A Critical Literature Review of the Direct, Adverse Effects of Neuroleptics*

*also known as antipsychotics

Essential Information for Mental Health Consumers, Carers, Families, Supporters and Clinicians

National Mental Health Consumer & Carer Forum

Dr Kate Dorozenko and Dr Robyn Martin

School of Occupational Therapy and Social Work
Curtin University

May 2017

ACKNOWLEDGEMENTS

We acknowledge and pay our respects to those who have lost their lives as a result of their experiences of mental distress, and the consumers who are impacted and at times, debilitated by the adverse effects of neuroleptic drugs.

We acknowledge the experiences of families and other supporters who stand beside their loved ones while advocating for change.

We would like to thank Lyn Mahboub for her expert input to this report. Lyn's input as Lived Experience Consultant has ensured our work is of the highest standard and never loses the central focus on consumers and families. We appreciate your capacity to stretch and challenge us morally, ethically and intellectually.

We acknowledge Deb Sobott, the National Mental Health Consumer and Carer Forum representative who has worked closely with us in developing the scope and design of the project. Your grace, generosity, intellect and humour remind us of why we are called to work in this area and in this way.

Finally, we thank the National Mental Health Consumer and Carer Forum who have funded this research. We believe your willingness to commission research in an area that is politically sensitive demonstrates leadership.

A Critical Literature Review of the Direct, Adverse Effects of Neuroleptics*

*also known as antipsychotics

Essential Information for Mental Health Consumers, Carers, Families, Supporters and Clinicians

Dr Kate Dorozenko and Dr Robyn Martin

School of Occupational Therapy and Social Work
Curtin University

May 2017

Contents

Foreword

Whilst it has been a privilege to write this foreword, I deeply regret the circumstances by which I have come to do so. My name is Debra and I am the mother of a son permanently injured by neuroleptic (antipsychotic) drugs.

I am also a mental health advocate and I have been very fortunate to be associated with and benefit from working alongside my colleagues at Curtin University in Western Australia. I am also a proud member of the National Mental Health Consumer and Carer Forum (NMHCCF) who supported my initial research into the dangers associated with neuroleptics by providing funding to commission this Critical Literature Review. On behalf of the NMHCCF, Curtin University researchers, Dr Kate Dorozenko, Dr Robyn Martin in collaboration with consumer academic Ms Lyn Mahboub have produced this compelling review which examines the direct and adverse effects of neuroleptic drugs.

So why was it important to commission such a review? If I were to answer that question in just one sentence I could look no further than psychiatrist, Niall (Jock) McLaren's statement; "In plain language, if you have mental problems these days, you live in dangerous times". The mortality rate of those diagnosed with schizophrenia is significantly higher in people prescribed neuroleptics, dying on average 19 years younger than the general population. The evidence provided in this review substantiates the fact that there are significant physical and psychological impacts associated with neuroleptic drugs. And yet, despite this crucial evidence, neuroleptics continue to be routinely prescribed and people continue to be subjected to the debilitating direct adverse effects and potential mortality.

If I was asked to write this foreword even 10 years ago, as a family member, I would have complied with the unwritten rules if I wanted to be taken seriously, I must be graceful; I must not be combative; I must not show emotion and above all, I must not give voice to my personal experience. I no longer occupy that innocent, unsullied space and the world my son and I now inhabit is tragic and cruel. I don't seek company in this world — I want you or the person you care for to pursue an informed pathway to a vastly different world and in order to find that alternative route and have the best conceivable chance of recovery, it is imperative that you cultivate an awareness. This review will start you on that journey to knowledge and awareness and I implore you to take advantage of the information within. Had I been privy to the findings within this review 20 years ago, our lives would have looked very different today and as such I cannot overstate its importance for consumers, families, carers and clinicians.

So how did my son and I end up where we subsist today? Wasn't my son in the system getting 'treatment'? Surely the system provided expert collaborative care and treatment? Well, actually — no. The treatment my son did get was standard and by that I mean an ever changing concoction of neuroleptics (polypharmacy) year after year despite rapid and visible deterioration in both his mental and physical state. I was a bystander to his fate with the profession of psychiatry having purposeful dominion over our lives. I anguished over my son's pleas for help. I cried when he begged me to not let them inject him. I was incensed when they dismissed my requests for cognitive behavioural therapy and ultimately, my heart broke when I witnessed his metamorphosis from a handsome young man full of hope to what he became. Whilst he remains my beautiful boy, today you will see him as an overweight, scarred old man who suffers the agony of tardive dyskinesia, the torment of akathisia, with multiple suicide attempts and no longer being able to utter one coherent sentence. Nothing can render a mother more wretched than watching her child's life dissolve before her eyes whilst being completely and utterly powerless to do anything.

It has been argued that the direct and adverse effects associated with neuroleptics would result in most drugs in general medicine being removed from the market. I find this remarkable, particularly so given this review not only provides us with a list of the most commonly prescribed neuroleptics in Australia but more importantly, exposes the dire adverse and direct effects associated with each of those neuroleptic drugs.

We have to ask ourselves, how is it neuroleptics continue to be the mainstay treatment given the dire mental and physical outcomes? Our unwillingness to embrace alternative safe treatments in the past has created this calamitous and dire situation which has, in turn, given birth to an industry that exists entirely to 'fix' the problems that we, ourselves, have created.

Importantly, the review states *"it became evident quickly that the literature was dominated by the voices and priorities of the clinical researchers and practitioners."* If the views of the professions are the 'only' views afforded weight in treatment decisions with the perspective of those whose lives who are critically impacted being ignored, how is it possible to arrive at a balanced viewpoint on what the optimal and least harmful pathway to recovery is? Regrettably we have a distance to go in terms of our lived experience being privileged and it is our obligation to forge a path to genuine privilege which is reflected in action. It is incumbent upon us to become the vanguard for change and it is, therefore, vital that we are informed. This review has the potential to serve as a gateway to knowledge and ultimately has the potential to give rise to a paradigm shift away from the default treatment focus on neuroleptics.

Whilst the researchers have stated that they have privileged and centred lived experience, it's also important to acknowledge their integrity in the writing of this review where they have examined the literature and presented an impartial and critical examination of their findings. On behalf of the members of the NMHCCF, I would like to express our profound gratitude to Dr Kate Dorozenko, Dr Robyn Martin and Ms Lyn Mahboub. Their professional commitment and personal dedication to this review extended far above and beyond their role as researchers.

And in conclusion, I would like to leave you with an excerpt from Professor Peter Gøtzsche's 'Psychiatry Gone Astray':

> *I am not against using drugs, provided we know what we are doing and only use them in situations where they do more good than harm. Psychiatric drugs can be useful sometimes for some patients, especially in short-term treatment, in acute situations. But my studies in this area lead me to a very uncomfortable conclusion:* ***Our citizens would be far better off if we removed all the psychotropic drugs from the market, as doctors are unable to handle them. It is inescapable that their availability creates more harm than good. Psychiatrists should therefore do everything they can to treat as little as possible, in as short time as possible, or not at all, with psychotropic drugs.***

Debra Sobott

National Mental Health Consumer & Carer Forum — WA Carer Representative

Executive Summary

This critical literature review of the adverse effects of neuroleptic drugs was commissioned by the National Mental Health Consumer and Carer Forum (NMHCCF) under the auspices of Mental Health Australia.

The NMHCCF was concerned that many consumers and family members are unaware of the direct, adverse effects associated with neuroleptics and the inconclusive, and at times contradictory, nature of the evidence underpinning their use. As such, the aim of this critical literature review was to provide information on neuroleptic drugs so that individuals and their families can make truly informed choices. Reflecting these aims, the scope of the review was broad. To ensure that the lived experience of individuals and their supporters remained at the centre, this work was guided by a series of co-produced values which reflected the commitment of the NMHCCF to raise the voice of lived experience, as well as a critical questioning of psychiatry and the assumptions that drive the use of neuroleptic drugs. Throughout all areas of literature examined, a distinct lack of engagement with the lived experiences of neuroleptics is evident. In summary, the voices of lived experience are rarely sought or reported in the literature.

The review begins with a brief overview of the history of neuroleptics. This section shows that early use of the drugs were favoured by psychiatrists as the management of 'patients' improved due to high levels of sedation and indifference. Overtime, neuroleptic drugs were branded as 'antipsychotics' and hypotheses related to the function of dopamine came to dominate. To date, no biochemical or physiological cause for psychosis has been conclusively identified; yet the dominant form of treatment rests on a hypothesis of chemical imbalance.

Prescribing practices are considered next and it is noted that the use of neuroleptic drugs has grown exponentially with over 80% of Australians diagnosed with schizophrenia or psychosis prescribed these drugs (Waterreus et al., 2012). Additionally, there is a trend of increasing off-label neuroleptic prescription for a whole host of conditions beyond psychosis including anxiety, depression, dementia, autism and attention deficit hyperactivity disorder.

Further, despite a lack of convincing evidence to support the routine use of combined neuroleptics and guidelines which warn against this practice, polypharmacy is common in clinical practice and associated with greater harm.

Efficacy of neuroleptics is then considered and the growing body of evidence that indicates the benefits of these drugs may have been overstated is examined. These studies report that in the short to medium term, neuroleptics produce modest gains for some people when compared to placebo, and this improvement is typically limited to a reduction in positive symptoms. Further, there is little evidence to suggest that maintaining people indefinitely on neuroleptics prevents relapse (Harrow, Jobe, & Faull, 2014; Wunderink, Nieboer, Wiersma, Sytema & Nienhuis, 2013). Although the introduction of second generation neuroleptics was touted as a new dawn in the treatment of psychosis, studies have shown that these more expensive drugs are no more efficacious or tolerable than first generation neuroleptics.

The review then considers the adverse effects of neuroleptic drugs. In contrast to the uncertainty surrounding the efficacy of neuroleptics, the direct, adverse effects of the drugs are known and well established. Notably, the life expectancy of people diagnosed with schizophrenia is 15–20 years shorter than the general population and this mortality gap is widening over time (Saha et al., 2007). Diabetes, cardiovascular disease, sedation, sexual dysfunction and movement disorders are associated with the use of neuroleptics and cause great distress and physical morbidity. These direct effects are not uncommon. For example, tardive dyskinesia, a neurological disorder characterised by involuntary, uncontrollable movements, is commonplace, leading to it being labelled "among the worst medically induced disasters in history" (Breggin, 2008, p. 84).

Typically consumers experience multiple adverse effects simultaneously, and the cumulative effect is reported to have a profound impact on quality of life. Consequently, some suggest that if the risks associated with neuroleptics occurred in general medicine, it is highly likely that the drugs would be removed from the market; yet psychiatry continues to use neuroleptics as the frontline response to psychosis.

The issues of withdrawal and adherence are also considered. The heavy burden of neuroleptics results in many consumers opting to not take these drugs as prescribed, or at all, which is commonly framed by clinicians as 'non-compliance' and seen as reflective of a lack of insight and evidence of 'mental illness'. For these reasons, consumers are reported to be reluctant to discuss discontinuation with clinicians due to a fear of judgement or the threat of being placed on a compulsory treatment order. The literature indicates that neuroleptics create a state of physical dependence and when ceased, produce distinctive withdrawal responses which are often interpreted as the re-emergence of the underlying 'illness' (relapse). There is a lack of clinical guidance or information for consumers on how to safely taper or withdraw from neuroleptics.

To conclude, the review examined alternative and conjunctive responses to psychosis such as Open Dialogue, Soteria and Hearing Voices Network. These approaches differ from dominant treatment approaches by seeking to understand the experience of psychosis and demonstrate that recovery is possible with or without neuroleptic drugs. Shared decision making and harm reduction approaches encourage the empowered use of neuroleptics in the recovery process and position the consumer as an active agent in their own recovery. Common to these approaches is the view that medication is just one tool among many that people may choose to use in their recovery. Despite emerging research demonstrating positive outcomes associated with these approaches they remain very much on the periphery.

The review shows that neuroleptics can have a role in personal recovery but as recovery is a unique, individual process, the role of the drugs will be different for each person. This review has highlighted the adverse and unwanted effects of neuroleptics which can, at times, be experienced as worse than the problem they were intended to relieve and can interfere with the recovery process. Individuals who are critically impacted by these drugs and their loved ones have much to contribute to the discourse surrounding neuroleptics and how they may be used to support personal recovery.

Background

This critical literature review on the iatrogenic and adverse effects of neuroleptic drugs has been commissioned by the National Mental Health Consumer and Carer Forum (NMHCCF) under the auspices of Mental Health Australia.

A NMHCCF representative approached Curtin University researchers with a list of areas of interest and these were considered, discussed and negotiated in relation to project aims, scope and budget. The first stage of the research involved a critical scoping review of literature on the iatrogenic and adverse effects of neuroleptic drugs, focussing on the following topics:

1. Scoping and definition of key terms.
2. History of neuroleptic usage.
3. An overview of commonly prescribed neuroleptics.
4. Prevalence and patterns of neuroleptic prescribing practices within Australia, Europe, United Kingdom and the United States of America.
5. Prevalence of polypharmacy and monotherapy prescribing practices within Australia, Europe, the United Kingdom and the United States of America.
6. Overview of efficacy of neuroleptics on psychosis.
7. Detailed analysis of physical and psychological iatrogenic effects arising from:
    a. Long term neuroleptic use.
    b. Polypharmacy and neuroleptic use.
8. Adverse effects associated with withdrawal and tapering of neuroleptics, including lived experience testimonies where available.
9. An overview of up to five alternative service delivery responses to psychosis and mental distress.
10. An overview of the issues associated with concurrent prescribing of neuroleptic and adjunctive medications (i.e. nicotine replacement, opiate replacements etc.)

Given the broad focus requested by the NMHCCF, the review is substantial, particularly as we have sought to include a wide range of views and ideas on each topic.

The second stage of the research focusses on the coproduction between the NMHCCF and the research team of information sheets and resource materials on key areas identified in the literature review (these are not included in this report). The approach taken by the research team has been guided by coproduction principles, by seeking the active involvement of NMHCCF members and inviting their direction, discernment and ideas for improvement. Our methodology is detailed later in the report, however it is important to note here that the NMHCCF communicated that it wanted the lived experience of using neuroleptic drugs to be central to the review and assessment of literature. The research team did not expect that a systematic review methodology would be possible as our initial scope of the literature across all 10 topics highlighted that the research evidence varied in method, size, reflexivity and rigour. Consequently, the research team worked with the NMHCCF to develop quality assessment criteria which considered existent literature from perspectives based on the following:

1. The lived experience of individuals and families is included and/or privileged.
2. The assertion that the benefits of neuroleptics outweigh the adverse effects is critically examined.
3. The idea that neuroleptics form an 'integral' component of recovery or treatment is critically examined.
4. The idea that professionals know what is in the consumer's best interests is critically examined.
5. The idea that clinicians are educated/informed in terms of side effects and purported efficacy and limitations of neuroleptics is critically examined.

6. The idea that all 'symptoms' are intolerable and must be eradicated is critically examined.
7. Which endorses the idea that people can (and should, where possible) make informed decisions about neuroleptics.
8. The limits of the scientific approach in psychiatry are considered.
9. An endorsement of a wide range of treatment and support responses is evident.

Given the broad focus of the project and our commitment to review the literature on the adverse effects of neuroleptic drugs using the principles the NHMCCF members valued (as noted in the bullet points above), it became evident quickly that the literature was dominated by the voices and priorities of clinical researchers and practitioners. That is, notions of efficacy and the adverse or iatrogenic effects of neuroleptic drugs rarely involve lived experience testimonies. We have found a resounding silence in the literature on the lived experience of neuroleptic drugs for both individuals prescribed the drugs and their families and supporters. Where these studies and research reports exist and relate to the 10 topics covered in the review we have referenced them. Where we have located lived experience accounts in the peer reviewed literature, we have included these. However, given the size of the project, we have not been able to systematically search and include those from internet sources such as **mythsandrisks.info**; **madinamerica.com**; **mindfreedom.org**; **rxisk.org**.

While the history (detailed later) of responses to psychosis shows that the introduction of neuroleptic drugs in the 1950s was heralded as a breakthrough, a questioning and critique of this response has emerged on the margins of, and sometimes within, psychiatry in more recent times. In particular, consumer and family advocates are highlighting the health problems associated with neuroleptic drugs.

