in health resources in the country.

5.2. Case vignettes

Example 1

Dear Whiskey,

*Sorry to trouble you. I'm the consultant on LEO currently. ********** suggested I approach you for some wisdom regarding the above chap, who is currently on LEO. In short, he's 52 from a Caribbean background, been on clozapine since 2003, previously well on 350mg po od. He's been on LEO six months after a period of non-compliance with associated relapse. We have slowly titrated up to 375mg po bd (tachycardia), remains unwell, level has been "therapeutic" for over a month (last 0.58 27/11/20). I've started some lamotrigine, thinking about aripiprazole and possibly, after talking with *****, aiming for level closer to 1. He is complaint and has side effects: tachycardia with postural drop noted, and hypersalivation. Gut motility not currently an issue.*

Previously seen by TREAT, and re-referred recently after significant dosage increase.

*Would be very grateful for your help as am a bit stuck. ***** wondered about National Psychosis Unit clinic?*

Example 2

Dear Whiskey,

******* troponin rose from blood on 25/11 to 64. Last week: trop 24. In the last month: trops 24-42. FBC, U+E and CRP normal. Has been refusing obs and ECG consistently, therefore we are unable to rule out myocarditis. He currently does not present with any signs or symptoms of MI or Myocarditis.*

Just wanted to ask your advice regarding Clozapine and what should we do, I think we can continue providing we monitor bloods consistently; however, ideally, he needs an ECG but difficult to obtain this if under restraint. I was also informed that the blood tests were quite difficult to get off from him yesterday.

Looking forward to your response

Sample 3
Dear Whiskey,

*Re: Ms **********
NHS **********
DoB: **********

Thank you very much in advance for helping us with this rather complicated case for clozapine rechallenge.

This 38-year-old lady with a history of heart failure, childhood leukaemia, hypothyroidism, asthma, schizoaffective disorder is floridly psychotic, despite being treated with antipsychotics (olanzapine and aripiprazole). Previously, she was treated with risperidone and quetiapine. The consultant psychiatrist wanted to re-start clozapine for this patient as she had previously been stabilised on this medicine for 13 years, and it was stopped December 2019 due to suspected myocarditis associated with clozapine.
After recent review from the cardiologist and heart failure consultant, they concluded that the patient developed dilated cardiomyopathy (not myocarditis) which was likely secondary to anthracycline treatment she received for childhood leukaemia. They did not think clozapine was the cause of dilated cardiomyopathy.

*We held a professional meeting with ******'s mom last week and clozapine rechallenge was considered by the consultant cardiologists and consultant psychiatrist. I shall send you a copy of the note and her medical history to your nhs.net email, which is more secure.*
*During the meeting, Dr **** recommended we could contact you for advice in regards to the clozapine dose titration regime and precautions as you may have experience with similar cases in clozapine rechallenge.*

Her current regular medications are:
****

The BNF and SPC stated that patients with clozapine-induced myocarditis or cardiomyopathy should not be re-exposed to clozapine. Our consultant psychiatrist is seeking advice from Denzapine Monitoring Service (DMS) if this clozapine rechallenge is an off-label use.

If you require any additional information, please let me know.

I am looking forward to hearing from you.

Many thanks

Sample 4

Hi Whiskey,

I am a psychiatrist in Ireland and I recently attended your team's day on treatment-resistant psychosis which I found really useful.

I wonder could I pick your brain about a clinical issue in relation to clozapine, renal failure and haemodialysis. Would it be possible to give you a ring some day and discuss this case with you please? Or if it would be more convenient for you I could send you more details by email

Thanks,

Catherine

*Dr.**************

Consultant Psychiatrist,

MCRN 12706

Louth Meath Rehabilitation Service,

St. Brigid's Hospital,

Ardee.

Sample 5

Dear Whiskey,

*I would like to thank you for the tremendous contribution you have made to the care and treatment of one of my patients on ****** ward.*

*I was extremely appreciative that at short notice you kindly gave your time from your schedule to meet with me, our ward pharmacist and his family in July 2020. Your explanations were greatly reassuring for my patient and his family and showed a high level of dedication and care to our patients in all departments at the ********* Hospital, given that you work with the PICU service and National Psychosis Service normally. I am also extremely grateful for your knowledge and specialist intervention which allowed us to continue my patient's treatment with clozapine following red results. This safely allowed us to continue his clozapine therapy after your specialist discussions with ZTAS clozapine monitoring service and prevented a psychotic relapse, given the patient's sensitivity to changes in clozapine. You also came to see my patient following this continuation of his clozapine treatment over a week later and have helpfully advised on other aspects of his treatment such as treatment of hypersalivation and constipation as major side effects of clozapine, which have been extremely beneficial to his ongoing care and treatment, given that he was recently discharged from Kings College Hospital. I am grateful that you have continued to advise on his care and treatment, which is greatly appreciated given your knowledge of treatment-resistant psychosis and patients on long-term clozapine, given your expertise with the National Psychosis Unit.*

You have also kindly advised on other patients under my care with treatment-resistant psychotic symptoms and I'm greatly appreciative of this, given your expertise with the management of treatment-resistant psychosis.

Thank you once again for supporting the care and treatment of my patients on Brook ward, particularly those with treatment-resistant psychosis and with your interventions I believe they are receiving the highest level of care available with our knowledge of the most up to date treatment options.

5.3. Underuse and variation in clozapine use in the United Kingdom:

The problem of the underuse of clozapine is universally recognised and acknowledged. There are ongoing efforts by different groups, organisations and nations to address the fundamental issues. In the USA in 2016, the National Association of State Mental Health Program Directors (NASMHPD) convened a national team of expert clinicians and researchers to identify and address barriers to clozapine use (Kelly et al., 2018). This effort resulted in a total of 36 recommendations to increase clozapine utilisation addressed to ten stakeholders. Unsurprisingly, key aspects of the recommendations focus on the prescriber (Love et al., 2016). Some of the highlights include:

- Prescribers of clozapine should establish links with primary care practices to assist in the management of side effects that may emerge during treatment with clozapine.
- Prescribers should continually seek to improve their knowledge base with lifelong learning on clozapine treatment.
- Less experienced prescribers should establish links with more experienced prescribers who can assist them in addressing issues that arise during clozapine treatment.
- Focus on clozapine in psychiatric residency and training programmes.
- Academic centres, in consultation with state or local mental health authorities, should encourage interdisciplinary consultation centres for community providers such as psychiatric pharmacists or nurse practitioners involved in the management of patients receiving clozapine.

In a recent systematic review of prescriber and institutional barriers and facilitators of clozapine use, Verdoux et al. (2012) examined 29 studies from 11 countries. They found that the main prescriber-related barriers to clozapine prescribing are lack of personal prescribing experience and concern with clozapine haematological monitoring and adverse effects. However, some of these concerns about clozapine about safety and adverse effects have been grossly exaggerated. For example, the risk of agranulocytosis and myocarditis was overestimated by Danish psychiatrists (Nielsen et al., 2010). This concern about clozapine adverse effects has been described as “clozaphobia” – the fear of professionals for prescribing clozapine (Cetin, 2014; Sreeraj et al., 2017). There have been concerted efforts in some countries such as New Zealand and the Netherlands, where specific interventions have yielded positive results in improving clozapine uptake. A programme of ongoing audits and feedback, educational meetings on clozapine, development of guidelines in the Auckland/Northland regions

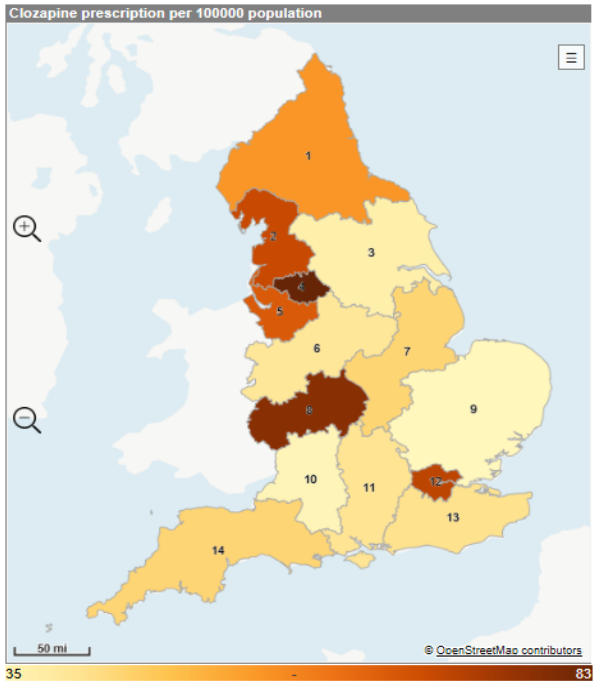
in New Zealand resulted in a substantial increase in clozapine uptake (Wheeler et al., 2009). In the Netherlands, the Dutch Clozapine Collaboration Group was set up in 2004. The group not only developed a more flexible, simple and practical guide to clozapine use, but engages in teaching and educational programmes to equip trainee psychiatrists and break down some of the rigid barriers to clozapine prescribing (Bogers et al., 2016; Schulte et al., 2010).

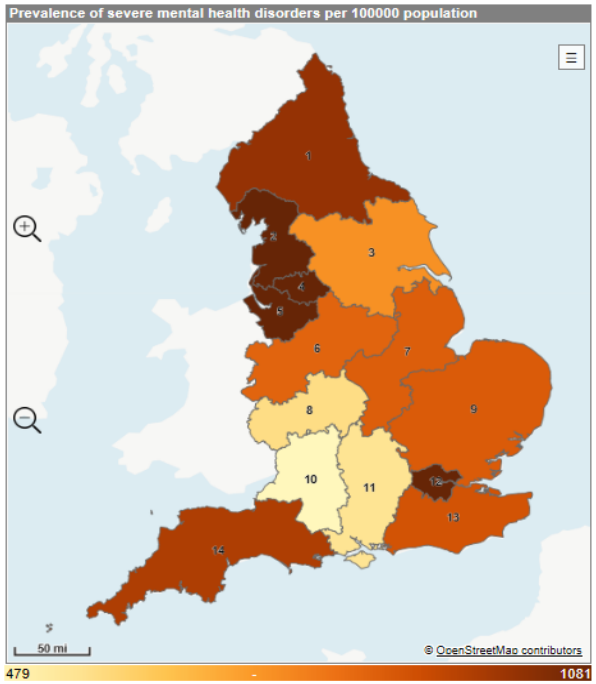
The rate of clozapine prescribing in the UK is considerably less than in New Zealand, the Netherlands and indeed many other European countries (PW 33, Whiskey et al., 2021). Working with colleagues in the NHS, academia, the National Institute for Health Research (NIHR) and in collaboration with the clozapine registries in the British pharmaceutical industry, we determined the extent of clozapine prescribing in the UK. We found more than a threefold variation in the prescribing rates in the country. Importantly, we found only one-third of the patients eligible for clozapine were being prescribed the drug. There is no national effort in the UK to address the variation and underuse of clozapine. There are no special clozapine educational programmes for trainee psychiatrists. I along with my colleagues at the National Psychosis Service of the South London and Maudsley NHS Trust do regular annual sessions on treatment-resistant schizophrenia on behalf of the Royal College of Psychiatrists. Admittedly, this is far from adequate in addressing the huge problem of clozapine underuse in the country. In Whiskey et al. (2021) (PW 33), we propose a hub and spoke model to increase local experience by leveraging regional or national expertise.

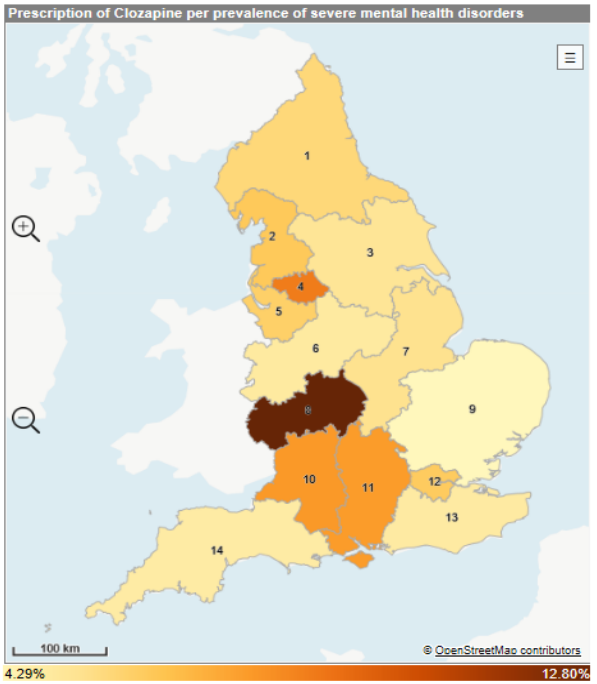
All the examples given in Section 6.1 of this chapter illustrate the need for a national strategy to address the multiplicity of barriers. In these cases, the clinicians can come to an expert they know or have been directed to and hopefully resolve the issues relating to clozapine use. Where this resource is unavailable, one can only expect that clozapine would be abandoned, giving rise to the regional inequity that we have described above. Figure 7 below is reproduced from PW 33 (Whiskey et al., 2021).