For example, bio-medical researchers argue in relation to schizophrenia: "Although extensive research has been performed, its aetiology and pathophysiology remain relatively unclear, and available treatments are only modestly effective and cause serious metabolic and neurological adverse effects" (Iseger & Boson, 2015, p. 153). Given the challenges from the margins and the statements from within psychiatry regarding the strength of the evidence base underpinning clinical practice, it is unsurprising that many of the terms commonly used in this area are contested, and have multiple (sometimes contradictory) definitions. Consequently, we offer a glossary of terms, identifying how we have used the term in this review.

Before moving on to the glossary, we believe it is important that we share our positionality. We do this as we value reflexivity, accountability and transparency in all areas of our practice. Our positioning is characterised by a curious and questioning stance which does not take any one way of understanding for granted. When we notice taken for granted assumptions and knowledge, we seek to understand the history of ideas which sit underneath and around these occurrences. Consequently, taken for granted or dominant ideas and practices are respectfully questioned and examined. Our work is guided by our deeply held belief that many forms of expertise exist and that for far too long the voice of lived experience has been subjugated and silenced, and often positioned as inferior to professionally developed expertise. Consequently, it is imperative to us that we privilege and centre lived experience in our work.

GLOSSARY

Adherence, concordance or compliance?

Traditionally, the terms compliance and non-compliance have been used to denote the ways in which individuals follow (or do not follow) the guidelines and advice from the professional who has prescribed the medication. As such, compliance denotes a relationship where the professional holds more power than the consumer (Weiss & Britten, 2009). More recently, the concept of adherence has entered the health lexicon. However, the National Institute for Health and Care Excellence (NICE) guidelines in the UK advise against adherence therapy in the treatment of schizophrenia (NICE, 2009). While much attention is paid by clinicians to promoting adherence, some argue that a more effective response would involve developing a deep understanding of the individual's worldview, and their previous experience of, and intentions about, neuroleptic drugs (Gibson, Brand, Burt, Boden, & Benson, 2013). Such an approach has the potential to create the conditions for "informed choice and shared decision making" (Le Geyt, Awenat, Tai, & Haddock, 2016, p. 2) and align with concordance principles. Weiss and Britten (2009) argue that concordance is a process of shared power which works toward agreement. There are a range of reasons why people enact agency in how they use neuroleptic drugs including the impact of direct effects and a sense that the drugs undermine, rather than support wellbeing (Gibson et al., 2013), and these factors are considered later in the document.

Antipsychotics or neuroleptics?

Both the terms antipsychotic and neuroleptic drugs are found in the research, policy and standards documentation and clinical practice. Some argue that the term antipsychotic is incorrect as suggested by the British Psychological Society: "the term 'antipsychotic' is rather misleading" (n.d. p. 94) as these drugs do not cure or correct 'psychosis'; instead they may assist in reducing distress. The history of these drugs is covered in the next section and it shows that when first introduced in the 1950s the drugs were observed to produce a state of neurological suppression characterised by sedation, disinterest and reduced responsiveness to external stimuli; which was considered helpful by psychiatrists and nursing staff (Ban, 2007; Moncrieff, 2013). The term 'neuroleptic' (from the Greek meaning 'to seize') reflects the view that these drugs produce a global, psychoactive effect rather than specifically targeting an underlying 'disease' or correcting an abnormal brain state (Le Geyt et al., 2016; Moncrieff, 2009; Moncrieff, 2013). This raises questions about whether these drugs act on a disease (called a disease centred action), or respond to the distress associated with psychosis — called a drug centred action (Moncrieff, 2013). To date, no biochemical or physiological cause for schizophrenia has been conclusively identified, and the aetiology of psychosis remains hypothesised (Breggin, 2016; Moncrieff, 2013). Given the ambiguity about whether the drugs are in actuality 'anti'-psychotic (meaning they cure or correct the disorder), we have followed the lead set by Le Geyt et al. (2016) who frame their use of the term neuroleptic in the following way: "To avoid making assumptions where interpretations of the evidence are inconclusive we will use the term neuroleptics, rather than antipsychotics in this review" (p. 13). Therefore, the term neuroleptics is used throughout this review.

Neuroleptic medication or neuroleptic drug?

According to the Oxford dictionary, the term medication is defined as "A drug or other form of medicine that is used to treat or prevent disease" ("Medication," n.d.). Drug, on the other hand, is defined as "A medicine or other substance which has a physiological effect when ingested or otherwise introduced into the body" ("Drug," n.d.). Given that neuroleptics produce a global physiological effect on the body rather than specifically treat a 'disease' we have chosen to use the term drug in this review.

Consumer, service user or people with lived experience?

We acknowledge the wide range of terms such as service user, consumer, patient, client, person with lived experience and psychiatric survivor. These terms reflect local contexts, historical moments, political influences and preferences. Given the prevalence of the term consumer in Australia, we have adopted it, although there are occasions when we refer to patient, as this is the language used in the particular study being discussed. We also acknowledge the critique and limitations of all terms, including consumer.

Family

The term 'carer' is commonly found in service delivery and research contexts. However, many family members and supporters negotiate a range of identities, some of which include caring (formal or informal). We have used the term family in this review to denote a wide range of biological and non-biological relationships between consumers and those who support them.

First and Second Generation Neuroleptics

Neuroleptics are categorised into two drug classes; first generation neuroleptics and second generation neuroleptics. The older, first generation neuroleptics were introduced in the 1950s and 1960s and are also referred to as 'typical' or 'conventional'. Popular first generation neuroleptics include chlorpromazine (Thorazine), perphenazine (Trilafon) and haloperidol (Haldol). These drugs work by blocking dopamine which can reduce the symptoms of psychosis by "… suppressing all mental and physical activity" (Moncrieff, 2009). These drugs also have the propensity to induce serious and debilitating movement disorders such as Parkinsonism and tardive dyskinesia (Adams, Awad, Rathbone, Thornley, & Soares-Weiser, 2014; Adams, Bergeman, Irving, & Lawrie, 2013).

In the 1990s and 2000s second generation or atypical neuroleptics were introduced, including olanzapine (Zyprexa), risperidone (Risperdal), quetiapin (Seroquel), ziprasidone (Geodon), aripiprazole (Abilify), and Clozapine (Clozaril). Although these compounds vary significantly in their pharmacological actions, they were promoted as having a lower propensity to induce movement disorders, and the prevailing opinion of the time was that second generation neuroleptics were vastly superior to the older, first generation neuroleptics in terms of efficacy and safety (Lieberman & Stroup, 2011; Moncrieff, 2007). Studies, however, have shown that the more expensive, second generation neuroleptics are no more efficacious than first generation neuroleptics, and the adverse effect profiles for these drugs are not clearly distinguishable from the older compounds (Leucht et al., 2009; Lieberman et al., 2005; Lieberman & Stroup, 2011). For these reasons, the categorisation of neuroleptics as 'first generation' or 'second generation' is considered by many to be a misnomer reflective of the marketing strategies of pharmaceutical companies, and critics have argued that "… the time has come to abandon the terms first-generation and second-generation antipsychotics, as they do not merit this distinction" (Tyrer & Kendall, 2008; p. 5).

Iatrogenic

The term 'iatrogenic' means inadvertently induced by the activity of a clinician or by a medical treatment. For example, tardive dyskinesia can be considered an iatrogenic condition as it is caused by neuroleptics (Breggin, 2011).

Insight

In psychiatry, this concept relates to the level of understanding an individual has about their diagnosis and its impacts, and is usually assessed and determined by professionals. Insight is subject to contestation from consumers, families and their allies. The basis of the contestation is that the traditional application denies individual meanings related to their lived experience. Australian Consumer Academic, Cath Roper argues:

> ***The only way I can demonstrate insight is to say that I know I am sick ... However, if I say that I don't have any insight, I am demonstrating that I do have it (even though I'm achieving this by admitting that I think I'm not sick). It is only by the judgements of others that my insight can be determined.*** *(Roper, cited in Hamilton & Roper, 2006, p. 421)*

The clinical operationalisation of 'insight' denies the reality and lived experience of the individual (Slade, 2009). The approach taken to insight has a direct relationship to the type of recovery understandings adopted by professionals, individuals and families. In personal recovery, the individual's meanings are privileged and foregrounded; yet if the treating team operates primarily from a clinical recovery perspective and their meanings about the lived experience of psychosis do not correspond to the individual's it is likely that they may frame the individual's views as lacking insight into the 'illness', its severity and impacts.

Mental distress or 'mental illness'?

The terms used to describe the experience reflect the author's values and knowledge base. The term 'mental illness' is associated with the bio-medical paradigm which locates the experience in a health and disease framework of understanding. In contrast, the term mental distress reflects a social constructionist framing of the experience. This review shows that the evidence base for describing psychosis as an illness is unstable, as are the claims for the efficacy of neuroleptic drugs. Therefore, we use the term mental distress in this review, and when referring to 'mental illness' we frame it as problematic by the use of inverted commas.

Psychosis or schizophrenia?

Psychosis is defined as "a syndrome characterised by one or more of the following symptoms: delusions, hallucinations, thought disorder, catatonia" (Howes & Murray, 2014, p. 1678). In contrast, schizophrenia is defined as an illness characterised by "psychotic and negative symptoms" (Howes & Murray, 2014, p. 1678). Johnstone argues that the term psychosis is positioned as "more user friendly and less stigmatizing" (2011, p. 5) than schizophrenia. Given that neuroleptic drugs are used in response to a wide range of 'psychotic symptoms' which may or may not be associated with a diagnosis of schizophrenia, we primarily use the term psychosis in this review; however some studies focus specifically on schizophrenia and we therefore adopt this term in those instances. Our position is that regardless of the diagnosis, neuroleptic drugs are used in response to what is considered psychosis and the drugs impact in similar ways, regardless of the diagnosis.

We also note that there is controversy and contestation around psychosis and schizophrenia, with questions raised about the scientific validity of these concepts (Boyle, 2002; Read, 2013) Put simply, these debates reflect differences of opinions and philosophical positions about whether psychosis can be classified as a biological dysfunction (usually of the brain), or as a social construct. Ideas situated in critical thought understand psychosis as understandable emotional, physical and psychological responses to trauma and other forms of distress (Read, Goodman, Morrison, Ross & Aderhold, 2004). However, some authors question the universalising linking of trauma and psychosis. Instead, they suggest a nuanced stance needs to be taken which includes specificity in defining trauma; ensuring that the focus extends beyond the individual experience of trauma to include consideration of poverty, racism and sexism; and ensuring perpetrator accountability (Johnstone, 2011). This review demonstrates that there is a large amount of research undertaken which rests on the belief that psychosis has a biological basis, and is best treated or managed with neuroleptic drugs. Sitting alongside this is an emerging body of knowledge which demonstrates that other frameworks of understanding and treatment responses can be beneficial to many people.

Recovery

The term and concept of recovery is subject to considerable research and discussion. More recently, it has become evident that that each type of recovery reflects a particular orientation to self-determination, participation and empowerment. The types of recovery include:

- ***Personal recovery*** which is driven and defined by the consumer; focussing on those areas and issues which are of most value to the individual. This could include a range of issues such as working with voice hearing, expressing oneself through creative means, studying, improving relationships and addressing problematic substance use patterns.
- ***Clinical recovery*** attends to symptoms of 'mental illness' and is more often than not a primary goal of clinicians. We also note that the reduction of distress is high on the agenda for individuals and their supporters and commonly, clinical recovery is a goal.
- ***Social recovery*** focusses on functionality and engagement in activities of daily living and meaningful activity. This is often a focus for practitioners and important to individuals and their families.

Relapse

Relapse is another term subject to contestation. In clinical practice it refers to individuals re-experiencing psychosis or associated symptoms. From a lived experience perspective, relapse may be contested and the construct of 'psychosis' rejected. Instead, the individual may consider they experience mental distress. Secondly, the person may view the re-emergence of distress or 'symptoms' as a rich learning opportunity to build resilience and deeper understanding of triggers.

‘Side effects’ or direct effects?

Whilst the notion of ‘side effects’ is commonly associated with all kinds of medication, we problematise this framing. It is argued that the phrase ‘side effects’ implies that the effects sit to one side and are of less importance to the main effects of the drug. As a consequence of the emergence of the disease-centred model of action the unwanted effects of neuroleptics, such as sedation and movement disorders, were separated, minimised and classified as ‘side effects’, rather than an intrinsic part of the drug’s action or a direct effect (Moncrieff, 2013). This review shows that many of the effects of neuroleptic drugs are serious and have a direct and profound impact on the lives of consumers and their families. For example, effects such as diabetes, cardiovascular disease and often irreversible Parkinson’s type effects are not to the side of people’s lives. For these reasons, we use the term direct effects, rather than ‘side effects’.

Withdrawal or discontinuation?

As with many topics in the psychiatric field, a range of terms are used to describe the experiences and processes associated with ceasing to use neuroleptic drugs. Often, these terms reflect the values orientation of the author. For example, the term discontinuation is more likely to be used by prescribers and practitioners to indicate that an individual has stopped using neuroleptic drugs. In contrast, those who emphasise the adverse and iatrogenic effects of neuroleptic drugs would be more inclined to use the term withdrawal. We use the terms interchangeably in this review to reflect the literature we have examined along with the wide variety of positions in relation to neuroleptic drugs.

The History of Neuroleptic Drugs

This section focusses on the history of neuroleptic drugs and does not discuss earlier treatment responses such as psychotherapies.

The introduction of neuroleptic drugs to psychiatry in the 1950s signalled a significant change in the conceptualisation and response to psychosis. In particular, this reinforced ideas that psychosis and associated diagnoses were symptoms, disorders and diseases of the brain. As a result, neuroleptic drugs were constructed as central to the treatment of psychosis.

Prior to the introduction of neuroleptics, drugs such as opiates, barbiturates and choral were used to contain and control distressing symptoms associated with psychosis (Ban, 2007). Other biological treatment responses which predate neuroleptic drugs reported by Berezin (2013) included insulin shock therapy (1920s to 1950s); frontal lobotomies (1930s to 1960s); and electro convulsive therapy (1930s to current day). Chlorpromazine was synthesised as an antihistamine in Paris in 1952 by Paul Charpentier and was used as an aid to anaesthetic (Ban, 2007; Sin & Roberts, 2006). In 1953, French psychiatrists working with 'psychotic military patients' commenced using the drug with the results leading to the introduction of chlorpromazine around the world. The first written reports of chlorpromazine use in Australia surfaced in 1955 (Ban, 2007).

The early use of neuroleptic drugs did not claim to cure or correct psychosis; rather they were observed to create disinterest, disconnection, disengagement and a "beatific quietude" (Sin & Roberts, 2007, p. 320). Within two years, the direct neurological effects were noted to include "decreased movement, reduced facial expression, loss of initiative, muscular rigidity ... symptoms of Parkinson's disease ... muscular spasms and involuntary movements" (Moncrieff, 2013, p. 33). One British study from 1954 reported that people treated with chlorpromazine were "quieter and more amenable to suggestion by the nursing staff" (Elkes & Elkes, 1954, p. 563, cited in Moncrieff, 2013, p. 33). These descriptions suggest that from a clinical management perspective, neuroleptic drugs assisted staff in managing, containing and responding to distress and psychotic symptoms.

The conceptualisation of neuroleptic drugs as drug centred changed after a large scale North American study conducted in 1964 by the US National Institute for Mental Health (NIMH). The study included three neuroleptic drugs and one placebo, concluding that the neuroleptic drugs improved "excitement, agitation ... anxiety ... incoherence of speech, social withdrawal ... apathy ... auditory hallucinations and persecutory delusions" (Moncrieff, 2013, p. 36). While the adverse effects created by neuroleptic drugs were noted, they were considered irrelevant (Moncrief, 2013). This study captured the attention of psychiatry; yet there appears to have been no critical engagement with the study limitations. As a result, ideas about neuroleptics changed and they were reframed as disease centred drugs which treated and corrected psychosis (Moncrieff, 2013). The capacity of neuroleptic drugs to sedate and manage behaviour was seen as beneficial to the process of deinstitutionalisation in the 1960s, particularly as there was a belief that there would be less risk to community members from people who were medicated for psychosis (Rogers et al., 1998).

While the idea that neuroleptic drugs corrected the symptoms of psychosis gained in popularity, the aetiology or causes of psychosis remain unknown. A number of hypotheses emerged about how neuroleptic drugs worked, including that at least six neurotransmitters were involved and that they blocked dopamine receptors. The excess dopaminergic neural activity was hypothesised to produce hallucinations and delusions (Ban, 2007; Sin & Roberts, 2006). This gave rise to the dopamine hypothesis in the

1970s which continues to dominate causal theories and treatment responses, although many ideas have been advanced involving other neurotransmitters. Many authors have commented on the order and nature of the reasoning underpinning the dopamine hypothesis, including Sin and Roberts, who argue: "The dopamine hypothesis came about in a 'cart before the horse' situation when a drug was found to be efficacious in the management of psychotic symptoms but the action that allowed this was not known" (2006, p. 320).

The basis of this influential set of ideas remains hypothetical to this day, and a range of studies have sought to examine the basis of the hypothesis. The hypothesis has changed over time with Howes and Kapur (2009) arguing that there are at least three versions of the dopamine hypothesis, which have emerged as new technologies increase the capacity to record neurological processes. Version II of the dopamine hypothesis emerged in the early 1990s and focussed on regions of the brain (prefrontal hypodopaminergia and subcortical hyperdopaminergia) to explain variations in dopamine effects. Version III is proposed by the authors based on their "selective" (Howes & Kapur 2009, p. 549) review of research evidence which identified five common streams. The basis for selection of the five streams is not articulated by the authors who also identify they have received funding from pharmaceutical companies. In conclusion, Howes and Kapur argue that as "so much is unknown, it is given that the hypothesis will be revised as more data become available." (2009, p. 556)

In contrast to the hypothetical nature of the aetiology and causes of psychosis, the literature presents a more definitive picture on how neuroleptic drugs work. Neuroleptic drugs block dopamine in the D2 receptor, which in turn, disrupts information flow between neurons. This is said to stop hallucinations and delusions, which are hypothesised to be caused by excessive dopamine (Bennett et al., 2007). It is also reported that D2 blockage causes direct effects such as extra-pyramidal symptoms (EPS) by blocking other receptors and inducing a range of other direct effects (Bennett, 2007).

Critical researchers and commentators argue that the history of neuroleptic drugs as outlined above has provided a form of legitimacy for psychiatry; particularly when these drugs were reframed from being drug centred in managing the symptoms of psychosis to disease centred and thereby correcting psychosis (Moncrieff, 2013).

This is supported in the following quote by a psychiatrist who reflects on the history and legacy of chlorpromazine on the eve of his retirement:

> ***The therapeutic success of CPZ (chlorpromazine) was instrumental in the reintegration of psychiatry with the other medical disciplines. It turned psychiatrists from caregivers to full-fledged physicians who can help their patients and not only listen to their problems.*** *(Ban, 2007, p. 498)*

Summary and Discussion — History

This brief overview of the history of neuroleptic drugs shows that the understanding of the drug's actions have changed over time. Initially, they were found useful for containing and managing distress and psychotic symptoms, and were thus considered to have a drug centred action. Based on one US study which claimed the drugs improved symptoms of psychosis, yet which did not explain how the drugs improved these symptoms, and did not consider adverse effects of the drugs relevant, they were reconfigured to be seen to have a disease centred action and to correct psychosis. This sits alongside the hypothetical nature of what psychosis is (i.e. excessive dopaminergic activity). As noted earlier, as some symptoms were observed to be ameliorated or improved by neuroleptic drugs an assumption developed that psychosis was a result of excess dopamine. This assumption continues to be the basis of most contemporary knowledge and practice responses to psychosis psychiatry. It can be argued that backward reasoning underpins the current day psychiatric practices which are located within a relatively tenuous evidence base.

What is the Efficacy of Neuroleptic Drugs?

The notion of clinical recovery which emphasises symptom management and the movement towards a 'cure' remains the dominant perspective in mental health, and the use of psychotropic drugs is seen as central to this approach (Piat, Sabetti, & Bloom, 2009).

Within the scientific literature, the 'effectiveness' or 'efficacy' of neuroleptics refers to their ability to eliminate or control the 'symptoms' associated with psychosis and schizophrenia, such as delusions and auditory hallucinations. We acknowledge that the goal of eliminating or controlling symptoms is primarily driven by clinicians, and this may or may not be aligned with the preferences of consumers and their families (Hellewell, 2002; Faulkner, 2015). For example, studies have shown that patients and clinicians often differ in their perceptions of the effectiveness of neuroleptics, with clinicians tending to value symptom control, whereas consumers and their families are more inclined to value freedom from the adverse, direct effects of neuroleptics (Day, Kinderman & Bentall, 1998; Hellewell, 2002). The high rates of 'non-compliance' or 'non-adherence' with neuroleptics also suggest that this form of treatment is not acceptable or tolerable for many people with the lived experience of 'symptoms' (Morrison, Meehan & Stomski, 2015; Rogers et al., 1998). Nevertheless, within the literature, the goals of clinical recovery continue to be privileged over personal recovery, and the disabling effects of neuroleptics (described later) are often positioned as preferable to hearing voices or the other 'symptoms' of psychosis (Morrison et al., 2015).

According to the Australian National Health and Medical Research Council (NHMRC) randomised control trials (RCTs) and systematic reviews of RCTs are considered the highest level of evidence (see Appendix 1) for evaluating new interventions, such as neuroleptic drugs (Faulkner, 2015; NHMRC, 2009).

It is interesting to note that the expert views of patients and their families do not feature in the hierarchy of evidence nor do qualitative studies, although there is an acknowledgement from the NHMRC that there are some research questions for which different designs may be more appropriate (NHMRC, 2009). In this section, we draw upon findings from a selection of studies including randomised control trials (RCTs), Cochrane reviews[1], and longitudinal naturalistic studies to examine the evidence for the effectiveness of neuroleptics in the treatment of early episode psychosis and longer-term diagnosis of schizophrenia and psychosis. In randomised, double-blind, placebo-controlled trials, participants are randomly allocated to an intervention group or a control group, where the participant receives a placebo rather than the active intervention or the drug (Jackson, 2006). In these trials, neither the participant nor the clinician know whether the participant is receiving the drug under investigation.

It is important to understand that RCTs are not without their limitations. First, in RCTs participants are typically grouped by diagnosis. What this fails to recognise is that people diagnosed with a particular 'mental disorder' are fundamentally different from each other and there will be individual differences in response to treatment interventions (Slade & Priebe, 2001).

1 Cochrane reviews are systematic assessments of evidence of the effects of health care interventions, intended to support people to make treatment decisions based on the most up-to-date and reliable evidence. Cochrane reviews are internationally recognised as the highest standard in evidence-based health care information (http://www.cochrane.org/what-is-cochrane-evidence).

The consequence of the group-level RCT design is that it creates an evidence base that implies that the diagnostic label 'schizophrenia' is a sufficient characterisation to base treatment decisions and as such almost all people who meet the diagnostic criteria for schizophrenia are prescribed neuroleptics, even though there is evidence to suggest that these drugs are ineffective for some people and cause considerable harm (Leucht et al., 2009; Lieberman et al., 2005; Slade & Priebe, 2001). Second, for the findings of RCTs to have external validity (the ability to be generalised beyond the trial to a wider population of people), the focus of outcome measures must be valued by patients (Faulkner, 2015.) That is, eliminating or reducing the symptoms of psychosis must be a priority of patients or issues will arise when it comes to translating the findings of the research into practice. Faulkner (2015) argues that the outcomes valued by consumers and their families, such as the impact of adverse effects on quality of life, are rarely measured in RCTs of drugs often resulting in patient 'non-compliance'. Finally, we note that the majority of randomised, double-blind, placebo-controlled trials published in prestigious and widely cited psychiatric journals have been funded by various companies from within the pharmaceutical industry (Perlis et al., 2005). Clinical trials with pharmaceutical industry support are nearly five times more likely to report positive findings when compared to those without this conflict of interest (Perlis et al., 2005). This sits alongside the tendency of academic journals to publish studies with significant findings more often than studies with small or negative effects; which is known as publication bias (Song, Hooper, & Loke, 2013). A number of systematic reviews[2] of the efficacy of neuroleptics report compelling evidence of publication bias (for example, Leucht et al., 2009), which is likely to lead to an overestimation of the effectiveness of these drugs (Hutton, Weinmann, Bola, & Read, 2013). These limitations are important to bear in mind when interpreting the results below.

2 A systematic review focusses on quantitative evidence previously reported. It assesses quality using consistent and usually, numeric criteria to present aggregated findings across a number of studies.

Table 1: *The National Health and Medical Research Council (NHMRC) levels of evidence hierarchy.*

Level	Design
I	A systematic review of level II studies
II	A randomised controlled trial
III-I	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: › Non-randomised, experimental trial Cohort study › Case-control study › Interrupted time series with a control group
III-3	A comparative study without concurrent controls: › Historical control study › Two or more single-arm studies › Interrupted time series without a parallel control group

NEUROLEPTICS FOR EARLY EPISODE PSYCHOSIS

Clinical practice guidelines developed by the Royal Australian and New Zealand College of Psychiatrists (RANZCP) recommend treating first episode psychosis with a low dose oral second generation neuroleptic (Galletly et al., 2016), and the majority of international practice guidelines suggest that treatment with neuroleptics be continued for at least a year after the first psychotic episode (Gaebel, Weinmann, Sartorius, Rutz, & McIntyre, 2005). At the heart of this recommendation is the assumption that early treatment with neuroleptics is inherently beneficial. However, a recent review of the impact of psychosocial interventions employed during the acute phase of a first episode psychosis, and where the commencement of neuroleptics was postponed, reported better long-term outcomes (small to medium effect size) when compared to treatment as usual where drugs were initiated immediately (Bola, Lehtinen, Cullberg, & Ciompi, 2009). Common to the five psychosocial treatments reviewed in the study was a focus on creating a safe, low-stress therapeutic environment with clear expectations and dependable relationships where the consumer was encouraged to be an active participant in their own recovery. In these psychosocial interventions, family members and supporters of the patient were seen to play an important role and were expected to be involved in the recovery process. Neuroleptics were postponed for a time limited period usually followed by a low dose as needed. Although this review did include quasi-experimental design studies, the findings demonstrate that early psychosocial treatment without neuroleptics has the potential for both better outcomes and reduced ongoing neuroleptic use (Bola et al., 2009). This sits alongside studies which report that approximately 40% of people with first or second episode psychosis recover without the use of these drugs (Bola & Mosher, 2003; Bola et al., 2006). The uncertainty surrounding the use of neuroleptics in the treatment of early episode psychosis is reflected in a recent Cochrane review which concluded; "Data are too limited to assess the effects of initial antipsychotic medication treatment on outcomes for individuals with an early episode of schizophrenia" (Bola, Kao, Soydan, & Adams, 2011, p. 2).

A recent randomised control trial by Wunderink, Nieboer, Wiersma, Sytema and Nienhuis (2013) has also cast doubt over the benefits of the long-term use of neuroleptics following a first psychotic episode. In this study, patients with first episode psychosis were assigned to one of two strategies; which comprised either maintenance treatment or drug discontinuation in which the drugs were gradually tapered and discontinued if feasible (Wunderink et al., 2007). The discontinuation strategy positioned the patient as a key player in his or her own treatment, and the approach supported patients to make decisions about neuroleptic treatment based on their own preferences (Wunderink et al., 2013). This approach can be likened to shared decision making (Deegan, 2007; Hoffman et al., 2014) which is discussed in greater detail later in this review. In this study, the discontinuation patients experienced more than twice the recovery rate (symptomatic and functional remission) than those patients who were assigned to maintenance treatment, 40.4% versus 17.6% respectively. Further, while the short-term relapse rates showed a significant disadvantage of the discontinuation strategy (Wunderink et al., 2007), in the long-term there were no significant differences in relapse rates between the two groups (Wunderink et al., 2013). Although these findings have yet to be replicated, this study challenges existing practices around the automatic and prolonged prescription of neuroleptic drugs.

Summary and Discussion — Neuroleptics for Early Episode Psychosis

Current guidelines recommend the use of a low dose neuroleptic to be continued for at least one year following the first episode of psychosis, however, there is emerging evidence to suggest that the postponement of treatment with neuroleptics and the tapering/discontinuation of these drugs may be associated with better outcomes. Acute psychosocial interventions have also shown promising results, demonstrating that people can recover after an episode of psychosis without the use of neuroleptics. These findings raise important questions about the evidence base for the current and usual practice of medicating most people with early episode psychosis.

NEUROLEPTICS FOR PEOPLE DIAGNOSED WITH SCHIZOPHRENIA AND PSYCHOSIS

First Generation Neuroleptics

Although second generation neuroleptics are generally preferred, approximately 15% of Australians with schizophrenia and psychosis take older compounds (Galletly et al., 2016; Morgan et al., 2011).
Recent Cochrane reviews of the two most commonly used first generation neuroleptics, chlorpromazine and haloperidol, have reported mixed outcomes (Adams et al., 2013; Adams et al., 2014). In these reviews, there was some evidence to suggest that compared to placebo, chlorpromazine reduced relapse and produced improvements in symptoms and functioning (Adams et al., 2014).
It is important to note, however, that the reviewers assessed the quality of evidence from the 55 studies included to be low, which has implications for how confident we can be with the results of this review.
The authors also concluded that chlorpromazine was clearly sedating, and increased the risk of a variety of often irreversible, debilitating movement disorders (such as tardive dyskinesia) and weight gain.
Similarly, the Cochrane review of haloperidol concluded it is "… a potent antipsychotic drug but has a high propensity to cause adverse effects" (Adams et al., 2013, p. 2). Based on moderate-quality evidence from 25 trials involving 4651 participants, haloperidol was found to be more effective in the treatment of schizophrenia than placebo, with more people allocated haloperidol improving in the first six weeks of treatment compared to those receiving placebo (Adams et al., 2013). Again, the data used in this review is not of the highest quality, which is to say that further research may change the estimate of the effect of haloperidol. Further, a significant number of participants experienced serious and debilitating effects as a direct consequence of taking haloperidol including muscle stiffness, uncontrollable shaking, tremors, sleepiness and restlessness, leading the authors to recommend that haloperidol not be used as the control drug in trials of new neuroleptics (Adams et al., 2013).

Summary and Discussion — Efficacy of First Generation Neuroleptics

Generally, placebo controlled trials of chlorpromazine and haloperidol are of poor quality which makes it difficult to draw firm conclusions about the effectiveness of these drugs in the treatment of schizophrenia and psychosis. While there is some evidence to suggest that these drugs may be better than placebo, this sits alongside severe and debilitating direct effects such as Parkinsonian movement disorders, urinary incontinence, hyper salivation (drooling), and sexual dysfunction.
Overall, much uncertainty remains surrounding the effectiveness of chlorpromazine and haloperidol more than 50 years after their introduction as 'antipsychotics'.

Second Generation Neuroleptics

The vast majority of people diagnosed with schizophrenia and psychosis in Australia are treated with second generation neuroleptics. A recent meta-analysis of 38 randomised control trials with 7323 participants comparing second generation neuroleptics with placebo reported that these drugs were significantly more efficacious than placebo in the treatment of overall symptoms, and this effect was considered moderate in size (Leucht et al., 2009). In this study, 41% of participants taking second generation neuroleptics were found to achieve a clinical response compared to 24% placebo, suggesting that just 17% of people benefit from these drugs in the short- to medium-term.