The next chapter looks at how regulatory controls constitute a barrier to clozapine use. These legal structures are notoriously difficult to change and it takes an inordinately long time for regulatory changes to occur.

NIHR | National Institute for Health Research







Code	NHS England Regional Office Name	Key (see map)	Clozapine prescriptions per 100,000 population	Severe Mental Health prevalence per 100,000 population	Prescription (%) per prevalence
E39000018	NHS England London	12	66.57	1,080.57	6.16%
E39000026	NHS England North West (Cheshire and Merseyside)	5	62.40	1,039.68	6.00%
E39000032	NHS England Midlands (North Midlands)	6	39.97	804.63	4.97%
E39000033	NHS England Midlands (West Midlands)	8	72.60	567.16	12.80%
E39000037	NHS England North West (Greater Manchester)	4	82.71	1,005.70	8.22%
E39000040	NHS England North West (Lancashire and South Cumbria)	2	65.34	1,048.19	6.23%
E39000041	NHS England South East (Hampshire, Isle of Wight and Thames Vall...	11	40.78	548.94	7.43%
E39000042	NHS England South East (Kent, Surrey and Sussex)	13	41.38	838.70	4.93%
E39000043	NHS England South West (South West North)	10	35.90	478.79	7.50%
E39000044	NHS England South West (South West South)	14	43.80	898.01	4.88%
E39000045	NHS England Midlands (Central Midlands)	7	43.86	816.48	5.37%
E39000046	NHS England East of England (East)	9	35.26	821.72	4.29%
E39000047	NHS England North East and Yorkshire (Cumbria and North East)	1	53.58	935.75	5.73%
E39000048	NHS England North East and Yorkshire (Yorkshire and Humber)	3	37.56	719.60	5.22%

Figure 7: Variation of clozapine use in the United Kingdom

CHAPTER 6: Barriers related to regulation

6.1. Introduction

Each country has a regulatory authority that is responsible for the licensing of medicinal products. In Europe, it is the responsibility of the European Medicines Agency (EMA) to ensure that all medicines distributed in and throughout the continent meet the required safety and efficacy standards. On occasions, medicines have a European Union-wide marketing authorisation, but on other occasions, the responsibility is decentralised to individual EU countries. The body that is responsible for this regulatory control in the UK is the Medicines and Healthcare Products Regulatory Agency (MHRA). It is the duty of every clinician and drug prescriber to be fully conversant with the licence of each medicine that they prescribe, in particular, what the licensed indications are, the dose, the contraindications and the special precautions for use. Where a drug is prescribed outside of the manufacturer's licence, then this is described as off-label prescribing.

It is thus the legal responsibility of a prescriber when a medicine is prescribed off-label, and so if undertaking such a practice, the prescriber or clinician must be satisfied with the evidence base for doing so. In this chapter, I review how some of the regulatory frameworks around clozapine constitute significant barriers to its greater utilisation in the treatment of schizophrenia.

6.2. Clozapine for suicide prevention in schizophrenia

Life expectancy is reduced in schizophrenia compared to the general population. On average, the life expectancy of patients with schizophrenia is reduced by between 10 and 25 years (Chang et al., 2011; Laursen et al., 2012; Jayatilleke et al., 2017). Of the excess mortality, 40% is attributed to suicide and other unnatural causes (Tiihonen et al., 2009). Suicide is a major cause of death in patients with schizophrenia. Compared with the general population, the risk of suicide is 12 times higher in people with schizophrenia (Saha et al., 2007). Half of the population with schizophrenia will experience suicidal ideation and one in ten patients will eventually kill themselves (Pompili et al., 2007; Chapman et al., 2015). The specific protective effect of clozapine against suicide has been demonstrated in trials. In the International Suicide Prevention Trial (InterSePT), clozapine was demonstrated to have greater efficacy in reducing suicidal behaviour compared to olanzapine in high-risk adult patients with schizophrenia or schizoaffective disorder. It is against this background that the FDA licensed the use of clozapine in the US to reduce the risk of current suicidal behaviour in patients with schizophrenia or schizoaffective disorder who are judged to be at chronic risk for re-experiencing suicidal behaviour.

Unlike the US, clozapine is not licensed for suicidality in the UK or Europe. Nonetheless, the benefit of clozapine in reducing suicide is clearly evident even if not licensed for this indication. For example, in a study of mortality in schizophrenia in Finland, clozapine was shown to

be associated with substantially lower mortality than other antipsychotics, due at least in part to its anti-suicide effect. These results have since been replicated by the 20-year follow-up study (Taipale et al., 2020).

It is evident that this regulatory discrepancy between the authorities in the US and Europe is detrimental to patients with schizophrenia in Europe.

6.3. Regulation relating to haematological monitoring

The requirement for regular blood monitoring as part of the licensing requirement is perhaps one of the greatest barriers to clozapine use. However, this requirement is neither standardised nor uniformly applied universally. The degree of limitation that it produces varies substantially from one country to another. To further consider this, we can look at different models of clozapine treatment in four countries, namely Iceland, the Netherland, the United Kingdom and the United States of America. In Iceland, there is no enforcement of mandatory blood monitoring. An analysis of clozapine use showed that in the first 18 weeks of treatment, only 12 of 83 patients (14.4%) had weekly blood tests. After 18 weeks, more than 40% of patients had blood tests once every six months or less (Ingimarsson et al., 2016). Indeed, it is this flexible approach to haematological monitoring that accounts for the low rates of attrition during clozapine treatment in Iceland, where more than seven in ten patients initiated on treatment remain on it in the long term. This is significantly higher than in countries where mandatory blood testing is rigidly enforced, with about half the patients discontinuing treatment (Whiskey et al., 2003 (PW 6); Krivoy et al., 2011; Davis et al., 2014; Legge et al., 2016). This assertion is also broadly supported by a survey of the international trends in clozapine use, where Iceland ranks considerably higher in clozapine use (Bachmann et al., 2017).

In the Netherlands, the country's Clozapine Collaboration Group recommends a more flexible approach to clozapine monitoring. According to the guidelines, after the first six months of treatment with clozapine, a patient with mental capacity can decide to stop regular blood tests, as the risk of dying from agranulocytosis would be about the same as the risk of dying in a traffic accident (Netherlands Clozapine Collaboration Group, 2009; Schulte et al., 2010). The group recommends that even if routine monitoring is discontinued, a blood test be carried out immediately upon any clinical suspicion of infection or agranulocytosis. Furthermore, even then, it recommends blood testing four times a year to observe possible trends.

In 2015, the United States adopted new monitoring criteria for clozapine treatment. The threshold for cessation of clozapine treatment under the guidance is lower than in Europe. Current UK guidelines mandate that in the general population, clozapine is ceased when white blood cell (WBC) count is $< 3 \times 10^9$/L or neutrophil count is $< 1.5 \times 10^9$/L, whereas the US guidelines recommend cessation when neutrophil counts are $< 1.0 \times 10^9$/L. Also, importantly, there is no necessity for evaluating total white cell count in deciding clozapine continuation. These changes have an immense clinical implication that could significantly increase clozapine utilisation (Sultan et al., 2017; Bastiampillai et al., 2016).

In the UK, mandatory monitoring is rigidly enforced. The policy is that without a blood test, no clozapine is dispensed. Weekly blood monitoring is required for the first 18 weeks, followed by fortnightly monitoring from 18-52 weeks, and then monthly thereafter. In 2020, with the unfortunate worldwide outbreak of COVID-19, there was a requirement to minimise patient contact to reduce transmission risk, and an opportunity to modify clozapine monitoring presented itself. At the South London and Maudsley NHS Foundation Trust, we decided that because the risk was very low, patients who had been on clozapine for one year could have blood testing once every 12 weeks (Gee et al., 2020). It is hoped that these changes will continue after the pandemic ends.

6.4. Regulation relating to hospitalisation for clozapine initiation

Historically, the initiation of clozapine required patient hospitalisation. In the UK and many other countries, thankfully that is no longer the case. Nonetheless, the clear majority of patients are started on clozapine as in-patients. Japan has probably the strictest guidelines anywhere in the world for clozapine initiation, requiring hospitalisation and weekly blood monitoring for 26 weeks (Nielsen et al., 2016). It is no wonder therefore that Japan has the lowest clozapine prescribing rates of developed countries (Bachmann et al., 2017).

In a survey of practitioner attitudes to clozapine initiation, dedicated staff or day hospital placements devoted to clozapine initiation were identified as the factors most likely to increase prescribing of clozapine (Gee et al., 2014). Making it easy for patients to start clozapine in the community or their homes would greatly facilitate an increase in uptake of the drug.

7. Concluding comments:

About a third of patients with schizophrenia have an illness that fails to respond to conventional antipsychotics and are described as treatment-resistant, or more accurately as treatment refractory.

In the last two decades, the focus of my clinical and research work has been devoted to this group of patients. Clozapine is the only proven, effective and licensed treatment. Unfortunately, it is grossly underused. Over the last year, I have had the time and the opportunity to reflect on my body of work in this field, to evaluate how my contribution has influenced patient care and to ponder on what the future holds for research in the psychopharmacology of refractory schizophrenia.

My PW 33 has shown conclusively the underuse of clozapine in the UK. It demonstrates a threefold variation in the use of clozapine in England, with only a third of eligible patients being prescribed the drug. In PW 6 (Whiskey et al., 2003), I showed that prescribers who use clozapine gain experience and confidence in prescribing. This reinforces their belief in its efficacy, which leads to an increase in clozapine prescribing rates in TRS.

Clozapine haematological monitoring is one of the major barriers to clozapine use. We also know that the stringent haematological monitoring of clozapine is not evidence-based and may constitute more of a hindrance. My PW 8 on restarting clozapine after neutropenia was a comprehensive roadmap for clinicians when rechallenging patients with a previous haematological reaction to clozapine. It served as an aide-memoire and universal reference source for psychiatrists. This public work led in no small measure to increasing clozapine uptake, and retaining patients in clozapine treatment. More recently in my PW 10, I was the first in the UK to utilise the more relaxed US clozapine monitoring criteria. From this work, we could re-establish patients who had hitherto not been allowed to receive clozapine treatment. This, in turn, led to PW 32, an influential work published in *Schizophrenia Bulletin.* From here, my colleagues and I are on a journey that I believe will ultimately lead to a relaxation of the rigid haematological monitoring requirement required by regulation.

Patients of African ancestry are disadvantaged with respect to clozapine treatment. This is due in part to BEN. My contribution in this area has, I believe, led to redressing the balance regarding access to clozapine treatment by black patients. In my PW 18, I drew attention to the issue. I have had the opportunity to revisit this same issue ten years later. To my greatest satisfaction, I discovered a four-fold increase in clozapine use in African-Caribbean patients over the period, largely due to an increase in the recognition of BEN.

No matter how effective a drug is in the treatment of a disease, it must be administered to the patient first. Many patients with schizophrenia have no insight into their condition and often refuse. I wrote the protocol for the use of intramuscular clozapine (PW 21) and we were the first unit in the UK to use it in treatment. My protocol has been widely adopted for

use throughout the country. In my PW 20, we publish our findings establishing intramuscular clozapine as a viable option in initiating and maintaining clozapine treatment, a modality that has now become common practice in the UK.

The occurrence of physical health conditions is the norm in patients with schizophrenia, as in all the general population. Unfortunately for many with TRS, these physical health conditions often lead to a reluctance in clozapine prescribing. Many of my public works (PW 13, 14, 15, 16, 17, 25) relate to the use of clozapine in patients with physical health conditions. Indeed, in these PWs, I have shown that clozapine need not be discontinued in the face of medical obstacles. Working with medical specialists, the outcome generally tends to be positive.

We understand that the outcome for patients with TRS is worse compared with patients whose illness responds to first-line antipsychotic drugs. More importantly, we now also know that delay in clozapine prescribing leads to poorer outcomes. As Provonost stated, "The biggest opportunity to improve patient outcomes is not discovering new therapies, but rather ensuring safe delivery of existing therapies".

There are many challenges in the neuropsychopharmacology of schizophrenia, including poor access to treatment, poor patient engagement in ongoing care, poor treatment response and cognitive deficits associated with the illness. For patients who fail to respond to clozapine, there is no evidenced-based treatment or recommendations and much work remains to be done in this area. There are different aspects that I envisage for my future work. First is ensuring that we start clozapine at the earliest determination of TRS. This would likely involve modifying the current treatment guidelines that clozapine is a second line for these patients. It would likely involve genetic testing to determine which patients have TRS from early onset schizophrenia. The next aspect is to understand the neurobiological basis of clozapine non-response. My clinical observations reveal that a subset of patients demonstrates reduced responsiveness to clozapine following psychotic relapses. I would like to identify predictors and clinical correlates of clozapine non-response. Cognition in schizophrenia is also an area I would like to explore further. My colleagues and I have shown that vortioxtine, a pro-cognitive antidepressant, may be used as an adjunct in TRS. Robust clinical trials looking at potential agents that would improve cognition in schizophrenia are clearly warranted. TRS need not consign patients to a life that is severely blighted by prolonged hospitalisation, poor quality of life and unproductivity. There is no greater joy for me than altering the negative trajectory of patients with TRS into a full, enjoyable and fulfilling life.