A meta-analysis of previous studies by Leucht et al. (2009) also examined the clinically meaningful difference between second generation neuroleptics and placebo. That is, what changes in symptom scores are needed to be considered clinically important? One of the primary outcomes of interest in the meta-analysis was the change in the Positive and Negative Syndrome Scale (PANSS) total score and from baseline to endpoint.
The PANSS is a 30-item questionnaire that measures symptoms such as voices and delusions (positive symptoms), as well as blunted affect and social withdrawal (negative symptoms). A 15 points reduction of the PANSS total score is classified as a minimal improvement in symptoms according to clinical judgement (Leucht et al., 2006). In this study, improvement on the PANSS was 10 points; meaning it failed to meet the threshold for minimal clinical improvement. These results led the authors to conclude that second generation neuroleptics were "no wonder drugs" (Leucht et al., 2009, p. 440) in terms of efficacy. Other studies have similarly reported improvements of limited clinical relevance (Khin, Chen, Yang, Yang & Laughren, 2012; Lepping, Sambhi, Whittington, Lane & Poole, 2011).

When comparing second generation neuroleptics olanzapine has been found to be more efficacious than aripiprazole, quetiapine, risperidone, and ziprasidone, and its efficacy was similar to that of amisulpride and clozapine (Leucht et al., 2009). It is important to note that the magnitude of the efficacy differences were small to medium, and most of the differences between the drugs were due to their effect on positive symptoms, rather than negative symptoms which remained less responsive to neuroleptics. These drugs also have their own unique adverse effect profile, which must be considered when interpreting the efficacy of a drug (Leucht et al., 2009).

Clozapine

Clozapine is recommended for those with psychotic symptoms that are often termed 'resistant' to other neuroleptics (Galletly et al., 2016). 'Treatment resistance' is defined as continued positive symptoms after trials of at least two different neuroleptics with different compounds at moderate doses (usually at least 300 mg chlorpromazine equivalents per day) for at least six weeks (Dold & Leucht, 2014; Galletly et al., 2016). It is estimated that approximately 10 to 30% of patients have little or no response to neuroleptic drugs (Hasan et al., 2012). Traditionally, definitions of 'treatment resistant schizophrenia' were centred on a lack of improvement in positive symptoms (Dold & Leucht, 2014). If other domains such as negative symptoms, cognitive impairment, social functioning, and quality of life were incorporated it is likely that prevalence of people deemed to have 'treatment resistant schizophrenia' would be much greater (Dold & Leucht, 2014; Hasan et al., 2012).

A review of 12 RCT studies (including 1916 patients) examining the efficacy of first and second generation neuroleptics, reported that clozapine was the only drug which was significantly more efficacious than older compounds in reducing the overall symptoms in 'treatment-resistant' patients (Chakos, Lieberman, Hoffman, Bradford, & Sheitman, 2001). In a more recent meta-analytic review comprising 212 RCTs and a total of 43 049 people diagnosed with schizophrenia, clozapine emerged as the most effective antipsychotic producing the greatest overall change in symptoms, followed by amisulpride, olanzapine, and risperidone (Leucht et al., 2013). Clozapine is associated with the life-threatening condition agranulocytosis (lowered white blood cell causing increased vulnerability to infection), which effects approximately 1% of people who take the drug (Alvir, Lieberman, Safferman, Schwimmer, & Schaaf, 1993).

For patients on clozapine, weekly blood monitoring for the first 18 weeks, and every four weeks thereafter is mandated (Galletly et al., 2016). Because of the heavy burden of these direct effects, clozapine is reserved specifically for people who have not responded to other treatments (Galletly et al., 2016).

Summary and Discussion — Efficacy of Second Generation Neuroleptics

Overall, studies suggest that in the medium to short term, second generation neuroleptics produce modest gains for some people when compared to placebo, and this improvement is typically limited to a reduction in positive symptoms. While some second generation neuroleptics may be somewhat more efficacious than others, this must be calibrated against their tolerability and unique adverse effect profile. Some patients who do not respond to trials of at least two different neuroleptics are prescribed clozapine, a potent atypical neuroleptic associated with the potentially fatal condition agranulocytosis. It is interesting to note the use of the term 'treatment resistant schizophrenia', as this label situates the problem within the individual, implying that clinicians are dealing with a particularly challenging strain of 'schizophrenia' rather than not having found a treatment that works.

Comparing the Efficacy of First and Second-Generation Neuroleptics

When second generation neuroleptics were introduced in the 1990s, they were touted as being vastly superior to the older, first generation neuroleptics in terms of both efficacy and tolerability (Lieberman & Stroup, 2011; Moncrieff, 2007). The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, initiated by the National Institute of Mental Health (NIMH) compared the effectiveness of different neuroleptics and cast considerable doubt over this clinical impression. CATIE was a long and comprehensive trial, including 1460 participants diagnosed with schizophrenia from across the United States being treated in a variety of settings, including private clinics and public mental health centres. Participants were randomly assigned to receive one of five neuroleptics; olanzapine, risperidone, quetiapine, and ziprasidone (the second generation neuroleptics), and perphenazine (the first-generation neuroleptic) (Lieberman et al., 2005). The most striking result of the CATIE study was that approximately 74 percent of participants discontinued their assigned neuroleptic before 18 months owing to inefficacy or intolerable adverse effects. Perphenazine was found to be equally as effective as the three newer neuroleptics (risperidone, quetiapine, and ziprasidone) and was as well tolerated. Olanzapine performed slightly better than the other drugs, but it had the most adverse metabolic effects, and was associated with the highest discontinuation rate as a result of intolerability (Lieberman et al., 2005; Lieberman & Stroup, 2011). In a commentary, the two lead authors of the CATIE study underscored the limitations of the newer neuroleptics; "CATIE helped to demonstrate that although the introduction of second-generation antipsychotic drugs brought new options for the treatment of psychosis, the major advance many hoped for remain elusive" (Lieberman & Stroup, 2011, p. 774).

Summary and Discussion — Comparing the Efficacy of First and Second Generation Neuroleptics

The impression that second generation neuroleptics are more efficacious and cause fewer direct effects when compared to older compounds has been called into question by CATIE, a large-scale effectiveness study. This study found that there were no robust efficacy differences between first and second generation neuroleptics and no significant differences in terms of overall tolerability. Despite these bleak results, prescribing patterns have not changed markedly as a result of the CATIE study, and the more expensive, second generation neuroleptics continue to the preferred treatment for schizophrenia and psychosis (Galletly et al., 2016; Lieberman & Stroup, 2011).

The Long Term Use of Neuroleptics

Australian clinical practice guidelines state:
"In established illness, it is generally considered advisable to continue maintenance treatment with the prescribed antipsychotic to which the person responded in the acute episode, as long as the efficacy and benefits outweigh the side effects" (Galletly et al., 2016, p. 2016).

Evidence for the long-term use of neuroleptics to prevent relapse, however, is inconclusive. A recent Cochrane review of 65 RCTs (involving 6493 patients) that sought to examine the effects of maintaining people diagnosed with schizophrenia on neuroleptics compared to withdrawing these agents concluded that "… nothing is known about the effects of antipsychotic drugs compared to placebo after three years" (Leucht et al., 2012, p. 27).

A 20-year study, known as the Chicago Follow-Up Study, that charted the progress of 139 patients diagnosed with schizophrenia and other psychotic disorders has cast further doubt over the assumption that long-term treatment with these drugs is inherently beneficial, suggesting that neuroleptic drug maintenance may in fact impede recovery (Harrow & Jobe, 2007; Harrow, Jobe, & Faull, 2014). Harrow and colleagues were interested in what happened to consumers considered to be in the early phase of the diagnosis and after their initial hospitalisation (mean age was 23). This study was not randomised, and no treatment was offered. Consumers were reassessed at five or six subsequent follow-ups over a 20-year period. At the 15 year follow up, Harrow and Jobe (2007) reported that those consumers who had either removed themselves or been removed from neuroleptics showed significantly better global functioning and outcome (including ability to work and quality of relationships) than those still being treated with neuroleptics. It is important to note that the subgroup of consumers who were no longer medicated were different on premorbid factors from those on neuroleptics and were more likely to have a good prognosis (Harrow & Jobe, 2007).

In their most recent report on the 20-year follow up, Harrow et al. (2014) found that when compared to un-medicated consumers diagnosed with schizophrenia, those individuals continuously prescribed neuroleptics showed significantly more psychotic activity, were hospitalised more frequently, were more anxious and had poorer cognitive functioning. Significantly more of these consumers had moderate or severe disruption in their work and social activity when compared to those who were un-medicated. It was also found that after the first few years, neuroleptics did not eliminate or reduce the frequency of psychosis in schizophrenia (Harrow et al., 2014). This brings into question whether these drugs are indeed 'anti' psychotic in their actions (Moncrieff, 2013).

The findings of Harrow and colleagues studies have been largely dismissed by psychiatry some of whom have asserted that because of its naturalistic, non-randomised design, it is not possible to attribute the poor outcomes experienced by the medicated consumers to the effects of neuroleptic drugs. Harrow and Jobe, have not however, claimed a causal relationship, stating:

> ***Overall, the longitudinal studies cited do not provide conclusive proof of a causal relationship between being off medications and being psychosis free. They do clearly indicate that not all schizophrenia patients need continuous antipsychotics for a prolonged period, providing extensive evidence of samples of medication-free schizophrenia patients with favorable outcomes..."*** *(2013, p. 964)*

Those critical of the use of neuroleptics, such as Whitaker (2010), go further and argue that Harrow's findings are clear evidence of the iatrogenic effects of neuroleptics.

Other Studies

World Health Organisation studies (Jablensky et al., 1992; Jablensky & Sartorius, 2008) have compared first episode schizophrenia course and outcomes in developing and developed countries, demonstrating consistent and marked differences. When compared to their counterparts in developed countries, patients in developing countries (such as India and Nigeria) were more likely to be in remission at two years follow up (62.8% compared to 36.9%) and experience significantly longer periods of unimpaired functioning in the community (42.9% compared to 31.6%). The researchers concluded that "being in a developed country was a strong predictor of not attaining a complete remission" (Jablensky et al., 1992, p. 90). Although the researchers cautioned that the superior outcomes for patients in developing countries could not be reduced to a single variable, they did note that only 16% of patients in developing countries were maintained on neuroleptics, compared to 61% of patients in the high-income, developed countries (Jablensky et al., 1992; Jablensky & Sartorius, 2008). It would seem that that the absence of modern psychiatric treatments (neuroleptics), together with collectivist social processes and family structures enable better outcomes for people diagnosed with schizophrenia (Breggin, 2013; Jablensky & Sartorius, 2008).

Summary and Discussion – Long Term Use of Neuroleptic Drugs

People diagnosed with schizophrenia and psychosis are often maintained indefinitely on neuroleptics based on the assumption that it will prevent relapse, however, there is very little systematic evidence attesting to the long-term benefits of these drugs (Harrow & Jobe, 2013; Leucht et al., 2012). A naturalistic longitudinal study demonstrated that individuals who did not take neuroleptics showed greater symptom recovery and better global functioning, highlighting that not all people diagnosed with schizophrenia and psychosis require neuroleptics to live positive, connected and productive lives. Other studies by the World Health Organisation have shown that modern psychiatric treatment in developed industrialised nations produced poorer results in the course and outcome of schizophrenia when compared to developing nations. Taken together these studies suggest that the range of forms of evidence and the emphasis on lifelong use of neuroleptics invite critical consideration of the current paradigm for treating schizophrenia and psychosis.

OVERALL SUMMARY AND DISCUSSION — EFFICACY

Despite the growing body of evidence suggesting that the benefits of neuroleptics have been overestimated, and are not well understood because of the at times, contradictory findings, these drugs continue to be considered the cornerstone of treatment for people diagnosed with schizophrenia and psychosis. Given the inconclusive nature of the evidence, it would seem advisable that clinicians exercise caution when prescribing neuroleptics, especially in the long term (Breggin, 2011). We also note that it is possible to manage and have mastery over the 'symptoms' of psychosis using little or no neuroleptic drugs (Romme, Escher, Dillon, Corstens & Morris, 2009), and which is explored further in the section titled 'Alternative Responses'.

Commonly Used Neuroleptic Drugs

The following list is not a comprehensive description of all neuroleptic drugs used in Australia, rather those most commonly reported as prescribed.

We had initially sought to include the manufacturer's list of the direct effects, but these have proven quite difficult to obtain. Therefore, we have relied on information from the Therapeutic Goods Association (TGA; Commonwealth of Australia).

The description of direct effects is presented on the TGA website according to less serious, more serious and requiring urgent medical attention categories. For the sake of brevity we have presented all information here, regardless of the category.

Active ingredient and name	Direct effects as listed by the TGA	
Zuclopenthixol (Clopixol)	› drowsiness › sleepiness › inability to sleep › abnormal dreams › headache › fatigue › depressed mood › anxiousness › nervousness, agitation › headaches › nasal congestion › dry mouth › constipation or diarrhoea › increased salivation or increased › sweating › nausea, vomiting, dyspepsia › weight and appetite changes › change in your menstrual periods › impaired sexual function › swelling of hands, ankles or feet › skin rash, itching › abnormal sensations, such as burning or prickling › changes in attention and memory	› dizziness or spinning sensation › painful or weak muscles › pain at the injection site › feeling generally unwell › sudden onset of unusual movements, including trembling and shaking of the hands and fingers, twisting movements of the body, or shuffling walk and stiffness of the arms and legs › worm-like movements of the tongue or other uncontrolled movements of the mouth, tongue, cheeks or jaws, which may progress to the arms and legs › inability to keep still › increased, slowed or unusual › muscle movements › feeling dizzy when standing up › irregular heart beat and changes in heart rate and blood pressure › fainting › blurred vision or difficulty focusing › difficulty passing urine › increased urination or other urinary disorder › high pressure in the eye

Continued

Active ingredient and name	Direct effects as listed by the TGA	
Zuclopenthixol (Clopixol) *Continued*	› unusual secretion of breast milk; breast enlargement in men › difficult or painful breathing › frequent infections such as fever, severe chills, sore throat or mouth ulcers › bleeding or bruising more easily than normal, nosebleeds › yellowing of the skin and/or eyes, also called jaundice › severe pain in the stomach with bloating, gut cramps and › vomiting › blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing	› serious allergic reaction (symptoms of an allergic reaction may include swelling of the face, lips, mouth or throat which may cause difficulty in swallowing or breathing, or hives) › sudden increase in body temperature, unusual stiffness of the muscles and changes in consciousness, especially in conjunction with fast heart rate and sweating. This may be due to a very rare condition called neuroleptic malignant syndrome, which has been reported with various neuroleptics
Trifluoperazine (Stelazine)	› drowsiness, fatigue, weakness › dizziness › restlessness › sleeplessness › dullness › headache › blurred vision or difficulty focussing › nausea › constipation › increased or decreased appetite, weight changes › dry mouth › blocked nose › impaired sexual function in men › painful, swollen breasts, or breast enlargement in men	› unusual secretion of breast milk › changes in your menstrual periods › swelling of your hands, feet and ankles › serious allergic reaction (swelling of the face, lips, mouth or throat which may cause difficulty in swallowing or breathing) › sudden onset of uncontrollable muscle spasms affecting the eyes, head, neck and body › sudden onset of pain in the legs, chest pain or difficulty in breathing › uncontrollable twitching or jerking movements of the arms and legs › sudden increase in body temperature, sweating, fast heartbeat, muscle stiffness, difficulty breathing (which may lead to reduced awareness or unconsciousness)

Continued

Active ingredient and name	Direct effects as listed by the TGA	
Risperdone (Risperdal)	› Difficulty thinking or working because of: » sleeplessness » headache » trembling » drowsiness, tiredness, difficulty in concentrating › Behavioural changes such as » agitation » anxiety › Joint or movement changes such as: » muscle stiffness » restlessness in the legs › Other changes such as: » weight gain » indigestion, nausea, abdominal pain, constipation » excessive thirst » frequent urination » blockage in the bowel » unusual secretion of breast milk » breast swelling » missed or irregular menstrual periods » involuntary movements of the tongue, face, mouth, jaws, arms, legs or trunk » heart or blood pressure	› Problems such as: » fall in blood pressure, particularly on standing. This will be apparent to you as light headedness or dizziness that » passes after a few seconds or after sitting down again » faster heart rate, slowed heart rate, heart beat irregularities » fever » abnormally high body temperature » rash, itching or hives on the skin; shortness of breath, wheezing or difficulty breathing; swelling of the face, lips, tongue or other parts of the body. If you have them, you may have had a serious allergic reaction to Risperdal » sudden weakness or numbness of the face, arms, or legs, especially on one side, or instances of slurred speech (these are called mini-strokes)
Quetiapine (Seroquel)	› feeling sleepy › weight gain, increased appetite › feeling weak › dry mouth › runny or stuffy nose (particularly in children) › indigestion, upset stomach, constipation, vomiting (mainly in elderly or children) › swelling of your hands, feet or ankles › blurred vision › abnormal dreams, nightmares › falling, feeling dizzy or faint on standing up	› difficulty in speaking › difficulty swallowing › rapid heart beat › symptoms of high sugar levels in the blood (including passing large amounts of urine, excessive thirst, increase in appetite with a loss of weight, feeling tired, drowsy, weak, depressed, irritable and generally unwell) › breast enlargement, unusual secretion of breast milk › long lasting and painful erection › fainting (particularly in children)

Continued

Active ingredient and name	Direct effects as listed by the TGA	
Quetiapine (Seroquel) *Continued*	› signs of frequent infections such as fever, chills, sore throat or mouth ulcers › bleeding or bruising more easily than normal › very marked drowsiness › reduced consciousness › abnormal muscle movements, including difficulty starting › muscle movements, shaking, restlessness or muscle stiffness without pain › worm-like movements of the tongue or other uncontrolled movements of the tongue, mouth, cheeks or jaw which may progress to the arms and legs	› a sudden increase in body temperature, with sweating, or a fast heart beat › fits (seizures) › severe allergic reaction (may include severe difficulty breathing, shock, swelling of the face, lips, tongue or other parts of the body, skin rash, hayfever, or you may feel faint) › severe upper stomach pain, often with nausea and vomiting (particularly in patients with other risk factors such as gallstones, alcohol consumption and/or increased levels of certain fats within the blood)
Olanzapine (Zyprexa)	› drowsiness › unusual tiredness or weakness › fever › restlessness or difficulty sitting still › increased appetite, weight gain › constipation, bloating › dry mouth › swelling of your hands, feet and ankles › aching joints › nose bleeds › dizziness, confusion, forgetfulness › symptoms of sunburn (such as redness, itching, swelling or blistering of the skin) which occur more quickly than normal › rash or allergic reaction › slow heart beat › changes in sexual functioning or sex drive in men or women › prolonged and/or painful erection › unusual secretion of breast milk › breast enlargement in men or women › symptoms of high sugar levels in the blood (including passing large amounts of urine, excessive thirst, having a dry mouth and skin and weakness). These may indicate the onset or worsening of diabetes reaction following abrupt discontinuation (profuse sweating, nausea or vomiting)	› absence of menstrual periods and changes in the regularity of menstrual periods › involuntary passing of urine or difficulty in initiating urination › unusual hair loss or thinning › sudden signs of an allergic reaction such as a skin rash, itching, shortness of breath or swelling of the face, lips or tongue › frequent infections such as fever, severe chills, sore throat or mouth ulcers › bleeding or bruising more easily than normal › seizures, fits or convulsions › yellowing of the skin and/or eyes › nausea, vomiting, loss of appetite, generally feeling unwell, fever, itching, yellowing of the skin and/or eyes › severe upper stomach pain often with nausea and vomiting (inflammation of the pancreas) › worm-like movements of the tongue, or other uncontrolled movements of the tongue, mouth, › cheeks, or jaw which may progress to the arms and legs › sudden increase in body temperature, sweating, fast heartbeat, muscle stiffness, high blood pressure and convulsions

Continued

Active ingredient and name	Direct effects as listed by the TGA	
Olanzapine (Zyprexa) *Continued*	› sharp chest pain, coughing of blood, or sudden shortness of breath › pain/tenderness in the calf muscle area	› muscle pain, muscle weakness and brown urine › heart palpitations and dizziness, which may lead to collapse
Haloperidol (Haldol and Serance)	› drowsiness or tiredness › restlessness, agitation, anxiety or excitement › confusion › headaches › inability to sleep › muscle weakness › difficulty in speaking and/or swallowing › increased or decreased sweating › dry mouth › indigestion › nausea and/or vomiting › increased appetite › loss of appetite › weight changes › constipation › diarrhoea › increased salivation › blurred vision or difficulty focussing › changes in skin colour (pale skin) › hot, dry skin › swelling of your hands, feet and/or ankles › painful, swollen breasts or breast enlargement in men › unusual secretion of breast milk › changes in your menstrual periods › impaired sexual function in men › loss of blood sugar control, including in diabetes › skin rash › pinkish, itchy swellings on the skin, also called hives or nettle rash › red, itchy spots which may blister or form raised, red, pale-centred marks › extremely high body temperature (fever) › symptoms of sunburn (such as redness, itching, swelling or blistering of the skin) which occur more quickly	› dizziness or spinning sensation (vertigo) › unable to pass urine › fast breathing › fast, pounding or irregular heart beats › signs of frequent infections such as fever, chills, sore throat or mouth ulcers › asthma and other breathing difficulties › bleeding or bruising more easily than normal › tiredness, headaches, being short of breath when exercising, dizziness and looking pale (anaemia) › yellowing of the skin and/or eyes › unusual movements, including trembling and shaking of the hands and fingers, twisting movements of the body, shuffling walk and stiffness of the arms and legs › sudden onset of uncontrollable muscle spasms affecting the eyes, head, neck and body › persistent painful erection (priapism) › seeing, feeling or hearing things that are not there (hallucinations) › worm-like movements of the tongue, or other uncontrolled movements of the tongue, mouth, cheeks, or jaw which may progress to the arms and legs › sudden signs of allergy such as skin rash, itching or hives; swelling of the face, lips, tongue or other parts of the body; shortness of breath, wheezing or difficulty breathing › swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing › severe spasms in the muscles of the shoulders, neck and upper body › convulsions, fits or seizures

Continued

Active ingredient and name	Direct effects as listed by the TGA	
Haloperidol (Haldol and Serance) *Continued*	› sudden increase in body temperature, with sweating, fast heartbeat, muscle stiffness and fluctuating blood pressure which may lead to coma (neuroleptic malignant syndrome)	› collapse
Fluphenazine (Modecate)	› feelings of restlessness › mask-like facial expression › greatly increased saliva › tremors › unusual mental/mood changes (e.g., depression, worsening of psychosis) › confusion › unusual dreams › frequent urination or difficulty urinating	› vision problems › weight change › swelling of the feet/ankles › fainting › skin discolouration › butterfly-shaped facial rash › joint/muscle pain › seizures
Clozapine (Clopine)	› tiredness, drowsiness or fatigue › dizziness, fainting, light-headedness › too much saliva › dry mouth › nasal congestion › weight gain › nausea, vomiting › constipation › diarrhoea › abdominal discomfort, heartburn or dyspepsia › change in the colour of the skin › mild fever › headache › vivid dreams › increased or decreased sweating › blurred vision › difficulty articulating words › sore throat, mouth ulcers, fever, any 'flu-like' symptoms such as swollen glands or other signs of infection › signs of an allergic reaction such as itching, skin rash, hives, swelling of the face, lips or tongue, difficulty in swallowing or breathing › a sudden increase in body temperature, sweating, fast heart beat and muscle stiffness which may be symptoms of neuroleptic malignant syndrome	› fast or irregular heart beat even when you are resting › signs that blood clots may have formed, such as sudden severe headache, sudden loss of coordination, blurred vision, slurred speech, numbness in an arm or leg, chest pain or shortness of breath › uncontrolled movements of the tongue, jaw (such as puffing at the cheeks, chewing movements, puckering of the mouth), face and mouth. These are symptoms of tardive dyskinesia › signs of pneumonia or lower respiratory tract infection such as difficulty breathing, coughing, and chest pain › confusion/disorientation › loss of co-ordination, tremor or rigidity › seizures or fits › jaundice, yellowing of the skin and/or eyes › urinary problems — difficulty passing urine (water) or blood in the urine; loss of bladder control › signs of loss of blood sugar control such as excessive thirst, passing large amounts of urine, dry mouth and skin › persistent painful erection › severe headache › loss of vision

Continued

Active ingredient and name	Direct effects as listed by the TGA	
Clozapine (Clopine) *Continued*	› muscle spasms, stiffness › abdominal or lower back pain › stomach pain accompanied by nausea and vomiting	› slurred speech › unusual bruising or bleeding › chest pain
Chlorpromazine (Largactil)	› dizziness or light headedness › skin problems or discolouration › agitation › drowsiness or tiredness › headache › constipation › nausea › dry mouth › nasal congestion › difficulty in urinating › blurred vision	› impotence › weight gain › sore throat, fever or any sign of infection › breathing difficulty › seizures or fits › unwanted muscle movements of the mouth, tongue, jaw, cheeks or arms and legs › hardness or rigidity of the muscles › fast heartbeat
Amisulpride (Solian)	› drowsiness › weight gain › dizziness › increased appetite › nausea › vomiting › constipation › dry mouth › insomnia › anxiety › agitation › problems with orgasm › sometimes trembling, noticeable muscle stiffness or spasm, slowness of movement, excess saliva, restlessness, an overwhelming urge to move and either distress or movements such as pacing, swinging of the legs while seated, rocking from foot to foot, or both can occur. This will usually be reduced if your dose of Solian is lowered by your doctor or if your doctor prescribes you an additional medicine	› high blood sugar has been reported in patients taking Solian. Symptoms of high sugar levels in the blood include passing more urine than normal, persistent excessive thirst, increased appetite with a loss in weight and weakness › muscle twitching › abnormal movements mainly of the face or tongue › fever › unexplained infections › faster breathing › sweating › muscle stiffness

Neuroleptic Prescribing

The vast majority of people diagnosed with schizophrenia and psychosis in Australia are treated with neuroleptics. In the most recent national survey of psychosis, three quarters of the participants were taking atypical neuroleptics, with 16.4% using clozapine (Waterreus et al., 2012).

The three most commonly prescribed neuroleptics in Australia are quetiapine (Seroquel), olanzapine (Zyprexa) and risperidone (Risperdal) (Department of Health, 2013), reflecting trends in the United States (Alexander, Gallagher, Mascola, Moloney, & Stafford, 2011) and United Kingdom (Ilyas & Moncrieff, 2012; Marston, Nazareth, Petersen, Walters, & Osborn, 2014). Just 15.2% of participant's in an Australian survey of psychosis were taking first generation neuroleptics (Waterreus et al., 2012).

Worldwide, the use of neuroleptic drugs is rising, mainly due to the dramatic increase in the prescription of second generation neuroleptics (Verdoux, Tournier, & Begaud, 2010). In Australia, there was a 217.7% increase in total atypical neuroleptic dispensing between 2000 and 2011, a trend reflected in every drug of its class (Stephenson, Karanges, & McGregor, 2013). Notably, in Australia the prescription of quetiapine (Seroquel) has grown by 82% from 2008 to 2011 (Department of Health, 2013). Similarly, in the United States, treatment visits that resulted in a prescription for second generation neuroleptics increased from one million in 1995 to 13.3 million in 2008 (Alexander et al., 2011). During the same period, the use of first generation neuroleptics either remained stable or decreased slightly (Department of Health, 2013; Ilyas & Moncrieff, 2012; Marston et al., 2014).

This dramatic change in prescribing practices has occurred despite large scale, independent studies failing to demonstrate convincing evidence that second generation neuroleptics were more effective or better tolerated than older compounds (Leucht et al., 2009; Lieberman et al., 2005). Recent studies have also suggested that the use of second generation neuroleptics has grown far beyond substitution for the older neuroleptics (i.e. Alexander et al., 2011; Marston et al., 2014). Second generation neuroleptics are now prescribed outside the approved indications (called off-label prescribing) for a host of conditions other than schizophrenia and psychosis, including dementia, depression, bipolar disorder, anxiety, personality and sleep disorders, attention deficit hyperactivity disorder (ADHD), autism and conduct disorder in children and adolescents (Marston et al., 2004; Stephenson et al., 2013; Verdoux et al., 2010). The widespread use of second generation neuroleptics for scientifically unsupported off-label conditions is worrying given the serious and distinct adverse effects of these drugs (discussed in 'The Direct Adverse Effects of Neuroleptics' section).

Summary and Discussion — Neuroleptic Prescribing

Neuroleptics are considered the mainstay treatment for schizophrenia and psychosis, with four out of every five Australians with this diagnosis prescribed the drugs (Waterreus et al., 2012). A dramatic rise in the use of second generation neuroleptics has occurred in recent years, despite studies suggesting that there are no robustly proven efficacy differences between first and second generation neuroleptics and no significant differences in overall tolerability. Increasingly, second generation neuroleptics are being used outside of approved indications (off-label), meaning that regulatory scrutiny has not occurred and supporting evidence is inconclusive, This is concerning in light of the known adverse effects associated with these drugs[3].

3 We note the 'Recovery Orientated Prescribing and Medicines Management Project' in the UK which developed guidelines on how recovery can be enabled when prescribing and supporting consumers to use medication (Devon Partnership NHS Trust, n.d.). These guidelines are based on the views and experiences of consumers who take medication, their supporters and service providers and offer a number of recommendations to help mental health workers support people to use medication in their recovery. The guidelines can be downloaded for free here: https://recoverydevon.co.uk/resources/

NEUROLEPTIC POLYPHARMACY

Neuroleptic polypharmacy, or the concurrent use of two or more neuroleptics, is a common and widespread practice (Barnes & Paton, 2011; Gallego, Bonetti, Zhang, Kane, & Correll, 2012). Neuroleptic combinations are commonly used to achieve a greater or more rapid therapeutic effect in cases where the response to monotherapy has been poor in targeting specific symptoms (for example, anxiety or insomnia), managing challenging behaviours such as persistent aggression or counteracting the adverse effects of the first neuroleptic (Barnes & Paton, 2011; Stahl, 2004). In addition, not uncommonly, attempts to switch neuroleptics are not completed leaving the consumer on a continuing regime of multiple neuroleptics (Barnes & Paton, 2011; Gallego et al., 2012). Currently, there is no convincing evidence that neuroleptic polypharmacy is more effective than a single neuroleptic for the treatment of schizophrenia or psychosis (Barnes & Paton, 2011), further Stahl writes:

> ***Given the widespread use of an atypical antipsychotic either with a conventional antipsychotic or with an atypical antipsychotic, it is amazing to see how little evidence or rationale there is upon which this practice is based.*** *(2004, p. 114)*

When compared to neuroleptic monotherapy, polypharmacy is associated with increased global adverse effect burden, and Parkinsonian side effects, sedation, cognitive impairment and diabetes associated with high dose prescribing (Barnes & Paton, 2011; Gallego, Nielsen, De Hert, Kane, & Correll, 2012). Given the risks and benefits of combining neuroleptics is equivocal, it is suggested that neuroleptic polypharmacy remain a last resort treatment option after monotherapy, switching and non-neuroleptic combinations have failed (Gallego et al., 2012). In their most recent guidelines for the clinical management of schizophrenia and related disorders, the Royal Australian and New Zealand College of Psychiatrists acknowledge the limited evidence to support the practice of neuroleptic polypharmacy and recommend that in cases where a consumer is receiving two or more neuroleptics the regime be reviewed regularly and simplified if possible (Galletly et al., 2016).

Despite the lack of evidence to support the routine use of combined neuroleptics and high adverse effect burden, polypharmacy is common in clinical practice and the term "dirty little secret" has been used by Stahl in the title of the article he published in (1999) to refer to this phenomenon. In their meta-analytic review of 147 studies on antipsychotic polypharmacy, Gallego et al. (2012) reported a median global prevalence of 19.6% of polypharmacy; although substantial variations existed between and within geographical locations. In Australia, the second national survey of psychosis revealed 63.4% of the 1825 participants were subject to polypharmacy (Waterreus et al., 2012). In Western Australia, John, Gee, Alexander, Ramankutty and Dragovic (2014) conducted a retrospective audit of the medical records of patients who were admitted to the inpatient beds of Bentley Adult Mental Health Service in 2010. They reported that 43.2% of patients were prescribed two or more different neuroleptics at discharge. The prevalence of neuroleptic polypharmacy among this cohort of patients is considerably higher than most other Australasian studies (John et al., 2014).