8. Final recommendations

a. **Education and Training**: The largest impact can only be achieved through training and education. The use of clozapine, its advantages, benefits and limitations must feature prominently in the training of psychiatrists. The spoke and hub training model can be utilised to develop local expertise in clozapine prescribing.

b. **Service developments:** Services should be developed by NHS organisations to facilitate early clozapine use as soon as treatment resistance is ascertained. This could include protocols to initiate clozapine treatment in the out-patient clinics.

c. **Relaxed and flexible haematological monitoring:** The current rigid regulatory framework for clozapine haematological monitoring is not evidence-based and is severely limiting. The first step would be the adoption of the US monitoring guidelines with a lower threshold for discontinuation of treatment. The next step would be to review the necessity for ongoing haematological monitoring after one year on treatment.

d. **Identification of Benign Ethnic Neutropenia (BEN):** To avoid unnecessary discontinuations and interruptions to treatment, it is essential that patients of black ancestry are assessed for BEN prior to treatment initiation. This can be done either by a simple genetic test or referral to a haematologist or both.

e. **Clozapine formulations:** There are benefits to having a diverse range of drug formulations. More work is needed in understanding the pharmacokinetics of the short-acting intramuscular clozapine. It is now possible to envisage a long-acting injection or a clozapine implant. This would of course require additional studies.

f. **Protocols for clozapine monitoring:** Clozapine is still frequently discontinued because there are either no monitoring protocols, or where they exist, they are not adhered to. Protocols to monitor for clozapine-induced myocarditis already exist, but adherence remains poor. Whereas, there are no well recognised algorithms for the monitoring and management of clozapine-induced constipation.

g. **National conference on clozapine use in resistant schizophrenia:** The United Kingdom has the expertise in the treatment of resistant schizophrenia. A national strategy can be developed to address the inequality in access to clozapine treatment and how to overcome the known and possibly unknown barriers to clozapine use.

References:

Abel, K.M., Drake, R. and Goldstein, J.M., 2010. Sex differences in schizophrenia. *International review of psychiatry*, 22(5), pp.417-428.

Adetifa, I.M.O., Hill, P.C., Jeffries, D.J., Jackson-Sillah, D., Ibanga, H.B., Bah, G., Donkor, S., Corrah, T. and Adegbola, R.A., 2009. Haematological values from a Gambian cohort–possible reference range for a West African population. *International Journal of Laboratory Hematology*, 31(6), pp.615-622.

Afuwape, S.A., Johnson, S., Craig, T.J., Miles, H., Leese, M., Mohan, R. and Thornicroft, G., 2006. Ethnic differences among a community cohort of individuals with dual diagnosis in South London. *Journal of Mental Health*, 15(5), pp.551-567.

Agid, O., Arenovich, T., Sajeev, G., Zipursky, R.B., Kapur, S., Foussias, G. and Remington, G., 2011. An algorithm-based approach to first-episode schizophrenia: response rates over 3 prospective antipsychotic trials with a retrospective data analysis. *The journal of clinical psychiatry*, *72*(11), pp.1439-1444.

Alawami, M., Wasywich, C., Cicovic, A. and Kenedi, C., 2014. A systematic review of clozapine-induced cardiomyopathy. *International journal of cardiology*, *176*(2), pp.315-320.

Aleman, A., Kahn, R.S. and Selten, J.P., 2003. Sex differences in the risk of schizophrenia: evidence from meta-analysis. *Archives of general psychiatry*, *60*(6), pp.565-571.

Alvir, J.M.J., Lieberman, J.A., Safferman, A.Z., Schwimmer, J.L. and Schaaf, J.A., 1993. Clozapine-induced agranulocytosis--incidence and risk factors in the United States. *New England Journal of Medicine*, *329*(3), pp.162-167.

American Psychiatric Association, 2013. *Diagnostic and statistical manual of mental disorders (DSM-5®)*. American Psychiatric Pub.

Amsler HA, Teerenhovi L, Barth E, Harjula K, Vuopio P. Agranulocytosis in patients treated with clozapine: a study of the Finnish epidemic. *Acta Psychiatrica Scandinavica*. 1977 Oct;56(4):241-8.

Anderman B, Griffith RW. Clozapine-induced agranulocytosis: a situation report up to August 1976. *European journal of clinical pharmacology*. 1977 May 1;11(3):199-201.

Atkin, K., Kendall, F., Gould, D., Freeman, H., Lieberman, J. and O'Sullivan, D., 1996. Neutropenia and agranulocytosis in patients receiving clozapine in the UK and Ireland. *The British Journal of Psychiatry*, *169*(4), pp.483-488.

Ayd FJ. Chlorpromazine: ten years' experience. *JAMA*. 1963 Apr 6;184(1):51-4.

Bachmann, C.J., Aagaard, L., Bernardo, M., Brandt, L., Cartabia, M., Clavenna, A., Coma Fusté, A., Furu, K., Garuoliené, K., Hoffmann, F. and Hollingworth, S., 2017. International trends in clozapine use: a study in 17 countries. *Acta Psychiatrica Scandinavica*, *136*(1), pp.37-51.

Bain BJ. Ethnic and sex differences in the total and differential white cell count and platelet count. Journal of clinical pathology. 1996 Aug 1;49(8):664-6.
Bain BA, Seed M, Godsland I. Normal values for peripheral blood white cell counts in women of four different ethnic origins. *Journal of clinical pathology*. 1984 Feb 1;37(2):188-93.

Bastiampillai, T., Gupta, A., Chan, S.K.W. and Allison, S., 2016. Changes for clozapine monitoring in the United States.

Bauer, S.M., Schanda, H., Karakula, H., Olajossy-Hilkesberger, L., Rudaleviciene, P., Okribelashvili, N., Chaudhry, H.R., Idemudia, S.E., Gscheider, S., Ritter, K. and Stompe, T., 2011. Culture and the prevalence of hallucinations in schizophrenia. *Comprehensive Psychiatry*, *52*(3), pp.319-325.

Beck, K., McCutcheon, R., Bloomfield, M.A.P., Gaughran, F., Reis Marques, T., MacCabe, J., Selvaraj, S., Taylor, D. and Howes, O.D., 2014. The practical management of refractory schizophrenia–the Maudsley Treatment Review and Assessment Team service approach. *Acta Psychiatrica Scandinavica*, *130*(6), pp.427-438.

Bellissima, B.L., Tingle, M.D., Cicović, A., Alawami, M. and Kenedi, C., 2018. A systematic review of clozapine-induced myocarditis. *International journal of cardiology*, *259*, pp.122-129.

Bender, S., Linka, T., Wolstein, J., Gehendges, S., Paulus, H.J., Schall, U. and Gastpar, M., 2004. Safety and efficacy of combined clozapine–lithium pharmacotherapy. *International Journal of Neuropsychopharmacology*, 7(1), pp.59-63.

Bhavsar, V., Boydell, J., Murray, R. and Power, P., 2014. Identifying aspects of neighbourhood deprivation associated with increased incidence of schizophrenia. *Schizophrenia Research*, *156*(1), pp.115-121.

Bhugra, D., Leff, J., Mallett, R., Der, G., Corridan, B., Rudge, S. Incidence and outcome of schizophrenia in whites, African-Caribbeans and Asians in London. *Psychological medicine*. 1997 Jul; 27(4):791-8

Bhugra, D., 2005. The global prevalence of schizophrenia. *PLoS medicine*, *2*(5).

Bogers, J.P., Schulte, P.F., Van Dijk, D., Bakker, B. and Cohen, D., 2016. Clozapine underutilization in the treatment of schizophrenia: how can clozapine prescription rates be improved? *Journal of clinical psychopharmacology*, 36(2), pp.109-111.

Boter, H., Peuskens, J., Libiger, J., Fleischhacker, W.W., Davidson, M., Galderisi, S., Kahn, R.S. and Eufest Study Group, 2009. Effectiveness of antipsychotics in first-episode schizophrenia and schizophreniform disorder on response and remission: an open randomized clinical trial (EUFEST). *Schizophrenia Research*, 115(2-3), pp.97-103.

Brown, S., Inskip, H. and Barraclough, B., 2000. Causes of the excess mortality of schizophrenia. *The British journal of psychiatry*, 177(3), pp.212-217.

Carbon, M. and Correll, C.U., 2014. Thinking and acting beyond the positive: the role of the cognitive and negative symptoms in schizophrenia. *CNS spectrums*, *19*(S1), pp.35-53.

Bürki, H.R., Ruch, W., Asper, H., Baggiolini, M. and Stille, G., 1974. Effect of single and repeated administration of clozapine on the metabolism of dopamine and noradrenaline in the brain of the rat. *European journal of pharmacology*, 27(2), pp.180-190.

Carbon, M., Hsieh, C.H., Kane, J.M. and Correll, C.U., 2017. Tardive dyskinesia prevalence in the period of second-generation antipsychotic use: a meta-analysis.

Casetta C, Gaughran F, Oloyede E, Onwumere J, Pritchard M, Shergill SS, Whiskey E, MacCabe JH. Real-world effectiveness of admissions to a tertiary treatment-resistant psychosis service: 2-year mirror-image study. *BJPsych Open*. 2020 Sep;6(5).

Casey, J.F., Bennett, I.F., Lindley, C.J., Hollister, L.E., Gordon, M.H. and Springer, N.N., 1960. Drug therapy in schizophrenia: a controlled study of the relative effectiveness of chlorpromazine, promazine, phenobarbital, and placebo. *AMA Archives of general psychiatry*, 2(2), pp.210-220.

Casey, D.E., Haupt, D.W., Newcomer, J.W., Henderson, D.C., Sernyak, M.J., Davidson, M., Lindenmayer, J.P., Manoukian, S.V., Banerji, M.A., Lebovitz, H.E. and Hennekens, C.H., 2004. Antipsychotic-induced weight gain and metabolic abnormalities: implications for increased mortality in patients with schizophrenia. *J Clin Psychiatry*, *65*(Suppl 7), pp.4-18.

Cetin, M., 2014. Clozaphobia: fear of prescribers of clozapine for treatment of schizophrenia.

Chang, C.K., Hayes, R.D., Perera, G., Broadbent, M.T., Fernandes, A.C., Lee, W.E., Hotopf, M. and Stewart, R., 2011. Life expectancy at birth for people with serious mental illness and other major disorders from a secondary mental health care case register in London. *PloS one*, 6(5), p.e19590.

Chapman, C.L., Mullin, K., Ryan, C.J., Kuffel, A., Nielssen, O. and Large, M.M., 2015. Meta-analysis of the association between suicidal ideation and later suicide among patients with either a schizophrenia spectrum psychosis or a mood disorder. *Acta Psychiatrica Scandinavica*, 131(3), pp.162-173.

Charles BA, Hsieh MM, Adeyemo AA, Shriner D, Ramos E, Chin K, Srivastava K, Zakai NA, Cushman M, McClure LA, Howard V. Analyses of genome wide association data, cytokines, and gene expression in African-Americans with benign ethnic neutropenia. *PloS one*. 2018 Mar 29;13(3): e0194400.

Cheng CK, Chan JU, Cembrowski GS, Van Assendelft OW. Complete blood count reference interval diagrams derived from NHANES III: stratification by age, sex, and race. *Laboratory Hematology*. 2004;10(1):42-53.

Chiu E, Burrows G, Stevenson J. Double-blind comparison of clozapine with chlorpromazine in acute schizophrenic illness. Australian and New Zealand Journal of Psychiatry. 1976 Dec;10(4):343-7.

Chong, H.Y., Teoh, S.L., Wu, D.B.C., Kotirum, S., Chiou, C.F. and Chaiyakunapruk, N., 2016. Global economic burden of schizophrenia: a systematic review. *Neuropsychiatric disease and treatment*, *12*, p.357.

Cohen, D., 2014. Prescribers' fear as a major side effect of clozapine. *Acta Psychiatrica Scandinavica*, *130*(2), p.154.

Cotter, S.M., Barber, N.D. and McKee, M., 1994. Survey of clinical pharmacy services in United Kingdom National Health Service hospitals. *American Journal of Health-System Pharmacy*, 51(21), pp.2676-2684.

Calvert, R.T., 1999. Clinical pharmacy—a hospital perspective. *British journal of clinical pharmacology*, 47(3), p.231.

Coker-Adeyemi, F. and Taylor, D., 2002. Clozapine plasma levels in patients switched from clozapine liquid to tablets. *Pharmaceutical Journal*, 269(7222), pp.650-652.

Conley, R.R. and Kelly, D.L., 2001. Management of treatment resistance in schizophrenia. *Biological psychiatry*, *50*(11), pp.898-911.

Correll, C.U., Leucht, S. and Kane, J.M., 2004. Lower risk for tardive dyskinesia associated with second-generation antipsychotics: a systematic review of 1-year studies. *American Journal of Psychiatry*, *161*(3), pp.414-425.

Correll, C.U. and Lauriello, J., 2020. Using long-acting injectable antipsychotics to enhance the potential for recovery in schizophrenia. *The Journal of Clinical Psychiatry*, *81*(4), pp.0-0.

Crilly, J., 2007. The history of clozapine and its emergence in the US market: a review and analysis. *History of psychiatry*, 18(1), pp.39-60.

Davis, J.M., Chen, N. and Glick, I.D., 2003. A meta-analysis of the efficacy of second-generation antipsychotics. *Archives of general psychiatry*, *60*(6), pp.553-564.

Davis, M.C., Fuller, M.A., Strauss, M.E., Konicki, P.E. and Jaskiw, G.E., 2014. Discontinuation of clozapine: a 15-year naturalistic retrospective study of 320 patients. *Acta Psychiatrica Scandinavica*, 130(1), pp.30-39.

De Hert, M., Correll, C.U. and Cohen, D., 2010. Do antipsychotic medications reduce or increase mortality in schizophrenia? A critical appraisal of the FIN-11 study. *Schizophrenia Research*, *117*(1), pp.68-74.

Di Forti, M., Quattrone, D., Freeman, T.P., Tripoli, G., Gayer-Anderson, C., Quigley, H., Rodriguez, V., Jongsma, H.E., Ferraro, L., La Cascia, C. and La Barbera, D., 2019. The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. *The Lancet Psychiatry*, 6(5), pp.427-436.

Divac, N., Prostran, M., Jakovcevski, I. and Cerovac, N., 2014. Second-generation antipsychotics and extrapyramidal adverse effects. *BioMed research international*, *2014*.

Downs, J. and Zinkler, M., 2007. Clozapine: national review of postcode prescribing. *Psychiatric Bulletin*, *31*(10), pp.384-387.

Elrod JK, Fortenberry JL. The hub-and-spoke organization design: an avenue for serving patients well. *BMC health services research*. 2017 Jul;17(1):25-33.

Engelhardt, D.M., Freedman, N., Glick, B.S., Hankoff, L.D., Mann, D. and Margolis, R., 1960. Prevention of psychiatric hospitalization with use of psychopharmacological agents. *Journal of the American Medical Association*, 173(2), pp.147-149.

Eranti, S.V., MacCabe, J.H., Bundy, H. and Murray, R.M., 2013. Gender difference in age at onset of schizophrenia: a meta-analysis. *Psychological medicine*, *43*(1), pp.155-167.

Esposito, D., Aouillé, J., Rouillon, F. and Limosin, F., 2003. Morning pseudoneutropenia during clozapine treatment. *The World Journal of Biological Psychiatry*, 4(4), pp.192-194.

Falkenburg, J. and Tracy, D.K., 2014. Sex and schizophrenia: a review of gender differences. *Psychosis*, *6*(1), pp.61-69.

Farooq, S., Choudry, A., Cohen, D., Naeem, F. and Ayub, M., 2019. Barriers to using clozapine in treatment-resistant schizophrenia: systematic review. *BJPsych bulletin*, 43(1), pp.8-16.

Fernandes, B.S., Williams, L.M., Steiner, J., Leboyer, M., Carvalho, A.F. and Berk, M., 2017. The new field of 'precision psychiatry'. *BMC medicine*, *15*(1), p.80.

Frogley, C., Taylor, D., Dickens, G. and Picchioni, M., 2012. A systematic review of the evidence of clozapine's anti-aggressive effects. *International Journal of Neuropsychopharmacology*, *15*(9), pp.1351-1371.

Gaebel, W., Weinmann, S., Sartorius, N., Rutz, W. and McIntyre, J.S., 2005. Schizophrenia practice guidelines: international survey and comparison. *The British Journal of Psychiatry*, *187*(3), pp.248-255.

Garcia, G., Crismon, M.L. and Dorson, P.G., 1994. Seizures in two patients after the addition of lithium to a clozapine regimen. *Journal of clinical psychopharmacology.*

Gee, S., Vergunst, F., Howes, O. and Taylor, D., 2014. Practitioner attitudes to clozapine initiation. *Acta Psychiatrica Scandinavica*, *130*(1), pp.16-24.

Gee SH, Shergill SS, Taylor DM. Patient attitudes to clozapine initiation. *International clinical psychopharmacology*. 2017 Nov 1; 32(6):337-42.

Gee S, Gaughran F, MacCabe J, Shergill S, Whiskey E, Taylor D. Management of clozapine treatment during the COVID-19 pandemic. *Therapeutic Advances in Psychopharmacology.* 2020 May; 10:2045125320928167.

Gerlach, J., Koppelhus, P., Helweg, E. and Monrad, A., 1974. Clozapine and haloperidol in a single-blind cross-over trial: therapeutic and biochemical aspects in the treatment of schizophrenia. *Acta Psychiatrica Scandinavica*.

Gibson, C. and Berliner, N., 2014. How we evaluate and treat neutropenia in adults. *Blood, The Journal of the American Society of Hematology*, 124(8), pp.1251-1258.

Girardin, F.R., Poncet, A., Blondon, M., Rollason, V., Vernaz, N., Chalandon, Y., Dayer, P. and Combescure, C., 2014. Monitoring white blood cell count in adult patients with schizophrenia who are taking clozapine: a cost-effectiveness analysis. *The Lancet Psychiatry*, 1(1), pp.55-62.

Gitlin, M.J., Cochran, S.D. and Jamison, K.R., 1989. Maintenance lithium treatment: side effects and compliance. *The Journal of clinical psychiatry*.

Gogtay, N., Vyas, N.S., Testa, R., Wood, S.J. and Pantelis, C., 2011. Age of onset of schizophrenia: perspectives from structural neuroimaging studies. *Schizophrenia bulletin*, 37(3), pp.504-513.

Green, M.F., 2006. Cognitive impairment and functional outcome in schizophrenia and bipolar disorder. *The Journal of clinical psychiatry*, 67, pp.3-8.

Griffith, R.W. and Saameli, K., 1975. Clozapine and agranulocytosis. *The Lancet*, 306(7936), p.657.

Haddy, T.B., Rana, S.R. and Castro, O., 1999. Benign ethnic neutropenia: what is a normal absolute neutrophil count? *Journal of Laboratory and Clinical Medicine*, 133(1), pp.15-22.

Haring, C., Meise, U., Humpel, C., Saria, A., Fleischhacker, W.W. and Hinterhuber, H., 1989. Dose-related plasma levels of clozapine: influence of smoking behaviour, sex and age. *Psychopharmacology*, *99*(1), pp.refS38-S40.

Hasan, A., Falkai, P., Wobrock, T., Lieberman, J., Glenthoj, B., Gattaz, W.F., Thibaut, F., Möller, H.J. and WFSBP Task Force on Treatment Guidelines for Schizophrenia, 2012. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, part 1: update 2012 on the acute treatment of schizophrenia and the management of treatment resistance. *The World Journal of Biological Psychiatry*, *13*(5), pp.318-378.

Hemphill, R.E., Pascoe, F.D. and Zabow, T., 1975. An investigation of clozapine in the treatment of acute and chronic schizophrenia and gross behaviour disorders. *South African medical journal= Suid-Afrikaanse tydskrif vir geneeskunde*, 49(51), pp.2121-2125.

Hennekens, C.H., Hennekens, A.R., Hollar, D. and Casey, D.E., 2005. Schizophrenia and increased risks of cardiovascular disease. *American heart journal*, 150(6), pp.1115-1121.

Hirsch, L., Yang, J., Bresee, L., Jette, N., Patten, S. and Pringsheim, T., 2017. Second-generation antipsychotics and metabolic side effects: a systematic review of population-based studies. *Drug safety*, *40*(9), pp.771-781.

Hjorthøj, C., Stürup, A.E., McGrath, J.J. and Nordentoft, M., 2017. Years of potential life lost and life expectancy in schizophrenia: a systematic review and meta-analysis. *The Lancet Psychiatry*, *4*(4), pp.295-301.

Honigfield, G., 1996. Effects of the clozapine national registry system on incidence of deaths related to agranulocytosis. *Psychiatric Services*.

Howes, O.D., Vergunst, F., Gee, S., McGuire, P., Kapur, S. and Taylor, D., 2012. Adherence to treatment guidelines in clinical practice: study of antipsychotic treatment prior to clozapine initiation. *The British Journal of Psychiatry*, *201*(6), pp.481-485.

Howes, O.D., McCutcheon, R., Agid, O., De Bartolomeis, A., Van Beveren, N.J., Birnbaum, M.L., Bloomfield, M.A., Bressan, R.A., Buchanan, R.W., Carpenter, W.T. and Castle, D.J., 2017. Treatment-resistant schizophrenia: treatment response and resistance in psychosis (TRRIP) working group consensus guidelines on diagnosis and terminology. *American Journal of Psychiatry*, *174*(3), pp.216-229.

Hsieh, M.M., Everhart, J.E., Byrd-Holt, D.D., Tisdale, J.F. and Rodgers, G.P., 2007. Prevalence of neutropenia in the US population: age, sex, smoking status, and ethnic differences. *Annals of internal medicine*, 146(7), pp.486-492.

Hsieh, M.M., Tisdale, J.F., Rodgers, G.P., Young, N.S., Trimble, E.L. and Little, R.F., 2010. Neutrophil count in African Americans: lowering the target cut-off to initiate or resume chemotherapy? *Journal of Clinical Oncology*, 28(10), p.1633.

Huguley, C.M., 1964. Drug-induced blood dyscrasias: II. Agranulocytosis. *JAMA*, 188(9), pp.817-818.

Huhn, M., Nikolakopoulou, A., Schneider-Thoma, J., Krause, M., Samara, M., Peter, N., Arndt, T., Bäckers, L., Rothe, P., Cipriani, A. and Davis, J., 2019. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *The Lancet*, *394*(10202), pp.939-951.

Ichihara, K., Ozarda, Y., Barth, J.H., Klee, G., Qiu, L., Erasmus, R., Borai, A., Evgina, S., Ashavaid, T., Khan, D. and Schreier, L., 2017. A global multicenter study on reference values: 1. Assessment of methods for derivation and comparison of reference intervals. *Clinica Chimica Acta*, 467, pp.70-82.

Idänpään-Heikkilä, J., Alhava, E., Olkinuora, M. and Palva, I., 1975. Clozapine and agranulocytosis. *The Lancet*, 306(7935), p.611.

Idänpään-Heikkilä, J., Alhava, E., Olkinuora, M. and Palva, I.P., 1977. Agranulocytosis during treatment with clozapine. *European journal of clinical pharmacology*, 11(3), pp.193-198.

Ingimarsson, O., MacCabe, J.H., Haraldsson, M., Jónsdóttir, H. and Sigurdsson, E., 2016. Neutropenia and agranulocytosis during treatment of schizophrenia with clozapine versus other antipsychotics: an observational study in Iceland. *BMC psychiatry*, 16(1), pp.1-8.

Ismail, D., Tounsi, K., Zolezzi, M. and Eltorki, Y., 2019. A qualitative exploration of clozapine prescribing and monitoring practices in the Arabian Gulf countries. *Asian journal of psychiatry*, *39*, pp.93-97.

Jayatilleke, N., Hayes, R.D., Dutta, R., Shetty, H., Hotopf, M., Chang, C.K. and Stewart, R., 2017. Contributions of specific causes of death to lost life expectancy in severe mental illness. *European Psychiatry*, 43, pp.109-115.

Jin, H., Meyer, J.M. and Jeste, D.V., 2004. Atypical antipsychotics and glucose dysregulation: a systematic review. *Schizophrenia Research*, *71*(2-3), pp.195-212.

Kahn, R.S., van Rossum, I.W., Leucht, S., McGuire, P., Lewis, S.W., Leboyer, M., Arango, C., Dazzan, P., Drake, R., Heres, S. and Díaz-Caneja, C.M., 2018. Amisulpride and olanzapine followed by open-label treatment with clozapine in first-episode schizophrenia and schizophreniform disorder (OPTiMiSE): a three-phase switching study. *The Lancet Psychiatry*, *5*(10), pp.797-807.

Kane, J., Honigfeld, G., Singer, J. and Meltzer, H., 1988. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. *Archives of general psychiatry,* 45(9), pp.789-796.

Kelly, D.L., Freudenreich, O., Sayer, M.A. and Love, R.C., 2018. Addressing barriers to clozapine underutilization: a national effort.

Knapp, M., Mangalore, R. and Simon, J., 2004. The global costs of schizophrenia. *Schizophrenia bulletin*, *30*(2), pp.279-293.