Summary and Discussion — Neuroleptic Polypharmacy

Neuroleptic polypharmacy is a common, widespread practice, despite there being no convincing evidence to indicate that polypharmacy is more effective than a single neuroleptic. This sits alongside substantial evidence that polypharmacy is associated with increased global direct effect burden. Overall, there appears to be substantial dissonance between everyday clinical practice and the recommendations of practice guidelines.

CONCURRENT PRESCRIBING OF NEUROLEPTICS AND OTHER DRUG INTERACTIONS

Our review of the literature on the interactions of antipsychotic and other drugs indicates that there has been limited research undertaken in this area. The available material is reported at the case or individual level (Schaffer, Yoon, & Zadezensky, 2009); or involves small scale studies with samples as small as 10 participants. Stephen Bleakley, a Registrar at the College of Mental Health Pharmacy in the United Kingdom writes: "Drug interactions are notoriously poorly studied with most only reported in case series or case reports" (2012, p. 20). The information available paints a picture of inconclusive evidence based on a series of hypotheses (reflective of the state of play in many related areas, such as the Dopamine Hypothesis). Consequently, our review is brief and highlights the key issues and areas of concern.

Drug interactions are classified as pharmacodynamic which relate to the effect of the drug on the body; or pharmacokinetic which indicates the effect of the body on the drug such as absorption, elimination, distribution (Kennedy, Jann, & Kutscher, 2013). As demonstrated in the earlier section on polypharmacy, it is not uncommon for a number of neuroleptic drugs to be prescribed simultaneously. Similarly, it is not uncommon for other drugs such as anti-depressants and antiepileptics (or mood stabilisers) to be prescribed simultaneously (Kennedy et al., 2013). In the face of limited evidence on the drug to drug interactions between antipsychotics and those drugs reported to produce adverse interactions such as antidepressants, antiepileptics, antibiotics, anticholinergics, antifungals and nicotine and caffeine, Spina and de Leon (2007, p. 4) argue:

> ***Avoidance of unnecessary polypharmacy, knowledge of the interaction profiles of individual agents, and careful individualization of dosage based on close evaluation of clinical response and, possibly, plasma drug concentrations are essential to prevent and minimize potentially adverse drug interactions in patients receiving new antipsychotics.***

Given this uncertain state of affairs, mental health practitioners require a high level awareness of potential drug interactions and Bleakley (2012, pp. 21–22) proposes three questions to guide mental health practice to minimise the likelihood of unplanned drug interactions:

1. ***Do other drugs change the intended effect or create similar adverse effects?***
   Bleakley argues that practitioners need "an understanding of the different profiles of each antipsychotic" (2012, p. 21); which could include heartbeat irregularities, decreased white blood cell count, increased sedation, constipation, urinary retention, blurred vision, lowered blood pressure, higher risk of seizures, weight gain and metabolic changes.

2. ***Do the different drugs impact on the pharmacokinetic effects of the neuroleptic drugs?***
   This relates to absorption, elimination, metabolism and distribution. For example, fluvoxamine (an antidepressant) significantly increases clozapine and olanzapine levels, creating the conditions for toxicity.

3. ***In what ways does the person's physical health interact with and exacerbate the impact of neuroleptic drugs and create risk to their health?***
   A range of physical health issues may be further compromised, including hepatic (liver) and renal systems, epilepsy and diabetes.

In relation to opioid replacement therapies (and any other central nervous system depressant substances such as alcohol or benzodiazepines), it is expected that increased sedation will occur. There are few reports of adverse drugs reactions between neuroleptic drugs and opioids and opioid replacement therapies such as Methadone and Buprenorphine (McCance-Katz, Sullivan, & Nallani, 2010). There is some evidence that alcohol used with neuroleptic drugs can increase extrapyramidal direct effects and other adverse effects of neuroleptic drugs are potentially exacerbated with alcohol use (Baxter, 2010).

Research on the interactions between tobacco and neuroleptic drugs, shows there are potentially toxic plasma levels of clozapine and olanzapine when smoking is ceased. NSW Health reports that clozapine, olanzapine, fluvoxamine and haloperidol plasma levels are lowered by the tar in cigarettes and when people stop smoking they should be monitored for "sedation, hypersalivation, hypotension, seizures ... other neurological effects, akathisia and prolonged QTc interval[4]" (n.d., p. 1). As the changes in plasma can take between two to four weeks to detect, and cessation of smoking may involve patterns of ceasing and smoking intermittently, plasma levels require careful monitoring (Bleakley, 2012).

Stimulant drugs such as amphetamines and caffeine may also interact with, and oppose, the action of neuroleptic drugs, and while the actual interaction is not known, it is hypothesised that amphetamines "inhibit adrenergic and dopaminergic activity" (Baxter, 2010, p. 222). Between four to five cups of coffee per day have been reported to increase clozapine levels (Bleakley, 2012).

Summary and Discussion — Neuroleptic and Other Drug Interactions

Limited empirical research attention has been paid to the interactions between neuroleptic drugs and other prescribed or illicit substances, with available literature relying on case reports and small studies. Our brief examination of the literature suggests that it is not possible to definitively report on interactions between antipsychotic and other drugs or substances. This is curious given the prevalence of polypharmacy prescribing practices and the high likelihood that consumers may use a range of other substances such as tobacco, alcohol, caffeine and illicit substances. The Australian report "People living with Psychotic Illness" (Morgan, et al, 2011) shows that people diagnosed with psychosis are between five and seven times more likely to use illicit substances and demonstrate higher usage patterns of tobacco and alcohol than the general population.

Case reports in the literature suggest there are a number of drugs such as antidepressants, antiepileptics, antibiotics, anticholinergics, antifungals, nicotine and caffeine which may interact with neuroleptic drugs. However, a robust evidence base which empirically documents the interactions does not exist. This means that people prescribed neuroleptic drugs, their families and mental health practitioners need to maintain an awareness of the potential for adverse drug interactions. In the case of practitioners, the questions proposed by Bleakley (2012) could provide a guide to practice. Similarly, they could be adapted by consumers and their supporters to engage in critical discussions with those who prescribe neuroleptic drugs and other medications so as to promote informed choice in relation to medication usage.

4 QTc interval elongation relates to irregularities in heartbeat

The Direct Adverse Effects of Neuroleptics

The significant and debilitating direct effects of neuroleptics have been known for many years. These effects are highly prevalent and have serious consequences.

First, the direct effects of neuroleptics are distressing, stigmatising and can impair quality of life (Awad & Vorunganti, 2004; Haddad & Sharma, 2007). Second, the adverse effects of neuroleptics can lead to physical morbidity (i.e. diabetes, cardiovascular disease, tardive dyskinesia) and in extreme cases, be fatal (i.e. neuroleptic malignant syndrome, agranulocytosis)[5]. Finally, the burden of these direct effects can lead to 'non-adherence' or 'non-compliance', which is associated with 'relapse' and other significant risks to the individual's health and wellbeing (Chiang, Klainin-Yobas, Ignacio, & Chng, 2011; DiBonaventura, Gabriel, Dupclay, Gupta, & Kim; Haddad & Sharma, 2007). Despite the far reaching consequences of neuroleptic adverse effects on individuals, they are poorly assessed[6] and documented in clinical studies (Longden & Read, 2016). Further, few studies investigate the experience of taking these drugs from the perspective of the individual (Awad & Vorunganti, 2004; Longden & Read, 2016; Moncrieff et al., 2009). In this section we present some of the common direct adverse effects of neuroleptic drugs, incorporating the voice of lived experience wherever possible.

5 These terms are explained in the subsequent text

6 Examples of tools used for measuring the direct effects associated with neuroleptic medication include; the Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS), the Simpson Angus Extrapyramidal Signs Scale (SAS), and the Dosage Record Treatment Emergent Symptom Scale (DOTES)

EXTRAPYRAMIDAL SIDE EFFECTS

> ***I am not able to think properly and am experiencing the world at about half the normal pace … Can't keep my mind focused and my eyes are slow*** *(The subjective experiences of a consumer taking olanzapine, cited by Moncrieff, 2013, p. 119).*

'Extrapyramidal side effects' (EPS) is the term used to describe the Parkinson's like symptoms produced by the degeneration of the dopamine nerve tracks in the extrapyramidal system of the brain (Moncrieff, 2009). EPS are serious direct effects which compromise daily living and can lead to stigmatisation (Divac, Prostran, Jakovcevski, & Cerovac, 2014; Hutton et al., 2013). Common EPS include Parkinsonism, acute dystonia, and akathisia which typically emerge within a few weeks of neuroleptic treatment (Divac et al., 2014; Haddad & Sharma, 2007). Parkinsonism is a neurological disorder resembling Parkinson's disease which includes symptoms such as a tremor, muscle stiffness, slowness of movement, shuffling gait, and drooling. Commonly mistaken for the negative symptoms of schizophrenia, approximately 15% of patients experience drug-induced Parkinsonism after only a few weeks of neuroleptic treatment (Nasrallah & Mulvihill, 2001).

The term 'acute dystonia' is used to describe a variety of conditions characterised by sustained abnormal postures and muscle spasms, especially of the head or neck, effecting approximately 10% of patients usually within the first few hours or days of commencing neuroleptic treatment (Divac et al., 2014; Nasrallah & Mulvihill, 2001; Moncrieff, 2009).

Painful spasms that are disfiguring and disabling, may impair the ability to walk (Breggin & Cohen, 2007). Acute dystonia can occasionally paralyse the neck muscles resulting in choking (Moncrieff, 2009). This can result in people being too frightened to continue treatment with neuroleptics (Bennett et al., 2012).

Among the worst effects of neuroleptics is akathisia or 'restless leg syndrome', a condition characterised by an inner agitation with a compulsion to move that affects approximately 20% of people who take neuroleptics (Adler et al., 1989; Breggin, 2011). Patients experiencing akathisia will move their hands or feet nervously or pace frantically in an effort to relieve the distress (Breggin, 2011). Akathisia is described as being torturous and difficult to articulate, as a patient from a study by van Putten expressed:

> ***My nerves are just jumping; I feel like I'm wired to the ceiling; I just feel impatient and nasty. I can't concentrate; it's like I got ants in my pants; my nerves are raw; I just feel on edge; I feel just nasty; I feel like jumping out of my skin; if this continues, I would rather be dead. I can't describe the feeling; I'm quivery from the waist up; I want to climb the walls; I feel all revved up; it's like I got diaper rash inside*** *(1975, p. 45).*

Akathisia is strongly also associated with depression and dysphoric responses to neuroleptics, and has been linked to decreased compliance, exacerbation of psychosis, violence, and attempted and completed suicide (Adler, Angrist, Reiter, Rotrosen., 1989; Breggin, 2011; Drake & Ehrlich, 1985). Suicide in the context of schizophrenia is described in greater detail later.

TARDIVE DYSKINESIA

Tardive dyskinesia (TD) is a neurological disorder associated with prolonged neuroleptic use and characterised by involuntary, uncontrollable movements that typically effect the muscles of the face, although other muscle groups may be involved (Haddad & Sharma, 2007; Moncrieff, 2009). Hallmark symptoms of TD include grimacing, tongue protrusion, lip puckering, and rapid eye blinking and it can also effect breathing, swallowing and speech (Moncrieff, 2009). Bizarre facial and bodily movements often lead to patients being treated more vigorously with neuroleptics, which ultimately worsens their TD (Breggin, 2008). Like other neurological diseases that cause abnormal movements such as Huntington's disease and Parkinson's disease, TD is associated with generalised cognitive and affective impairment and dementia (Breggin, 2011; Moncrieff, 2013). Structural brain changes caused by neuroleptics are discussed later.

The overall prevalence of TD is high, affecting approximately 20-30% of individuals who have received long-term neuroleptic treatment (American Psychiatric Association, 2000; Llorca, Chereau, Bayle, & Lancon, 2002). The annual risk of TD is 5% for the early years, with cumulative rates over 5 years being between 20 and 26% (Morgenstern & Glazer, 2002). Middle-aged and elderly individuals appear to develop TD more often, with one study reporting a cumulative incidence of TD of 26%, 52%, and 60% after one, two, and three years exposure to neuroleptics respectively (Jeste, Caligiuri, & Paulsen, 1995). In the vast majority of cases, TD is irreversible leaving many disabled:

> ***The widespread use of neuroleptics has unleashed an epidemic of neurological disease on the world. Even if TD were the only irreversible disability produced by these drugs, this would be among the worst medically induced disasters in history*** *(Breggin, 2008, p. 84).*

Neuroleptic-induced EPS and TD are well recognised in the context of older, first-generation neuroleptic drugs, and as discussed previously, second-generation neuroleptics were promoted as being virtually free of EPS. The findings of the CATIE study, however, have cast doubts over this clinical impression concluding that there were no statistically significant differences between rates of dystonia, Parkinsonism, akathisia, and TD when comparing the older compound perphenazine and the newer, second-generation neuroleptics (Nasrallah, 2007). Similarly, the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1) found that the incidence of EPS did not differ between atypical and conventional cohorts during 12 month follow up (Jones et al., 2006). Anticholinergic medication is primarily used to treat or prevent EPS induced by neuroleptics, however this medication can introduce additional, distressing symptoms including blurred vision, constipation, dry mouth, cognitive impairment and delirium (Lieberman, 2004; Ogino, Miyamoto, Miyake, & Yamaguchi, 2014). In some cases, the profound impact on global cognitive functioning has the potential to outweigh the benefits of using this medication, and for these reasons, the prophylactic and long-term use of anticholinergic medication is not recommended (Ogino et al., 2014).

Summary and Discussion — Extrapyramidal 'Side' Effects

This consideration of the range of extrapyramidal direct effects shows that they can manifest in many ways and are not uncommon. These direct effects are often incorrectly assessed as negative symptoms and treated with higher doses of neuroleptic drugs. There is considerable stigma associated with EPS and this is unsurprising when we consider they manifest in tremors, stiffness, pacing, bizarre facial expressions, drooling and shuffling. While second generations are marketed as producing less EPS, studies have shown this is not the case.

METABOLIC AND CARDIOVASCULAR ADVERSE EFFECTS

> ***I've never been able to eat as much as I did when I was on Zyprexa. I gained 40 lbs in no time and my mind was in a constant fog of lethargy and indifference. I didn't care about anything. I just wanted to sit around and eat*** *(The subjective experiences of a consumer taking olanzapine, cited by Moncrieff, 2013, p. 121).*

In the most recent population-based survey of 1825 Australians with psychosis, over 75% of participants were overweight or obese, and the mean amount of weight gained in the six months prior to the survey was nine kilograms (Galletly et al., 2012). Rates of diabetes in people diagnosed with schizophrenia is two to four times that of the general population, and compared to matched controls, the risk for coronary heart disease is 34% higher in men with schizophrenia and 50% higher in women (Goff et al., 2005). When compared to the general population, people with a diagnosis of schizophrenia have, on average, many risk factors which predispose them to developing cardiovascular disease and diabetes, including higher rates of smoking, unhealthy diet, physical inactivity, and poorer primary health care (Daumit et al., 2008; De Hert, Schreurs, Vancampfort, & Van Winkel, 2009; Galletly et al., 2012). Furthermore, it has also been suggested by some that impaired glucose regulation and insulin resistance may be an intrinsic part of the schizophrenia 'disease' (Bushe & Holt, 2004). The notion of a biological vulnerability to diabetes, however, has been refuted by a recent, large study which found that drug-naïve first episode psychosis consumers did not differ from healthy controls in their baseline measures of glucose and lipid metabolites, nor in the prevalence of diabetes or its precursors (Sengupta et al., 2008). Furthermore, Le Noury et al. (2008) reported that of the patients treated in hospital for psychosis between 1875 and 1924 (the pre-neuroleptic era), the incidence of diabetes at admission was zero, and no patients were diagnosed with the condition throughout the 15 years of follow-up. Similarly, none of the 394 consumers hospitalised with psychosis between 1994 and 2006 had Type 2 diabetes at the time of admission, however, after just a few years of treatment, individuals developed diabetes at twice the rate of the general population.