Korst, D.R., 1959. Agranulocytosis caused by phenothiazine derivatives. *Journal of the American Medical Association*, 170(17), pp.2076-2081.

Krivoy, A., Malka, L., Fischel, T., Weizman, A. and Valevski, A., 2011. Predictors of clozapine discontinuation in patients with schizophrenia. *International clinical psychopharmacology*, 26(6), pp.311-315.

Krivoy A, Joyce D, Tracy D, Gaughran F, MacCabe J, Lally J, Whiskey E, Sarkar SN, Shergill SS. Real-World Outcomes in the Management of Refractory Psychosis. *The Journal of clinical psychiatry*. 2019 Sep;80(5).

Kumari, V. and Postma, P., 2005. Nicotine use in schizophrenia: the self-medication hypotheses. *Neuroscience and Biobehavioral Reviews*, *29*(6), pp.1021-1034.

Lakhotia, R., Aggarwal, A., Link, M.E., Rodgers, G.P. and Hsieh, M.M., 2019. Natural history of benign ethnic neutropenia in individuals of African ancestry. *Blood Cells, Molecules, and Diseases*, 77, pp.12-16.

Lally, J., Malik, S., Krivoy, A., Whiskey, E., Taylor, D.M., Gaughran, F.P., Flanagan, R.J., Mijovic, A. and MacCabe, J.H., 2017. The use of granulocyte colony-stimulating factor in clozapine rechallenge: a systematic review. *Journal of clinical psychopharmacology*, 37(5), pp.600-604.

https://www.lambeth.gov.uk/sites/default/files/State%20of%20Borough%202016%20-%20v3.pdf (accessed 22/07/2020)

Lambo, T.A., 1957. Chlorpromazine jaundice. *British medical journal*, 2(5052), p.1048.

Latimer, E., Wynant, W., Clark, R., Malla, A., Moodie, E., Tamblyn, R. and Naidu, A., 2013. Underprescribing of clozapine and unexplained variation in use across hospitals and regions in the Canadian province of Quebec. *Clinical schizophrenia and related psychoses*, *7*(1), pp.33-41.

Laursen, T.M., 2011. Life expectancy among persons with schizophrenia or bipolar affective disorder. *Schizophrenia Research*, 131(1-3), pp.101-104.

Laursen, T.M., Munk-Olsen, T. and Vestergaard, M., 2012. Life expectancy and cardiovascular mortality in persons with schizophrenia. *Current opinion in psychiatry*, 25(2), pp.83-88.

Legge, S.E., Hamshere, M., Hayes, R.D., Downs, J., O'Donovan, M.C., Owen, M.J., Walters, J.T. and MacCabe, J.H., 2016. Reasons for discontinuing clozapine: a cohort study of patients commencing treatment. *Schizophrenia Research*, 174(1-3), pp.113-119.

Legge, S.E., Pardiñas, A.F., Helthuis, M., Jansen, J.A., Jollie, K., Knapper, S., MacCabe, J.H., Rujescu, D., Collier, D.A., O'Donovan, M.C. and Owen, M.J., 2019. A genome-wide association study in individuals of African ancestry reveals the importance of the Duffy-null genotype in the assessment of clozapine-related neutropenia. *Molecular psychiatry*, 24(3), pp.328-337.

Leucht, S., Davis, J.M., Engel, R.R., Kane, J.M. and Wagenpfeil, S., 2007. Defining 'response' in antipsychotic drug trials: recommendations for the use of scale-derived cutoffs. *Neuropsychopharmacology*, *32*(9), pp.1903-1910.

Leucht, S., Corves, C., Arbter, D., Engel, R.R., Li, C. and Davis, J.M., 2009. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *The Lancet*, 373(9657), pp.31-41.

Leucht, S., Cipriani, A., Spineli, L., Mavridis, D., Örey, D., Richter, F., Samara, M., Barbui, C., Engel, R.R., Geddes, J.R. and Kissling, W., 2013. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *The Lancet*, 382(9896), pp.951-962.

Leucht, S., Leucht, C., Huhn, M., Chaimani, A., Mavridis, D., Helfer, B., Samara, M., Rabaioli, M., Bächer, S., Cipriani, A. and Geddes, J.R., 2017. Sixty years of placebo-controlled antipsychotic drug trials in acute schizophrenia: systematic review, Bayesian meta-analysis, and meta-regression of efficacy predictors. *American Journal of Psychiatry*, 174(10), pp.927-942.

Leung, J.G., Cusimano, J., Gannon, J.M., Milgrom, O., Valcourt, S.C., Stoklosa, J.B., Kemp, M., Olsufka, W., Vickery, P.B., Nichols, S.D. and Crouse, E.L., 2019. Addressing clozapine underprescribing and barriers to initiation: a psychiatrist, advanced practice provider, and trainee survey. *International clinical psychopharmacology*, 34(5), pp.247-256.

Lieberman, J.A., Safferman, A.Z., Pollack, S., Szymanski, S., Johns, C., Howard, A., Kronig, M., Bookstein, P. and Kane, J.M., 1994. Clinical effects of clozapine in chronic schizophrenia: response to treatment and predictors of outcome. *American Journal of Psychiatry*, *151*(12), pp.1744-1752.

Lim, E.M., Cembrowski, G., Cembrowski, M. and Clarke, G., 2010. Race-specific WBC and neutrophil count reference intervals. *International journal of laboratory hematology*, 32(6p2), pp.590-597.

Lim, E., Miyamura, J. and Chen, J.J., 2015. Racial/ethnic-specific reference intervals for common laboratory tests: a comparison among Asians, Blacks, Hispanics, and White. *Hawai'i Journal of Medicine and Public Health*, 74(9), p.302.

Litvak, R. and Kaelbling, R., 1971. Agranulocytosis, leukopenia, and psychotropic drugs. *Archives of general psychiatry*, 24(3), pp.265-267.

Lomas, J., 1954. Chlorpromazine and agranulocytosis. *British Medical Journal*, 2(4883), p.358.

Love RC, Kelly DL, Freudenreich O, et al: Clozapine Underutilization: Addressing the Barriers. Alexandria, VA, National Association of State Mental Health Program Directors, Sept 2016. http://nasmhpd.org/sites/default/files/Assessment%201_Clozapine %20Underutilization.pdf

Manu, P., Sarvaiya, N., Rogozea, L.M., Kane, J.M. and Correll, C.U., 2016. Benign Ethnic Neutropenia and Clozapine Use: A Systematic Review of the Evidence and Treatment Recommendations. *The Journal of clinical psychiatry*, 77(7), pp.e909-16.

Marcus, P. and Snyder, R., 1995. Reduction of comorbid substance abuse with clozapine. *The American journal of psychiatry*.

Masuda, T., Misawa, F., Takase, M., Kane, J.M. and Correll, C.U., 2019. Association with hospitalization and all-cause discontinuation among patients with schizophrenia on clozapine vs other oral second-generation antipsychotics: a systematic review and meta-analysis of cohort studies. *JAMA psychiatry*, 76(10), pp.1052-1062.

McGrath, J., Saha, S., Chant, D. and Welham, J., 2008. Schizophrenia: a concise overview of incidence, prevalence, and mortality. *Epidemiologic reviews*, 30(1), pp.67-76.

Meltzer, H.Y., 1997. Treatment-resistant schizophrenia-the role of clozapine. *Current medical research and opinion*, 14(1), pp.1-20.

Meltzer, H.Y., Alphs, L., Green, A.I., Altamura, A.C., Anand, R., Bertoldi, A., Bourgeois, M., Chouinard, G., Islam, M.Z., Kane, J. and Krishnan, R., 2003. Clozapine treatment for suicidality

in schizophrenia: international suicide prevention trial (InterSePT). *Archives of general psychiatry*, 60(1), pp.82-91.

Meyer, N., Gee, S., Whiskey, E., Taylor, D., Mijovic, A., Gaughran, F., Shergill, S. and MacCabe, J.H., 2015. Optimizing outcomes in clozapine rechallenge following neutropenia: a cohort analysis. *The Journal of clinical psychiatry*, 76(11), pp.1410-1416.

Mizuno, Y., McCutcheon, R.A., Brugger, S.P. and Howes, O.D., 2020. Heterogeneity and efficacy of antipsychotic treatment for schizophrenia with or without treatment resistance: a meta-analysis. *Neuropsychopharmacology*, *45*(4), pp.622-631.

Munro, J., O'Sullivan, D., Andrews, C., Arana, A., Mortimer, A. and Kerwin, R., 1999. Active monitoring of 12760 clozapine recipients in the UK and Ireland. *The British Journal of Psychiatry*, 175(6), pp.576-580.

Nalls, M.A., Wilson, J.G., Patterson, N.J., Tandon, A., Zmuda, J.M., Huntsman, S., Garcia, M., Hu, D., Li, R., Beamer, B.A. and Patel, K.V., 2008. Admixture mapping of white cell count: genetic locus responsible for lower white blood cell count in the Health ABC and Jackson Heart studies. *The American Journal of Human Genetics*, 82(1), pp.81-87.

NICE guidelines for schizophrenia 2002. Guidance on the Use of Newer (Atypical) Antipsychotic Drugs for the Treatment of Schizophrenia Drugs for the Treatment of Schizophrenia. Technology. *Technology Appraisal Guidance,* 43. London: NICE.

Nikolić, N., Kilbride, K. and Preston, P., 2019. Clozapine rapid retitration in the community: an assertive approach can prevent admissions. *BJPsych Advances,* 25(1), pp.70-71.

Nielsen, J., Dahm, M., Lublin, H. and Taylor, D., 2010. Psychiatrists' attitude towards and knowledge of clozapine treatment. *Journal of psychopharmacology*, *24*(7), pp.965-971.

Nielsen, J., Røge, R., Schjerning, O., Sørensen, H.J. and Taylor, D., 2012. Geographical and temporal variations in clozapine prescription for schizophrenia. *European Neuropsychopharmacology*, *22*(11), pp.818-824.

Nielsen, J., Correll, C.U., Manu, P. and Kane, J.M., 2013. Termination of clozapine treatment due to medical reasons: when is it warranted and how can it be avoided? *The Journal of clinical psychiatry*, *74*(6), pp.603-613.

Nielsen, J., Young, C., Ifteni, P., Kishimoto, T., Xiang, Y.T., Schulte, P.F., Correll, C.U. and Taylor, D., 2016. Worldwide differences in regulations of clozapine use. *CNS drugs*, 30(2), pp.149-161.

Ochoa, S., Usall, J., Cobo, J., Labad, X. and Kulkarni, J., 2012. Gender differences in schizophrenia and first-episode psychosis: a comprehensive literature review. *Schizophrenia research and treatment*, *2012*.

Palmer, S.E., McLean, R.M., Ellis, P.M. and Harrison-Woolrych, M., 2008. Life-threatening clozapine-induced gastrointestinal hypomotility: an analysis of 102 cases. *The Journal of clinical psychiatry*, *69*(5), pp.759-768.

Patel, M.X., 2012. Clinician hesitation prior to clozapine initiation: is it justifiable? *The British Journal of Psychiatry*, *201*(6), pp.425-427.

Patel, N.C., Dorson, P.G. and Bettinger, T.L., 2002. Sudden late onset of clozapine-induced agranulocytosis. *Annals of Pharmacotherapy*, 36(6), pp.1012-1015.

Perälä, J., Suvisaari, J., Saarni, S.I., Kuoppasalmi, K., Isometsä, E., Pirkola, S., Partonen, T., Tuulio-Henriksson, A., Hintikka, J., Kieseppä, T. and Härkänen, T., 2007. Lifetime prevalence of psychotic and bipolar I disorders in a general population. *Archives of general psychiatry*, 64(1), pp.19-28.

Perry, P.J., Miller, D.D., Arndt, S.V. and Cadoret, R.J., 1991. Clozapine and norclozapine plasma concentrations and clinical response of treatment-refractory schizophrenic patients. *The American journal of psychiatry*.

Phillips, P. and Johnson, S., 2003. Drug and alcohol misuse among in-patients with psychotic illnesses in three inner-London psychiatric units. *Psychiatric Bulletin*, 27(6), pp.217-220.

Pisciotta, A.V., 1959. Hematological safeguards during treatment with the phenothiazine derivatives. *Journal of the American Medical Association*, 170(6), pp.662-664.

Pisciotta, A.V., 1969. Agranulocytosis induced by certain phenothiazine derivatives. *JAMA*, 208(10), pp.1862-1868.

Pisciotta, A.V., 1978. Drug-induced agranulocytosis. *Drugs*, 15(2), pp.132-143.

Pisciotta, A.V., Ebbe, S., Lennon, E.J., Metzger, G.O. and Madison, F.W., 1958. Agranulocytosis following administration of phenothiazine derivatives. *The American journal of medicine*, 25(2), pp.210-223.

Pompili, M., Amador, X.F., Girardi, P., Harkavy-Friedman, J., Harrow, M., Kaplan, K., Krausz, M., Lester, D., Meltzer, H.Y., Modestin, J. and Montross, L.P., 2007. Suicide risk in schizophrenia: learning from the past to change the future. *Annals of general psychiatry*, 6(1), pp.1-22.

Povlsen, U.J., Norrng, U., Fog, R. and Gerlach, J., 1985. Tolerability and therapeutic effect of clozapine: a retrospective investigation of 216 patients treated with clozapine for up to 12 years. *Acta Psychiatrica Scandinavica*, 71(2), pp.176-185.

Pretty, H.M., Gosselin, G., Colpron, G. and Long, L.A., 1965. Agranulocytosis: a report of 30 cases. *Canadian Medical Association Journal*, 93(20), p.1058.

Pronovost, P.J., Nolan, T., Zeger, S., Miller, M. and Rubin, H., 2004. How can clinicians measure safety and quality in acute care? *The Lancet*, *363*(9414), pp.1061-1067.

Rajagopal, S., 2005. Clozapine, agranulocytosis, and benign ethnic neutropenia.

Reich, D., Nalls, M.A., Kao, W.L., Akylbekova, E.L., Tandon, A., Patterson, N., Mullikin, J., Hsueh, W.C., Cheng, C.Y., Coresh, J. and Boerwinkle, E., 2009. Reduced neutrophil count in people of African descent is due to a regulatory variant in the Duffy antigen receptor for chemokines gene. *PLoS Genet*, 5(1), p.e1000360.

Reiner, A.P., Lettre, G., Nalls, M.A., Ganesh, S.K., Mathias, R., Austin, M.A., Dean, E., Arepalli, S., Britton, A., Chen, Z. and Couper, D., 2011. Genome-wide association study of white blood cell count in 16,388 African Americans: the continental origins and genetic epidemiology network (COGENT). *PLoS Genet*, 7(6), p.e1002108.

Reininghaus, U., Dutta, R., Dazzan, P., Doody, G.A., Fearon, P., Lappin, J., Heslin, M., Onyejiaka, A., Donoghue, K., Lomas, B. and Kirkbride, J.B., 2015. Mortality in schizophrenia and other psychoses: a 10-year follow-up of the ÆSOP first-episode cohort. *Schizophrenia Bulletin*, 41(3), pp.664-673.

Rössler, W., Salize, H.J., van Os, J. and Riecher-Rössler, A., 2005. Size of burden of schizophrenia and psychotic disorders. *European Neuropsychopharmacology*, *15*(4), pp.399-409.

Rostami-Hodjegan, A., Amin, A.M., Spencer, E.P., Lennard, M.S., Tucker, G.T. and Flanagan, R.J., 2004. Influence of dose, cigarette smoking, age, sex, and metabolic activity on plasma clozapine concentrations: a predictive model and nomograms to aid clozapine dose adjustment and to assess compliance in individual patients. *Journal of Clinical Psychopharmacology*, *24*(1), pp.70-78.

Rummel-Kluge, C., Komossa, K., Schwarz, S., Hunger, H., Schmid, F., Lobos, C.A., Kissling, W., Davis, J.M. and Leucht, S., 2010. Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: a systematic review and meta-analysis. *Schizophrenia Research*, *123*(2-3), pp.225-233.

Rummel-Kluge, C., Komossa, K., Schwarz, S., Hunger, H., Schmid, F., Kissling, W., Davis, J.M. and Leucht, S., 2012. Second-generation antipsychotic drugs and extrapyramidal side effects:

a systematic review and meta-analysis of head-to-head comparisons. *Schizophrenia Bulletin*, *38*(1), pp.167-177.

Saha, S., Chant, D., Welham, J. and McGrath, J., 2005. A systematic review of the prevalence of schizophrenia. *PLoS medicine*, *2*(5).

Saha, S., Chant, D. and McGrath, J., 2007. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? *Archives of general psychiatry*, *64*(10), pp.1123-1131.

Samara, M.T., Dold, M., Gianatsi, M., Nikolakopoulou, A., Helfer, B., Salanti, G. and Leucht, S., 2016. Efficacy, acceptability, and tolerability of antipsychotics in treatment-resistant schizophrenia: a network meta-analysis. *JAMA Psychiatry*, *73*(3), pp.199-210.

Schulte, P.F., Cohen, D., Bogers, J.P., van Dijk, D. and Bakker, B., 2010. A Dutch guideline for the use of clozapine. *Australian and New Zealand Journal of Psychiatry*, 44(11), pp.1055-1056.

Senn, H.J., Jungi, W., Kunz, H. and Põldinger, W., 1977. Clozapine and agranulocytosis. *The Lancet*, 309(8010), p.547.

Seppälä, N.H., Leinonen, E.V., Lehtonen, M.L. and Kivistö, K.T., 1999. Clozapine serum concentrations are lower in smoking than in non-smoking schizophrenic patients. *Pharmacology and toxicology*, *85*, pp.244-246.

Sharpley, M., Hutchinson, G., Murray, R.M. and McKenzie, K., 2001. Understanding the excess of psychosis among the African-Caribbean population in England: review of current hypotheses. *The British Journal of Psychiatry*, 178(S40), pp.s60-s68.

Shine, B., McKnight, R.F., Leaver, L. and Geddes, J.R., 2015. Long-term effects of lithium on renal, thyroid, and parathyroid function: a retrospective analysis of laboratory data. *The Lancet*, 386(9992), pp.461-468.

Shoenfeld, Y., Alkan, M.L., Asaly, A., Carmeli, Y. and Katz, M., 1988. Benign familial leukopenia and neutropenia in different ethnic groups. *European journal of haematology*, 41(3), pp.273-277.

Shopsin, B., Klein, H., Aaronsom, M. and Collora, M., 1979. Clozapine, chlorpromazine, and placebo in newly hospitalized, acutely schizophrenic patients: a controlled, double-blind comparison. *Archives of General Psychiatry*, 36(6), pp.657-664.

Siskind, D., McCartney, L., Goldschlager, R. and Kisely, S., 2016. Clozapine v. first-and second-generation antipsychotics in treatment-refractory schizophrenia: systematic review and meta-analysis. *The British Journal of Psychiatry*, *209*(5), pp.385-392.

Simeone, J.C., Ward, A.J., Rotella, P., Collins, J. and Windisch, R., 2015. An evaluation of variation in published estimates of schizophrenia prevalence from 1990– 2013: a systematic literature review. *BMC psychiatry*, *15*(1), p.193.

Siskind, D., Siskind, V. and Kisely, S., 2017. Clozapine response rates among people with treatment-resistant schizophrenia: data from a systematic review and meta-analysis.

Small, J.G., Klapper, M.H., Malloy, F.W. and Steadman, T.M., 2003. Tolerability and efficacy of clozapine combined with lithium in schizophrenia and schizoaffective disorder. *Journal of clinical psychopharmacology*, 23(3), pp.223-228.

Smith, M., Hopkins, D., Peveler, R.C., Holt, R.I.G., Woodward, M. and Ismail, K., 2008. First-v. second-generation antipsychotics and risk for diabetes in schizophrenia: systematic review and meta-analysis. *The British Journal of Psychiatry*, *192*(6), pp.406-411.

Spencer, B.W., Williams, H.R., Gee, S.H., Whiskey, E., Rodrigues, J.P., Mijovic, A. and MacCabe, J.H., 2012. Granulocyte colony-stimulating factor (G-CSF) can allow treatment with clozapine in a patient with severe benign ethnic neutropenia (BEN): a case report. *Journal of Psychopharmacology*, 26(9), pp.1280-1282.

Spina, E., Avenoso, A., Facciolà, G., Scordo, M.G., Ancione, M., Madia, A.G., Ventimiglia, A. and Perucca, E., 2000. Relationship between plasma concentrations of clozapine and norclozapine and therapeutic response in patients with schizophrenia resistant to conventional neuroleptics. *Psychopharmacology*, *148*(1), pp.83-89.

Sreeraj, V.S., Dinakaran, D., Nagendrappa, S., Rao, N.P., Kesavan, M., Varambally, S. and Venkatasubramanian, G., 2017. Clozaphobia: Is avoidance of clozapine in diabetes warranted? *Asian journal of psychiatry*, 28, pp.142-145.

Stroup, T.S., Gerhard, T., Crystal, S., Huang, C. and Olfson, M., 2014. Geographic and clinical variation in clozapine use in the United States. *Psychiatric Services*, 65(2), pp.186-192.

Sultan, R.S., Olfson, M., Correll, C.U. and Duncan, E.J., 2017. Evaluating the effect of the changes in FDA guidelines for clozapine monitoring. *The Journal of clinical psychiatry*, 78(8), p.e933.

Taipale, H., Mehtälä, J., Tanskanen, A. and Tiihonen, J., 2018. Comparative effectiveness of antipsychotic drugs for rehospitalization in schizophrenia—a nationwide study with 20-year follow-up. *Schizophrenia Bulletin*, 44(6), pp.1381-1387.

Taipale, H., Tanskanen, A., Mehtälä, J., Vattulainen, P., Correll, C.U. and Tiihonen, J., 2020. 20-year follow-up study of physical morbidity and mortality in relationship to antipsychotic treatment in a nationwide cohort of 62,250 patients with schizophrenia (FIN20). *World Psychiatry*, 19(1), pp.61-68.

Taylor, D.M., Young, C. and Paton, C., 2003. Prior antipsychotic prescribing in patients currently receiving clozapine: a case note review. *The Journal of clinical psychiatry*, *64*(1), pp.30-34.

Thobakgale, C.F. and Ndung'u, T., 2014. Neutrophil counts in persons of African origin. *Current opinion in hematology*, 21(1), pp.50-57.

Tortelli A, Errazuriz A, Croudace T, Morgan C, Murray RM, Jones PB, Szoke A, Kirkbride JB. Schizophrenia and other psychotic disorders in Caribbean-born migrants and their descendants in England: systematic review and meta-analysis of incidence rates, 1950–2013. *Social psychiatry and psychiatric epidemiology*. 2015 Jul 1; 50(7):1039-55.

Tracy DK, Joyce DW, Sarkar SN, Fernandez MJ, Shergill SS. Skating on thin ice: pragmatic prescribing for medication refractory schizophrenia. *BMC psychiatry*. 2015 Dec 1; 15(1):174.

Tiihonen, J., Lönnqvist, J., Wahlbeck, K., Klaukka, T., Niskanen, L., Tanskanen, A. and Haukka, J., 2009. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *The Lancet*, *374*(9690), pp.620-627.

Tungaraza, T.E. and Farooq, S., 2015. Clozapine prescribing in the UK: views and experience of consultant psychiatrists. *Therapeutic advances in psychopharmacology*, *5*(2), pp.88-96.

van den Oord, E.J., Chan, R.F. and Aberg, K.A., 2018. Successes and challenges in precision medicine in psychiatry. *JAMA Psychiatry*, *75*(12), pp.1269-1270.

van der Klauw, M.M., Goudsmit, R., Halie, M.R., van't Veer, M.B., Herings, R.M., Wilson, J.P. and Stricker, B.H.C., 1999. A population-based case-cohort study of drug-associated agranulocytosis. *Archives of internal medicine*, 159(4), pp.369-374.

Verdoux, H., Quiles, C., Bachmann, C.J. and Siskind, D., 2018. Prescriber and institutional barriers and facilitators of clozapine use: a systematic review. *Schizophrenia Research*, *201*, pp.10-19.

Wheeler, A., Humberstone, V. and Robinson, G., 2009. Outcomes for schizophrenia patients with clozapine treatment: how good does it get? *Journal of Psychopharmacology*, 23(8), pp.957-965.

Whiskey, E., Wykes, T., Duncan-McConnell, D., Haworth, E., Walsh, N. and Hastilow, S., 2003. Continuation of clozapine treatment: practice makes perfect. *Psychiatric Bulletin*, *27*(6), pp.211-213.

Whiskey, E., Taylor D. Restarting Clozapine after Neutropenia. *CNS drugs*. 2007 Jan 1;21(1):25-35.

Whiskey, E., Olofinjana, O. and Taylor, D., 2011. The importance of the recognition of benign ethnic neutropenia in black patients during treatment with clozapine: case reports and database study. *Journal of psychopharmacology*, 25(6), pp.842-845.

Whiskey, E., Dzahini, O., Ramsay, R., O'Flynn, D., Mijovic, A., Gaughran, F., MacCabe, J., Shergill, S. and Taylor, D., 2019. Need to bleed? Clozapine haematological monitoring approaches a time for change. *International clinical psychopharmacology*, 34(5), pp.264-268.

World Health Organization, 2004. *International statistical classification of diseases and related health problems* (Vol. 1). World Health Organization.

Xiao-Hong L, Xiao-Mei Z, Lu L, Zheng W, Shi-bin W, Wen-wang R, Wang S, Ng CH, Ungvari GS, Wang G, Yu-Tao X. The prevalence of agranulocytosis and related death in clozapine-treated patients: a comprehensive meta-analysis of observational studies. *Psychological medicine*. 2020 Mar 1;50(4):583-94

Zhang, M., Owen, R.R., Pope, S.K. and Smith, G.R., 1996. Cost-effectiveness of clozapine monitoring after the first 6 months. *Archives of general psychiatry*, 53(10), pp.954-958.