It is well recognised that neuroleptics have the potential to trigger metabolic dysregulation which may predispose people to develop diabetes and cardiovascular diseases, especially in drug-naive, first episode psychosis and paediatric populations (De Hert et al., 2009; De Hert, Detraux, Van Winkel, Yu, & Correll, 2012; Moncrieff, 2013). Although all neuroleptics have the potential to induce weight changes, second generation neuroleptics are more likely than older compounds to carry an increased risk of adverse metabolic effects, with several recent reviews concluding that olanzapine and clozapine are associated with the greatest weight gain and cholesterol and glucose elevation (Lieberman et al., 2005; Rummel-Kluge et al., 2010). The metabolic effects of neuroleptics combined with heavy sedation, feelings of dysphoria, and EPS which serve to limit mobility compound weight gain. Further, certain neuroleptics can cause cardiac arrhythmias (irregular heart beat) which can progress to ventricular fibrillation and sudden death (Haddad & Anderson, 2002). People taking neuroleptics (both first and second generation) are at twice the risk of sudden cardiac death when compared to those not exposed to these drugs (Ray, Chung, Murray, Hall, & Stein, 2009).

The metabolic and cardiovascular effects of neuroleptics have been largely ignored by clinicians. Despite clinical guideline recommendations, there is a low rate of baseline and follow-up assessment of cardiovascular and metabolic abnormalities in patients treated neuroleptic drugs (De Hert, Van Winkel, Silic, Van Eyck, & Peuskens, 2010). This neglect reflects the unwavering assumption that these drugs are necessary in the treatment of schizophrenia and psychosis, and the tendency to focus on the EPS induced by these drugs (Hutton et al., 2013; Longden & Read, 2016).

Summary and Discussion — Metabolic and Cardiovascular Adverse Effects

This exploration of the literature shows that while second generation neuroleptic drugs are more likely to create risk for, and adverse effects related to, metabolic functioning, all drugs impact negatively. Overall, individuals treated with neuroleptic drugs are at higher risk of cardiovascular disease and diabetes. While the evidence for the life-threatening adverse effects of neuroleptic drugs is substantial, there is limited response by psychiatry, other than monitoring and awareness. Given the compelling nature of the evidence, it would seem a rethink of the benefits of the drugs is needed; particularly when their efficacy is contested and uncertain.

HORMONAL EFFECTS AND SEXUAL DYSFUNCTION

> ***I lost my ability to feel emotions, I lost my libido, I lost my drives, I lost my ability to get an erection***
> *(The subjective experiences of a consumer taking risperidone, as cited by Moncrieff, 2013, p. 120).*

Neuroleptics have the propensity to cause high levels of the hormone prolactin (hyperprolactinaemia) by reducing dopamine activity (Haddad & Sharma, 2007; Moncrieff, 2009). Elevated levels of prolactin can stimulate the growth of breast tissue in men, produce changes to the menstrual cycle (irregular menses or absent menses), and can cause an excessive growth of hair, acne, lactation, infertility, and the bone-wasting condition osteoporosis (Haddad & Sharma, 2007; Moncrieff, 2009). Hyperprolactinaemia is an important underlying cause of decreased libido, impaired arousal, and impaired orgasm in men and women receiving neuroleptics (Culter, 2003). Sedation, weight gain, and decreased mobility associated with EPS also contribute to sexual dysfunction (Cutler, 2003; Haddad & Sharma, 2007; Moncrieff, 2009). Sexual dysfunction is very common affecting between 30-80% of patients on neuroleptics (Baggaley, 2008). A meta-analysis by Serretti and Chiesa (2011) reported that quetiapine, ziprasidone, perphenazine, and aripiprazole were associated with lower rates of sexual dysfunction (16–27%), compared to olanzapine, risperidone, haloperidol, clozapine, and thioridazine which were associated with much higher rates (40-60%). Other studies, however, have shown that differences among antipsychotics regarding the occurrence of sexual dysfunction are less marked (Üçok, İncesu, Aker, & Erkoç, 2007).

Sexual dysfunction has been described as the unspoken side effect of neuroleptics (Peuskens, Sienaert, & De Hert, 1998). Most clinical trials do not systematically assess sexual functioning, and instead rely on consumers to spontaneously report sexual side effects (Kelly & Conley, 2004). This approach is likely to lead to an underestimation of actual occurrences. The lack of recognition is also due to clinicians not routinely enquiring and consumers not feeling comfortable raising the issue (Cutler, 2003; Peuskens et al., 1998).

The impact of sexual dysfunction on the lives of those taking neuroleptics is not fully appreciated by some clinicians who may view sexual problems as relatively minor or unimportant when addressing symptoms associated with schizophrenia and psychosis (Cutler, 2003). This is in contrast to the experiences of people diagnosed with schizophrenia. For example, in a study of 213 people, sexual dysfunction was rated the most severe direct effect of neuroleptics (Lambert et al., 2004). Sexual dysfunction has implications for self-esteem and intimate relationships (McCann & Clark, 2004).

Summary and Discussion — Hormonal Effects and Sexual Dysfunction

The reviewed studies highlight that sexual dysfunction is a common experience for people taking neuroleptic drugs. Despite this, it does not appear to be a routine component of clinical intervention or support. While some studies suggest this may be due to clinicians not placing the same amount of emphasis on loss of libido and associated issues, we suggest it may also be that clinicians feel uncomfortable in this area of practice. Given that sexuality is a core component of identity and expression, the lack of response from most clinicians is problematic and concerning.

ANTICHOLINERGIC EFFECTS

The anticholinergic effects of neuroleptics are distressing and include dry mouth, blurred vision, constipation, urinary retention, increased heartrate, excessive salivation, cognitive impairment and delirium (Lieberman, 2004; Ogino et al., 2014). Despite being a very common adverse effect of neuroleptics, many studies do not report data on anticholinergic effects and those that do tend to be limited to short-term studies of less than 12 weeks (Ozbilen & Adams, 2009; Ozbilen & Rattehall, 2012). Further, the concurrent use of anticholinergic medication to offset EPS induced by neuroleptics makes it difficult to determine the prevalence of neuroleptic anticholinergic effects (Ozbilen & Adams, 2009; Ozbilen & Rattehall, 2012). Clozapine and olanzapine are considered highly anticholinergic agents, but two recent reviews of oral and long-acting depot neuroleptics, concluded that anticholinergic symptoms are associated with the use of all neuroleptics, and the newer, second generation neuroleptics are not clearly distinguishable from older, inexpensive compounds (Ozbilen & Adams, 2009; Ozbilen & Rattehall, 2012).

Generally, clinicians do not consider anticholinergic effects to be as problematic or significant as other adverse effects induced by neuroleptics, such as EPS, but studies have shown that consumers do not necessarily agree (Day et al., 1998; Fakhoury, Wright, & Wallace, 2001; Longden & Read, 2016). Dry mouth (or xerostomia) is a common anticholinergic effect, and when combined with inadequate oral hygiene, poor nutrition, substance use, and the metabolic disturbances induced by neuroleptics it is a major risk factor in the development of oral health problems, such as dental caries, gum disease and tooth loss (Kisely, 2016; Pelletier, Deni, & Lesage, 2017). Poor oral health is associated with many chronic diseases (such as cancer and cardiovascular disease) and can also affect eating, speech and self-esteem (Kisely, 2016; Pelletier et al., 2017). Left untreated, some anticholinergic symptoms can cause serious and potentially lethal medical complications, particularly in older people (Lieberman, 2004; Ozbilen & Adams, 2009). For example, the mortality rate on clozapine due to constipation is three times higher than that for agranulocytosis (De Hert et al., 2011). The early detection and management of anticholinergic effects is crucial (De Hert et al., 2011; Lieberman, 2004).

Summary and Discussion — Anticholinergic Effects

The anticholinergic effects of neuroleptics are common and can have serious consequences if left untreated, yet in research and in clinical practice they remain a neglected area. Recent research has revealed that there are no major differences between first and second generation neuroleptics in relation to anticholinergic effects. As with many areas related to the overall topic, lived experience accounts are few and far between. Therefore, an in depth understanding of the impact of anticholinergic effects is not well established.

COGNITIVE ADVERSE EFFECTS

> ***I was sleeping over 14 hours a night and was so hung over during the day I could hardly go about my normal routines, I couldn't even get myself dressed to go out to the store*** *(The subjective experiences of a consumer using taking olanzapine, as cited by Moncrieff, 2013, p. 119).*

Sedation resulting from neuroleptic drugs tends to be dose related and is most pronounced in the first generation drugs haloperidol and chlorpromazine and the newer compounds clozapine, olanzapine and quetiapine (Haddad & Sharma, 2007). Sedation is consistently identified as one of the most prevalent and severe direct effects of neuroleptics (Chiang et al., 2011; Day et al. 1998; Fakhoury et al., 2001). A participant in a study by Rogers et al. (1998) explains: "Well you just sort of, you're walking around like a zombie and you're like sort of you can't join in with things, I wouldn't be talking to you like what I'm talking now …" (p. 1318).

The cognitive effects of neuroleptics can make working, studying and social interactions challenging and present a barrier to achieving a good life (personal recovery). Studies have shown that professionals tend to minimise or ignore the profound cognitive impacts of neuroleptics, and do not fully appreciate the significance of tiredness and sedation on people's lives (Seale, Chaplin, Lelliott, & Quirk, 2007). A qualitative study of the lived experience of young adults with schizophrenia by McCann and Clark found that sedation was interpreted differently by clinicians and those on neuroleptics as captured in this participant quote: "They all thought that it was doing me good, but that was because I was asleep nearly 18 hours a day" (2004, p.792). In their analysis of 92 outpatient consultations where neuroleptics were reviewed, Seale et al. (2007) reported that consumers tended to initiate discussion of sedation and mental clouding much more often than doctors who preferred to discuss blood monitoring. When consumers raised concerns about the sedative effects of their medication, they were often dismissed by their psychiatrist who either offered no response, went on to change the subject, or disagreed with their interpretation of their experience.

Summary and Discussion — Cognitive Adverse Effects

Sedation is identified by consumers as a major problematic direct effect of neuroleptic drugs. Studies have shown that this concern is not shared by professionals and when individuals raise the issue, it is often dismissed. Such a response does not reflect a stance which values lived experience and appears to prioritise clinical goals over the goals of personal recovery. Similarly, this response fails to meet current policy directives which state that consumers and their families are to be meaningfully involved in treatment assessments, plans and decisions.

STRUCTURAL BRAIN CHANGES

> ***No emotions, only a weird, spacey, empty feeling, no arousal, no excitement, no joy, nothing***
> *(The subjective experiences of a consumer taking risperidone, as cited by Moncrieff, 2013, p. 119).*

Most CT and MRI studies suggest that people diagnosed with long-term schizophrenia have smaller brains and larger brain cavities or ventricles when compared to healthy controls (Moncrieff, 2013; Moncrieff & Leo, 2010). The structural differences observed in the brains of people diagnosed with schizophrenia were originally thought to be related to the underlying 'disease' process, particularly the damaging effects of untreated psychosis on the brain (Moncrieff, 2013). This led to early intervention with neuroleptics to 'protect' the brain from the harmful effects of psychosis. However, the iatrogenic effects of neuroleptics on the brain are now beginning to be recognised. A longitudinal study of 211 people diagnosed with schizophrenia involving 674 MRI scans revealed a strong and statistically significant association between the dose of neuroleptic that a consumer received over their lifetime and the amount of brain volume loss detected (Ho, Andreasen, Ziebell, Pierson, & Magnotta, 2011). People in this study had received minimal neuroleptic treatment at the time of their first MRI scan and were followed for approximately seven years. Treatment with neuroleptics was found to have a significant influence on brain volumes even after accounting for potential confounds, such as illness and symptom severity and alcohol and illicit substance use, leading the authors to conclude that:

> ***Antipsychotics were designed for the purpose indicated by their name, i.e., to arrest psychosis. Not only is it probable that antipsychotics do not treat the fundamental pathophysiologic mechanism of schizophrenia (i.e., the brain disease), but we perhaps must also entertain the possibility that they might have potentially undesirable effects of brain tissue volume reductions*** *(Ho et al., 2011, p. 135).*

Brain volume changes are associated with poorer executive functioning, greater negative and positive symptoms (Gur et al., 1998; Ho et al., 2003; Ho et al., 2011). Indeed, some argue that neuroleptics may be responsible for some of the changes that are usually attributed to schizophrenia (Moncrieff & Leo, 2009). Given the evidence that the effects of neuroleptics on brain structure are dose dependent, it is proposed that prescribing the lowest possible effective dose is essential (Weinmann & Aderhold, 2010).

Summary and Discussion — Structural Brain Changes

As with other areas reported in this review, a new evidence base is emerging which challenges previous findings and ideas about the impact of neuroleptic drugs on the brain. This evidence is pointing to a negative link between neuroleptic drugs and brain volume changes. These changes impact individuals in a range of ways and is dose dependent; suggesting the need for a cautious approach to be employed in prescribing practices until further research is undertaken.

NEUROLEPTIC MALIGNANT SYNDROME

Neuroleptic malignant syndrome (NMS) is a potentially life-threatening complication of neuroleptic treatment that is estimated to affect between .02 and 3.23% of people receiving inpatient services (Lazarus, Mann, & Caroff, 1989). All neuroleptics are capable of inducing NMS, including the newer compounds, and risk factors for the development of the syndrome include dehydration, high doses of neuroleptics, rapid rate of neuroleptic loading, switching or discontinuing neuroleptics, a previous history of NMS, and organic brain syndrome or brain injury (Mann, Caroff, Keck, & Lazarus, 2003; Pelonero, Levenson & Pandurangi, 1998). The clinical features of NMS are fever, severe muscle rigidity, tremor, autonomic dysfunction (i.e. high blood pressure, postural hypotension, rapid heart rate), altered mental status (i.e. confusion, delirium), and elevated serum creatine kinase and white blood cell count (Pelonero et al., 1998; Robertson, 2012). NMS has the potential to be fatal if misdiagnosed, and a significant number of patients experience persistent, long-term consequences of NMS including contractures, deep vein thrombosis, pulmonary embolism, renal failure, and brain damage as a result of prolonged fever (Pelonero et al., 1998; Robertson, 2012). Breggin draws parallels between NMS and an acute, severe episode of encephalitis concluding that:

> ***The rates for NMS, as well as its potential severity and lethality, make it an extreme risk for patients receiving antipsychotic drugs. A risk of this size would probably result in most drugs in general medicine being removed from the market*** *(2008, p. 76).*

Summary and Discussion — Neuroleptic Malignant Syndrome

While the available evidence on NMS suggests it is not a common occurrence, its potentially fatal impacts are of serious concern. Given studies have shown that the monitoring of adverse effects by clinicians is variable and sometimes non-existent, the potential for NMS is of concern.

MORTALITY

The rate of mortality, as defined by the number of deaths in a given population, is the most robust outcome measure of disease, and is considered the gold standard indicator of clinical performance (Brown, Kim, Mitchell, & Inskip, 2010). People diagnosed with schizophrenia have a mortality rate between two and three times that of the general population (Brown et al., 2010; Saha, Chant, & McGrath, 2007), which equates to a loss of approximately 15 to 20 years of life expectancy (Wahlbeck, Westman, Nordentoft, Gissler, & Laursen, 2011). This exceeds the difference in life expectancy between the Aboriginal and Torres Strait Islander population and the non-Indigenous population, which is approximately 10 years (Australian Institute of Health and Welfare, 2014). This mortality gap has widened over time indicating that people diagnosed with schizophrenia have not fully benefited from the improvements in health outcomes available to the general population (Brown et al., 2010; Laursen, Munk-Olsen, & Vestergaard, 2012; Saha et al., 2007).

Mounting evidence suggests that physical diseases, particularly circulatory and respiratory diseases, make the most significant contribution to the shortened lifespan seen in people diagnosed with schizophrenia (Brown et al., 2010; Laursen, 2011). Reasons for excess early mortality due to physical diseases include unhealthy lifestyle factors (smoking, poor diet, lack of exercise), poor access to good-quality physical health care, and the direct effects of neuroleptic treatment (Laursen et al., 2012; Lawrence, Holman & Jablensky, 2001; Weinmann & Aderhold, 2010). As previously discussed throughout this review, neuroleptics are known to cause many adverse effects, including weight gain, diabetes, and cardiac arrhythmias. The role of these adverse effects in the shortened lifespan of people diagnosed with schizophrenia is gaining recognition, but more rigorously designed, prospective studies are needed to draw firm conclusions (Weinmann, Read, & Aderhold, 2009).