Zhang, J.P., Gallego, J.A., Robinson, D.G., Malhotra, A.K., Kane, J.M. and Correll, C.U., 2013. Efficacy and safety of individual second-generation vs. first-generation antipsychotics in first-episode psychosis: a systematic review and meta-analysis. *International Journal of Neuropsychopharmacology*, 16(6), pp.1205-1218.

Zhang, Y., Liu, Y., Su, Y., You, Y., Ma, Y., Yang, G., Song, Y., Liu, X., Wang, M., Zhang, L. and Kou, C., 2017. The metabolic side effects of 12 antipsychotic drugs used for the treatment of schizophrenia on glucose: a network meta-analysis. *BMC psychiatry*, 17(1), p.373.

Zullino, D.F., Delessert, D., Eap, C.B., Preisig, M. and Baumann, P., 2002. Tobacco and cannabis smoking cessation can lead to intoxication with clozapine or olanzapine. *International clinical psychopharmacology*, 17(3), pp.141-143.

Appendix 1: Public works

Public Works	Title	Theme/Additional Information
1	**Whiskey, E.** and Taylor, D., 2005. Evaluation of an antipsychotic information sheet for patients. *International Journal of Psychiatry in Clinical Practice*, *9*(4), pp.264-270.	Providing information for patients with schizophrenia
2	Taylor, D., Mir, S., Mace, S. and **Whiskey, E.,** 2002. Co-prescribing of atypical and typical antipsychotics–prescribing sequence and documented outcome. *Psychiatric Bulletin*, *26*(5), pp.170-172.	Rational antipsychotic prescribing
3	**Whiskey, E**., Werneke, U. and Taylor, D., 2001. A systematic review and meta-analysis of Hypericum perforatum in depression: a comprehensive clinical review. *International clinical psychopharmacology*, *16*(5), pp.239-252.	Systematic review
4	**Whiskey, E**. and Taylor, D., 2004. Pramipexole in unipolar and bipolar depression. *Psychiatric Bulletin*, *28*(12), pp.438-440.	New treatment options in affective illness
5	**Whiskey, E**. Depression in cardiovascular disease. In -Case studies in Psychopharmacology: the use of drugs in Psychiatry.	Interaction between physical and mental health
6	**Whiskey, E.,** Wykes, T., Duncan-McConnell, D., Haworth, E., Walsh, N. and Hastilow, S., 2003. Continuation of clozapine treatment: practice makes perfect. *Psychiatric Bulletin*, *27*(6), pp.211-213.	Clinician-related factors in underutilisation of clozapine
7	**Whiskey, E.** and Taylor, D., 2004. Comment-Broad Spectrum-Generic clozapine: Opportunity or threat? *Pharmaceutical Journal*, *273*(7309), pp.112-112.	Regulation as a factor in clozapine underutilisation
8	**Whiskey, E.** and Taylor, D., 2007. Restarting Clozapine after Neutropenia. *CNS drugs*, *21*(1), pp.25-35.	Drug-related factors in clozapine underutilisation: Clozapine-related adverse effects
9	Meyer, N., Gee, S., **Whiskey, E.,** Taylor, D., Mijovic, A., Gaughran, F., Shergill, S. and MacCabe, J.H., 2015. Optimizing outcomes in clozapine rechallenge following neutropenia: a cohort analysis. *The Journal of clinical psychiatry*, *76*(11), pp.1410-1416.	Drug-related factors in clozapine underutilisation: Clozapine-related adverse effects
10	**Whiskey, E**., Dzahini, O., Ramsay, R., O'Flynn, D., Mijovic, A., Gaughran, F., MacCabe, J., Shergill, S. and Taylor, D., 2019. Need to bleed? Clozapine haematological monitoring approaches a time for change. *International clinical psychopharmacology*, *34*(5), pp.264-268.	Underutilisation relating to regulatory controls and clozapine adverse effects

11	Lally, J., Malik, S., Krivoy, A., **Whiskey, E**., Taylor, D.M., Gaughran, F.P., Flanagan, R.J., Mijovic, A. and MacCabe, J.H., 2017. The use of granulocyte colony-stimulating factor in clozapine rechallenge: a systematic review. *Journal of clinical psychopharmacology*, *37*(5), pp.600-604.	Drug-related factors in clozapine underutilisation: Clozapine-related adverse effects
12	Lally, J., Malik, S., **Whiskey, E**., Taylor, D.M., Gaughran, F.P., Krivoy, A., Flanagan, R.J., Mijovic, A. and MacCabe, J.H., 2017. Clozapine-associated agranulocytosis treatment with granulocyte colony-stimulating factor/granulocyte-macrophage colony-stimulating factor: a systematic review. *Journal of Clinical Psychopharmacology*, *37*(4), pp.441-446.	Drug-related factors in clozapine underutilisation: Clozapine-related adverse effects
13	Patel, R.K., Moore, A.M., Piper, S., Sweeney, M., **Whiskey, E.,** Cole, G., Shergill, S.S. and Plymen, C.M., 2019. Clozapine and cardiotoxicity–A guide for psychiatrists written by cardiologists. *Psychiatry Research*, *282*, p.112491.	Clinician and drug-related factors in underutilisation of clozapine
14	Sweeney, M., **Whiskey, E**., Patel, R.K., Tracy, D.K., Shergill, S.S. and Plymen, C.M., 2020. Understanding and managing cardiac side effects of second-generation antipsychotics in the treatment of schizophrenia. *BJPsych Advances*, 26(1), pp.26-40.	Clinician and drug-related factors in underutilisation of clozapine
15	Joy, G., **Whiskey, E**., Bolstridge, M., Porras-Segovia, A., McDonagh, T.A., Plymen, C.M. and Shergill, S.S., 2017. Hearts and Minds: Real-Life Cardiotoxicity With Clozapine in Psychosis. *Journal of clinical psychopharmacology*, 37(6), pp.708-712.	Drug-related factors in clozapine underutilisation: Clozapine-related adverse effects
16	**Whiskey, E.,** Yuen, S., Khosla, E., Piper, S., O'Flynn, D. and Taylor, D., 2020. Resolution without discontinuation: heart failure during clozapine treatment. *Therapeutic Advances in Psychopharmacology*, *10*, p.2045125320924786.	Patient and drug-related factors in clozapine underutilisation
17	Hindley, G., **Whiskey, E.** and Gall N. Tachycardia in: Practice Guidelines for Physical Health in Psychiatry.	Drug-related factors in clozapine underutilisation: Clozapine-related adverse effects
18	**Whiskey, E**., Olofinjana, O. and Taylor, D., 2011. The importance of the recognition of benign ethnic neutropenia in black patients during treatment with clozapine: case reports and database study. *Journal of psychopharmacology*, 25(6), pp.842-845.	Patient and drug-related factors in clozapine underutilisation
19	Spencer, B.W., Williams, H.R., Gee, S.H., **Whiskey, E**., Rodrigues, J.P., Mijovic, A. and MacCabe, J.H., 2012. Granulocyte colony-stimulating factor (G-CSF) can allow treatment with clozapine in a patient	Patient and drug-related factors in clozapine underutilisation

	with severe benign ethnic neutropenia (BEN): a case report. *Journal of Psychopharmacology*, 26(9), pp.1280-1282.	
20	Casetta, C., Oloyede, E., **Whiskey, E**., Taylor, D.M., Gaughran, F., Shergill, S.S., Onwumere, J., Segev, A., Dzahini, O., Legge, S.E. and MacCabe, J.H., 2020. A retrospective study of intramuscular clozapine prescription for treatment initiation and maintenance in treatment-resistant psychosis. *The British Journal of Psychiatry*, *217*(3), pp.506-513.	Underutilisation relating to the drug – Drug formulation
21	**Whiskey E.,** Protocol for the use of intramuscular clozapine in South London and Maudsley NHS Foundation Trust.	Drug-related factors in clozapine underutilisation: Clozapine-related adverse effects
22	Oloyede, E., Dzahini, O., **Whiskey, E.** and Taylor, D., 2019. Clozapine and Norclozapine Plasma Levels in Patients Switched Between Different Liquid Formulations. *Therapeutic drug monitoring.*	Drug-related factors in clozapine underutilisation: Clozapine-related adverse effects
23	Keshavarzi, F., Fox, T., **Whiskey, E**. and Taylor, D., 2020. Change in plasma concentration of clozapine and norclozapine following a switch of oral formulation. *Therapeutic Advances in Psychopharmacology*, 10, p.2045125319899263.	Drug-related factors in clozapine underutilisation: Clozapine-related adverse effects
24	**Whiskey, E.,** O'Flynn, D. and Taylor, D., 2018. Clozapine, HIV and neutropenia: a case report. *Therapeutic advances in psychopharmacology*, 8(12), pp.365-369.	Patient and drug-related factors in clozapine underutilisation
25	Rodriguez, V., Hanley, K., Arias, A.J., Quattrone, D., Kuforiji, J., **Whiskey, E**. and Shergill, S.S., 2020. Successful clozapine rechallenge following recurrent clozapine-associated pancreatitis: a case report. *BMC Pharmacology and Toxicology*, *21*(1), pp.1-5.	Underutilisation relating to the patient – Medical comorbidity
26	Lowe, P., Krivoy, A., Porffy, L., Henriksdottir, E., **Whiskey, E**. and Shergill, S.S., 2018. When the drugs don't work: treatment-resistant schizophrenia, serotonin and serendipity. *Therapeutic advances in psychopharmacology*, 8(1), pp.63-70.	Finding alternatives to clozapine in treatment-resistant schizophrenia
27	**Whiskey, E.,** Vavrova, M., Gaughran, F. and Taylor, D., 2011. Melperone in treatment-refractory schizophrenia: a case series. *Therapeutic advances in psychopharmacology*, 1(1), pp.19-23.	Finding alternatives to clozapine in treatment-resistant schizophrenia

28	Krivoy, A., Joyce, D., Tracy, D., Gaughran, F., MacCabe, J., Lally, J., **Whiskey, E.,** Sarkar, S.N. and Shergill, S.S., 2019. Real-World Outcomes in the Management of Refractory Psychosis. *The Journal of clinical psychiatry*, 80(5).	Measuring the impact of clozapine in treatment-resistant schizophrenia
29	Gaughran, F., Stringer, D., Berk, M., Smith, S., Taylor, D., **Whiskey, E**., Landau, S., Murray, R., McGuire, P., Gardner-Sood, P. and Wojewodka, G., 2020. Vitamin D supplementation compared to placebo in people with First Episode psychosis-Neuroprotection Design (DFEND): a protocol for a randomised, double-blind, placebo-controlled, parallel-group trial. *Trials*, 21(1), pp.1-12.	Understanding the neurobiology of schizophrenia
30	Segev, A., Evans, A., Hodsoll, J., **Whiskey, E.,** Sheriff, R.S., Shergill, S. and MacCabe, J.H., 2019. Hyoscine for clozapine-induced hypersalivation: a double-blind, randomized, placebo-controlled cross-over trial. *International clinical psychopharmacology*, 34(2), pp.101-107.	Managing clozapine adverse effects
31	Green, A., Stephenson, T., **Whiskey, E**. and Shergill, S.S., 2019. Closure beyond clozapine: successfully averting rebound symptoms in a patient with schizoaffective disorder and agranulocytosis. *BJPsych Open*, *5*(3).	Drug-related factors in clozapine underutilisation: Clozapine-related adverse effects
32	Oloyede, E., Casetta, C., Dzahini, O., Segev, A., Gaughran, F., Shergill, S., Mijovic, A., Helthuis, M., **Whiskey, E.,** MacCabe, J.H. and Taylor, D., 2021. There Is Life After the UK Clozapine Central Non-Rechallenge Database. *Schizophrenia Bulletin*.	Regulation and drug-related factors in clozapine underutilisation: Clozapine-related adverse effects
33	**Whiskey, E**., Barnard, A., Oloyede, E., Dzahini, O., Taylor, D., and Shergill S. An evaluation of the variation and underuse of clozapine in the United Kingdom. *Acta Psychiatrica Scandinavica. https://doi.org/10.1111/acps.13280.*	Clinician-related factors in underutilisation of clozapine

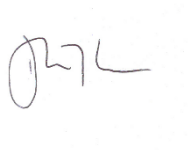
Appendix 2: Confirmation and declaration of authorship

PW	Title	Eromona Whiskey's contribution
1	Evaluation of an antipsychotic information sheet for patients. *International Journal of Psychiatry in Clinical Practice*, *9*(4), pp.264-270.	First author, writing the first and final draft for submission
2	Co-prescribing of atypical and typical antipsychotics–prescribing sequence and documented outcome. *Psychiatric Bulletin*, *26*(5), pp.170-172.	Data collection and analysis
3	A systematic review and meta-analysis of Hypericum perforatum in depression: a comprehensive clinical review. *International clinical psychopharmacology*, *16*(5), pp.239-252.	Conceptualisation of project, literature search, first author, produced first draft and final draft for submission
4	Pramipexole in unipolar and bipolar depression. *Psychiatric Bulletin*, *28*(12), pp.438-440.	Conceptualisation, first author, writing the first and final draft for submission
5	Depression in cardiovascular disease. In *Case studies in Psychopharmacology: the use of drugs in Psychiatry.*	Writing the book chapter
6	Continuation of clozapine treatment: practice makes perfect. *Psychiatric Bulletin*, *27*(6), pp.211-213.	Conceptualisation of project, first author, produced first draft and final draft for submission
7	Comment-Broad Spectrum-Generic clozapine: Opportunity or threat? *Pharmaceutical Journal*, *273*(7309), pp.112-112.	Writing the first and final draft for submission
8	Restarting Clozapine after Neutropenia. *CNS drugs*, *21*(1), pp.25-35.	Literature search, producing the first and final draft for submission
9	Optimizing outcomes in clozapine rechallenge following neutropenia: a cohort analysis. *The Journal of clinical psychiatry*, *76*(11), pp.1410-1416.	Contributed to data collection and analysis and revising the manuscript
10	Need to bleed? Clozapine haematological monitoring approaches a time for change. *International clinical psychopharmacology*, *34*(5), pp.264-268.	Conceptualisation of project, first author, produced first draft and final draft for submission

11	The use of granulocyte colony-stimulating factor in clozapine rechallenge: a systematic review. *Journal of clinical psychopharmacology*, *37*(5), pp.600-604.	Contributed to revising the manuscript
12	Clozapine-associated agranulocytosis treatment with granulocyte colony-stimulating factor/granulocyte-macrophage colony-stimulating factor: a systematic review. *Journal of Clinical Psychopharmacology*, *37*(4), pp.441-446.	Contributed to revising the manuscript
16	Resolution without discontinuation: heart failure during clozapine treatment. *Therapeutic Advances in Psychopharmacology*, *10*, p.2045125320924786.	Conceptualisation of project, first author, produced first draft and final draft for submission
17	Tachycardia in: *Practice Guidelines for Physical Health in Psychiatry*.	Contributed to writing and reviewing the first and final drafts
18	The importance of the recognition of benign ethnic neutropenia in black patients during treatment with clozapine: case reports and database study. *Journal of psychopharmacology,* 25(6), pp.842-845.	Conceptualisation of project, first author, produced first draft and final draft for submission
19	Granulocyte colony-stimulating factor (G-CSF) can allow treatment with clozapine in a patient with severe benign ethnic neutropenia (BEN): a case report. *Journal of Psychopharmacology*, 26(9), pp.1280-1282.	Contributed to the first draft and revising the final manuscript
20	A retrospective study of intramuscular clozapine prescription for treatment initiation and maintenance in treatment-resistant psychosis. *The British Journal of Psychiatry*, *217*(3), pp.506-513.	Conceptualisation of the project, contributed to data collection and the first draft and thoroughly revising the final manuscript
21	Protocol for the use of intramuscular clozapine in South London and Maudsley NHS Foundation Trust.	Writing the first and final draft for the Trust
22	Clozapine and Norclozapine Plasma Levels in Patients Switched Between Different Liquid Formulations. *Therapeutic drug monitoring.*	Contributed to data collection, analysis and reviewing and revising the final manuscript
23	Change in plasma concentration of clozapine and norclozapine following a switch of oral formulation. *Therapeutic Advances in Psychopharmacology*, 10, p.2045125319899263.	Conceptualisation, project supervision, reviewing and revising the final manuscript

24	Clozapine, HIV and neutropenia: a case report. *Therapeutic advances in psychopharmacology*, 8(12), pp.365-369.	Conceptualisation of project, first author, produced first draft and final draft for submission
27	Melperone in treatment-refractory schizophrenia: a case series. *Therapeutic advances in psychopharmacology*, 1(1), pp.19-23.	Conceptualisation of project, first author, produced first draft and final draft for submission
29	Vitamin D supplementation compared to placebo in people with First Episode Psychosis-Neuroprotection Design (DFEND): a protocol for a randomised, double-blind, placebo-controlled, parallel-group trial. *Trials*, 21(1), pp.1-12.	Contributed to the design, including parameters for inclusion and exclusion. Revising the final draft
32	There Is Life After the UK Clozapine Central Non-Rechallenge Database. *Schizophrenia Bulletin*.	Contributed to the conceptualisation, project supervision, reviewing and revising the final manuscript

I confirm that the statements above, accurately represent Eromona Whiskey's contribution to the stated Public Works (PWs)

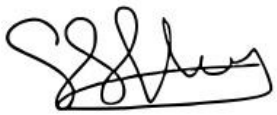


Professor David Taylor BSc MSc PhD FRCPsych(Hon) FRCPEdin FFRPS FRPharmS
Professor of Psychopharmacology, Kings College London

Confirmation and declaration of authorship

PW	Title	Eromona Whiskey's contribution
13	Clozapine and cardiotoxicity–A guide for psychiatrists written by cardiologists. *Psychiatry Research*, *282*, p.112491.	Contributed to the literature search and revising the manuscript
14	Understanding and managing cardiac side effects of second-generation antipsychotics in the treatment of schizophrenia. *BJPsych Advances*, 26(1), pp.26-40.	Contributed to the literature search, writing of the first draft and revising the final manuscript
15	Hearts and Minds: Real-Life Cardiotoxicity with Clozapine in Psychosis. *Journal of clinical psychopharmacology*, 37(6), pp.708-712.	Contributed to the data collection, supplied intellectual content and context and revising the final manuscript
25	Successful clozapine rechallenge following recurrent clozapine-associated pancreatitis: a case report. *BMC Pharmacology and Toxicology*, *21*(1), pp.1-5.	Contributed to revising the manuscript and supplying intellectual content, reviewing and revising the final draft
26	When the drugs don't work: treatment-resistant schizophrenia, serotonin and serendipity. *Therapeutic advances in psychopharmacology*, 8(1), pp.63-70.	Contributed to writing the first draft, reviewing and revising the final draft
28	Real-World Outcomes in the Management of Refractory Psychosis. *The Journal of clinical psychiatry*, 80(5).	Contributed to data collection and reviewing and revising the final draft
30	Hyoscine for clozapine-induced hypersalivation: a double-blind, randomized, placebo-controlled cross-over trial. *International clinical psychopharmacology*, 34(2), pp.101-107.	Contributed to data collection and reviewing and revising the final draft
31	Closure beyond clozapine: successfully averting rebound symptoms in a patient with schizoaffective disorder and agranulocytosis. *BJPsych Open*, *5*(3).	Contributed to the conceptualisation, project supervision, reviewing and revising the final manuscript
33	An evaluation of the variation and underuse of clozapine in the United Kingdom. *Acta Psychiatrica Scandinavica. https://doi.org/10.1111/acps.13280.*	Contributed to the conceptualisation, writing the first and final draft for submission

I confirm that the statements above, accurately represent Eromona Whiskey's contribution to the stated Public Works (PWs)



10 April 2021

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Appendix 3

Guidelines for the use of intramuscular clozapine treatment

What is IM clozapine?

Intramuscular clozapine is an unlicensed product made in the Netherlands by Brocacef and imported to the UK via Durbin PLC. It is a clear yellow solution for injection. The strength of the injection is 25mg/ml and each ampoule contains 5mls (125mg). It is administered by deep intramuscular injection into the gluteal muscle. The injection is painful and the maximum volume that can be injected into each site is 4ml (100mg). For doses greater than 100mg daily, the dose may be divided and administered into two sites.

Who can have IM clozapine?

Clozapine injection may only be prescribed and administered on the direct written authority of the Director of Pharmacy (david.taylor@slam.nhs.uk). The injection is indicated only for patients with a treatment-refractory psychotic disorder who are refusing oral treatment. It can be used for patients who have never been exposed to clozapine previously or patients previously treated with clozapine and known to have responded, but relapsed owing to non-compliance. The need for clozapine injection must be agreed by the MDT, approved by the SOAD and fully documented in EPJS using the assessment form (see Appendix 1).

What is the objective of using IM Clozapine?

The aim of using clozapine injection is a short-term intervention to initiate clozapine for patients who refuse medication, with a view to converting to oral clozapine as soon as possible.

Registration of patients for IM Clozapine

All patients for IM clozapine must be registered with the Zaponex Treatment Access System (ZTAS) as the objective is to use the injection for the shortest possible time before switching to oral treatment. After treatment with clozapine injection has been agreed by the MDT and approved by the SOAD, ZTAS will be informed of the treatment plan and the patient registered accordingly. The usual clozapine mandatory baseline and weekly blood monitoring and the necessary precautions for amber and red warnings apply.

How long can the treatment continue?

Clozapine injection should be used for the shortest duration possible. Before administering each injection, the patient should be offered clozapine orally. The need for ongoing IM treatment must be reviewed regularly by the MDT. In general, the injection should be used for no longer than two weeks. In exceptional cases, the injection may be used for longer than two weeks if approved by the MDT, SOAD and Director of Pharmacy.

What is the oral equivalent of the IM?

The oral bioavailability of clozapine is about half that of the intramuscular injection. For example, 50mg daily of the IM injection is roughly equivalent to 100mg daily of the tablets.

Starting clozapine injection

The patient must be registered with ZTAS the week before commencing treatment. Treatment should start on a Monday whenever possible. Clozapine should be prescribed on the main drug chart and annotated 'see separate clozapine titration sheet'. Each dose on the titration sheet must be signed and dated by the prescriber. The sheet (see Appendix 2) must be attached to the main drug chart. **The patient should always be offered the tablets first** and if the patient continues to refuse, then the injection is administered. **Nursing staff must clearly indicate the route of administration used on the titration sheet.**

Monitoring of patients on IM clozapine treatment

Baseline assessment before starting clozapine must include ECG, FBC, lipids, plasma glucose, U&Es, LFT, CRP and troponin. It is anticipated that daily monitoring of blood pressure, pulse, respiratory rate and temperature will be difficult for many patients; every effort must be made

to obtain these, and patient refusal of observations must be documented. Importantly, patients should be observed for any signs of being unwell, such as pallor, cough, shortness of breath, sweating etc.

After each injection has been given the patient must be observed every 15 minutes for the first two hours to check for excess sedation. Monitor respiratory rate, pulse, temperature and blood pressure pre-dose, 15 and 30 minutes post dose and 2 hours post dose.

The usual weekly blood tests should be performed while on treatment; the sample could be taken at the same time as the administration of clozapine injection if needed.

Costs

Clozapine injections cost around £100 per injection (or part thereof, as any unused portion must be discarded).

Appendix 1: Clozapine Injection MDT Assessment Form

Name of patient	
Date of birth	
Indication for clozapine	
Date patient registered with ZTAS	
Are there any significant physical health comorbidities that contra-indicate the use of clozapine?	
Previously on clozapine? If yes, state reason clozapine was stopped previously	
Date of Director of Pharmacy approval	
Date of SOAD approval	
Date MDT discussion documented in ePJS	

Appendix 2: Clozapine Injection Titration Chart

Week One

Name: **Date of birth:**

ALWAYS OFFER ORAL CLOZAPINE FIRST

Day	Date	Oral dose	IM clozapine *ONLY if oral refused*	Prescriber's signature	Specify route given Oral or IM	Given by	Pre-Dose				15-mins post-dose				30-mins post dose				2-hours post dose			
							RR	Pulse	Temp	BP	RR	Pulse	Temp	BP	RR	Pulse	Temp	BP	RR	Pulse	Temp	BP
1		10mg	5mg (0.2ml)																			
2		25mg	12.5mg (0.5ml)																			
3		25mg	12.5mg (0.5ml)																			
4		50mg	25mg (1ml)																			
5		50mg	25mg (1ml)																			
6		75mg	37.5mg (1.5ml)																			
7		75mg	37.5mg (1.5ml)																			

Clozapine Injection Titration Chart (continued)

Week Two

Name: **Date of birth:**

ALWAYS OFFER ORAL CLOZAPINE FIRST

Day	Date	Oral dose	IM clozapine *ONLY if oral refused*	Prescriber's signature	Specify route given Oral or IM	Given by	Pre-Dose				15-mins post-dose				30-mins post dose				2-hours post dose			
							RR	Pulse	Temp	BP	RR	Pulse	Temp	BP	RR	Pulse	Temp	BP	RR	Pulse	Temp	BP
8		100mg	50mg (2ml)																			
9		100mg	50mg (2ml)																			
10		125mg	62.5mg (2.5ml)																			
11		125mg	62.5mg (2.5ml)																			
12		150mg	75mg (3ml)																			
13		150mg	75mg (3ml)																			
14		175mg	87.5mg (3.5ml)																			