Suicide has consistently been identified as an important contributor to the excess mortality observed in people diagnosed with schizophrenia (Laursen et al., 2012; Saha et al., 2007). Using two databases of admissions; one historical (1875–1924) and the other contemporary (1994–2010), Healy et al. (2012) examined the outcome data for people diagnosed with schizophrenia and other non-affective psychoses. In this analysis, suicide emerged as the most common cause of death in schizophrenia in the contemporary period, suggesting that there is something unique about the modern delivery of care that contributes to suicide in this population (Healy et al., 2012). Healy et al. (2012) propose that one contributing factor may be neuroleptic treatment, and suggest that the high rate of suicide observed in the first year of treatment is consistent with an initial exposure of vulnerable individuals to the dysphoric effects of neuroleptics and severe akathisia (as previously described). Despite suicide rates in schizophrenia being substantially higher than they were before these drugs were introduced, many clinicians believe that schizophrenia causes suicide.

Calls have been made for an increased focus on the physical health of people diagnosed with schizophrenia and psychosis, and the development of specifically targeted programs to address modifiable risk factors that contribute to excess mortality (Laursen, 2011; Lawrence et al., 2001). This includes measures that target suicide. A more proactive and integrated approach to health care is needed for this population to ensure physical diseases and conditions are diagnosed early, treated and managed sufficiently (Laursen et al., 2012; Lawrence et al., 2001).

Summary and Discussion — Mortality

The lives of people with diagnosed with schizophrenia and psychosis are approximately 15 to 20 years shorter than that of the general population, and this mortality gap has widened over time. Natural causes of death, particularly circulatory diseases, account for the largest portion of excess mortality. Unhealthy lifestyle factors, neuroleptic treatment, and the late diagnosis and insufficient treatment of physical diseases have been identified as reasons for excess early mortality. The risk of suicide in people diagnosed with schizophrenia and psychosis is high, with some arguing that the dysphoric nature of neuroleptics contributes to this risk. Regardless, the rate of mortality for people with diagnosed with schizophrenia and psychosis is unacceptably high and requires urgent attention.

OVERALL SUMMARY AND DISCUSSION — ADVERSE EFFECTS OF NEUROLEPTIC DRUGS

This overview highlights that the direct effects of neuroleptics have a significant and profound impact on the lives of those who take these drugs. It is important to note that often the adverse effects of neuroleptics are considered in isolation (as we have presented them in this review), when in reality, consumers may experience several adverse effects at any one time. In their qualitative study that explored Australian consumers' experiences of neuroleptics, Morrison et al. (2015) reported that on average, each consumer experienced six to seven direct effects. The cumulative effect of many adverse effects can have a profound impact on consumers' quality of life and ability to cope, as one consumer in this study explained: "I can handle the illness, but I don't know if I can handle this medication" (p. 4).

Perhaps what is most striking about the literature exploring the adverse effects of neuroleptics is that the voices of those directly impacted, the consumers who take these drugs and their loved ones who support them, were missing. Overwhelmingly, research articles were authored by psychiatrists, clinical psychologists, mental health nurses, and others who offered a clinical perspective about how consumers experience the 'side effects' of neuroleptics, with little or no examination of their power and positioning. The privileging of clinician perspectives is reflected in the paternalistic notions of 'compliance' and 'adherence', where the decision not to take medication is often viewed as a symptom of 'illness' and non-existent insight (Hamilton & Roper, 2006; Rogers et al., 1998). The few studies that examine the nuances and intricacies of taking neuroleptics beyond the adherent/non-adherent binary highlight that the use of medication is a dynamic behaviour influenced by the complex interaction of many factors.

Consumers' attempts to balance the risks and benefits of neuroleptics can often leaving them feel as though they are in a no-win situation. A woman who had taken haloperidol for psychotic symptoms described the suppression of interest caused by the drug, referring to what she saw as the benefits of this state, as well as a sense of loss:

> ***Although I felt very well, I felt as if I had absolutely nothing to talk about. I kept wondering about whatever [it] was that had been so interesting during most of my life that I had suddenly lost… But I was very much in contact with reality and for that I was thankful*** *(cited in Moncrieff, 2013, p. 118).*

Murphy et al. (2015) used the analogy of a double edged sword to capture consumers' experiences; on the one hand, these drugs had the potential to reduce or level out distressing symptoms, but on the other hand, they introduced a range of adverse effects that impacted on their overall health and wellbeing. For many consumers the source of the distress, whether it be the symptoms of the 'illness' or the adverse effects of the drug, are irrelevant; the main concern is to maximise wellbeing, and wellbeing is personally defined (Carrick, Mitchell, Powell, & Lloyd, 2004). The heavy burden of the direct effects of neuroleptics lead many consumers to opt not to take these drugs.

Withdrawal and Discontinuation

The following discussion on withdrawal and discontinuation of neuroleptic drugs sits within the context of significant uncertainty about the universal efficacy of neuroleptic drugs (British Psychological Society, n.d.).

While a systematic review of the literature on withdrawal and discontinuation was not undertaken, an extensive set of searches were completed in an attempt to locate relevant information. Our searching resonates with arguments put forward by other authors in that limited evidence exists on withdrawal or discontinuation rates for neuroleptic drugs (Le Geyt et al, 2016). Of the available studies, it is suggested that at least 50% of people attempt discontinuation once, but more often than not, multiple times, and around 80% do not take the drugs in the prescribed manner (Gibson et al., 2013; Larsen-Barr, 2016). Of the small number of studies which focus on consumer lived experiences, it is reported that between 22 and 56% remain neuroleptic free (Larsen-Barr, 2016: Salomon & Hamilton, 2013). The research evidence is dominated by the views and ideas of researchers and clinicians, meaning that the voice of lived experience is relatively invisible. Larsen-Barr chose to address this in her PhD thesis and argues: "Within the research literature, the discourse about AMs (neuroleptic drugs) has largely involved clinicians and researchers, with few opportunities for people using these medications to contribute to the conversation" (2016, p. 9).

CLINICAL VIEWS

The clinically informed literature argues that individuals choose to discontinue neuroleptic drugs for a range of reasons, including:

- A desire for improved wellbeing, which neuroleptic drugs are assisting with.
- Intolerable direct effects.
- Consumers assess the diagnosis to be incorrect and invalid.
- There has been no further evidence of psychosis.
- People find new ways to manage mental distress.
- A desire to experience emotions and avoid emotional numbness (which is associated with neuroleptic drug use).
- Reduced energy.
- Specific life experiences like pregnancy or breastfeeding.

(Livingston, 2012; Mind, 2016)

Traditionally, the decision to discontinue neuroleptic drugs has been framed by the psychiatric professions as reflective of a lack of insight and self-evident confirmation and proof of 'mental illness' (British Psychological Society, n.d.). As noted in the glossary, while the construct of insight is commonly applied in psychiatry, it is contested on numerous fronts. Authors in this field suggest that decisions about discontinuation should be weighed up with an assessment of benefits and advantages undertaken in a collaborative manner between the consumer and practitioners.

It is also argued that withdrawal requires careful monitoring by clinicians (Taylor, Paton, & Kapur, 2009) and means that "the clinician and the patient have to choose between two unwelcome risks: relapse and adverse effects of continued treatment" (Gilbert, Harris, McAdams & Jeste, 1995, p. 184). Despite this, some researchers suggest that "a physician may be held liable either for withdrawing neuroleptic therapy or 'precipitating' a relapse or for maintaining neuroleptic therapy and 'predisposing' to TD" (Gilbert et al., 1995, p. 186).

The limited research into, and reporting on withdrawal, tapering and discontinuation has been noted for close to 40 years with Gardos et al., reporting in 1978 that "the effects of withdrawal of neuroleptic drugs have not been adequately studied" (p. 1321). Of the very few systematic reviews or narrative analyses on the topic, one argues:

> ***Unfortunately there is no clear guidance in the available literature about what type of patients can be withdrawn from neuroleptic drug therapy and for how long, as well as the optimal way of stopping drug therapy. To our knowledge, there has been no recent, comprehensive review of this important but controversial topic*** *(Gilbert et al., 1995, p. 184).*

Furthermore, psychiatrist Martin Livingston claimed in 2012 that "there is no evidence based guidance" (p. 38) for the discontinuation of neuroleptic drugs. In the section titled 'Alternative Responses' later in this review, we consider how consumers and their supporters have responded to this gap in the research and knowledge.

When it comes to discontinuing neuroleptic drugs, the consensus is that gradual withdrawal minimises direct effects and the emergence of rebound psychosis; which is discussed later in this section (Breggin, 2013; Gardos et al., 1978; Howland, 2010; Taylor et al., 2009). This hypothesis rests on the idea that pharmacodynamic adaptation occurs over a longer period of time and gradual withdrawal reduces the impact and severity of physiological and psychological withdrawal symptoms (Breggin, 2013; Howland, 2010; Moncrieff, 2006). The direct effects which result from neuroleptic discontinuation are many and varied and often mirror symptoms associated with psychosis. Common withdrawal responses reported to affect between 17 and 75% of people in the first two weeks include "nausea, vomiting, diarrhoea, perspiration, restlessness, insomnia, rhinorrhoea, headaches, increased appetite, and giddiness" (Gardos et al., 1978, p. 1321). Other withdrawal responses which may occur in the short, medium and longer term include extra pyramidal syndrome, dystonia, akathisia, tardive dyskinesia, anxiety, tremors, restlessness, headaches, heart palpitations, and neuroleptic malignant syndrome (Breggin 2013; Howland, 2010).

RAPID ONSET PSYCHOSIS

A wide range of terms are used in addition to rapid onset psychosis and these include; rebound psychosis, supersensitivity psychosis, dopamine supersensitivity psychosis, covert psychosis, tardive psychosis, iatrogenic supersensitivity psychosis, breakthrough dopamine supersensitivity psychosis, withdrawal psychosis and psychotic relapse. The term rapid onset psychosis will be used in this discussion as the lack of evidence and consensus on the cause and trajectory of the phenomenon is inconclusive and mostly hypothetical. Moncrieff (2006) further points out that as the evidence for the hypothesised dopamine supersensitivity psychosis is inconclusive, a neutral term like rapid onset psychosis is more fitting.

As with the terminology, the definition of rapid onset psychosis is contested and varied. For example, it is variously hypothesised as occurring in response to a discontinuation of neuroleptic drugs (Chouinard, Jones & Annable, 1980; Suzuki et al, 2014). Yet, it is also suggested by the same authors that it occurs when 'treatment resistant' individuals who have not responded to polypharmacy prescribing practices and higher doses of neuroleptic drugs go on to experience worsening or new episodes of psychosis (Chouinard et al., 1980; Suzuki et al, 2014). Regardless of the various hypotheses about rapid onset psychosis, it is argued that dopamine receptors are 'supersensitive' after being blocked by neuroleptic drugs and consequently the brain responds with "imbalances in dopamine-cholinergic counter-regulatory systems" (Howland, 2010, p. 13). These arguments are based on small studies (for example the supersensitivity psychosis concept was published by Chouinard et al., in 1980 based on case reports of 10 people and studies on rats). So, while it is not uncommon for people to experience what looks like psychotic symptoms when they discontinue neuroleptic drugs, the reason why is not based in empirical evidence and is subject to hypothetical reasoning. Additionally, insufficient research has been undertaken to identify if significant differences exist between withdrawal responses to first generation and second generation drugs (Howland, 2013).

Despite the lack of empirical and conclusive evidence related to withdrawal responses, it is common to assume that an emergent psychosis relates to the 'underlying illness' as suggested by Moncrieff:

> ***Clinical practice is still dominated by the assumption that adverse effects following drug discontinuation are attributable to the re-emergence of the underlying illness. However, the consequences of withdrawing psychiatric drugs are complex and may relate either to the underlying illness, to the process of drug withdrawal itself, or to psychological or contextual factors.*** *(2006, p. 4)*

Without comprehensive psychosocial and medical histories and careful monitoring, it is difficult to differentiate between 'psychiatric symptoms' and those associated with withdrawal (Suzuki et al, 2014). The limited research on withdrawal and discontinuation tends to have significant limitations such as small and heterogeneous sample sizes (such as Chouinard et al., 1980, mentioned above); the concept of relapse not being consistently defined across studies, non-differentiation between psychotic and emotional responses, samples which include neuroleptic drug naïve participants and people withdrawn from the drugs before the study commenced (Larsen-Barr, 2016; Moncrieff, 2006).

CONSUMER VIEWS

As noted earlier, the lived experience of consumers who discontinue neuroleptic drugs is missing from the literature and "less research has been undertaken into people's first-hand experiences of antipsychotic discontinuation" (Salomon & Hamilton, 2013, p. 160). However, a small number of studies have focussed their attention in this area and show that reasons for withdrawing include:

- Neuroleptic drugs were perceived as unhelpful and counter to ideas about wellbeing
- A desire to recover without drugs
- Direct effects; and concerns about dependency (Gibson et al, 2013; Larsen-Barr, 2016).

Additionally, Larsen-Barr (2016) found that many people reported preparing for discontinuation by undertaking independent research on withdrawal responses, seeking the support of family and friends and planning for adverse reactions.

A qualitative study involving 12 people found that consumers had a "personal theory" (Le Geyt et al., 2016, p. 5), based on information provided by psychiatric staff as well as through their own research on the discontinuation process. Participants reported that they were given little information about neuroleptic drugs at the time of prescribing and when information was provided it focussed on benefits, rather than risks or direct effects. This raises questions about informed consent for people prescribed neuroleptic drugs if partial information is provided. Similarly, reflections about power relations between prescribers and consumers are brought to the fore in this discussion (Larsen-Barr, 2016). In developing their personal theory on discontinuation, participants undertook cost-benefit analyses of risks and advantages and then considered these in light of their values and life goals. The following quote highlights how the development of knowledge is contextual and emergent:

> ***Receiving professional explanations of psychosis and treatment gave many participants a way to make sense of their experiences, which fitted with cultural expectations of illness and cure and was both normalizing and validating. As such, early theories of acceptability and need were often shaped by professional theories, consistent with biomedical models of mental illness and high in favour of taking neuroleptics*** *(Le Geyt et al., 2016, pp. 7-8).*

The studies which centre consumer experience highlight the caution and reluctance people have in relation to discussions with psychiatric staff about neuroleptic drug discontinuation. Reasons given for not discussing the topic include experiencing professionals as reluctant to support consumers in this regard; the threat of involuntary treatment; being dismissed as lacking insight; not being taken seriously; and being perceived as 'non-compliant' (Gibson et al, 2013; Larsen-Barr, 2016; Le Geyt, et al., 2016; Salomon & Hamilton, 2013). Consequently it is noted that:

> ***A number of people described deliberately withholding information about their attempt (to discontinue) from prescribers and family members due to fear of discouragement, being seen as 'non-compliant and/or being placed on a compulsory treatment order as a result*** *(Larsen-Barr, 2016, p. 97).*

Another study reported similar findings, identifying that "power imbalances (and) ... feeling controlled, dismissed and disempowered were prevalent" (Le Geyt et al., 2016, p. 8). This speaks of the relationship with clinical staff being significant in the experience of discontinuing neuroleptic drugs; particularly in light of:

> ***Some of the more serious risks described by respondents such as rehospitalization, attempted suicide, and incarceration, may have been mitigated if communication channels between people in recovery and clinicians were more open during this time period*** *(Salomon & Hamilton, 2013, p. 163).*

SUPPORTING WITHDRAWAL AND DISCONTINUATION

The absence of clinical guidelines for withdrawal and discontinuation are counter to contemporary health paradigms which promote person-centred practices, informed choice and shared decision making (Le Geyt et al., 2016). Further, it is argued that rather than the clinical preoccupation with compliance or adherence (which the National Institute of Care Excellence guidelines advise against in the UK when working with people diagnosed with schizophrenia and bi-polar affective disorder); an exploratory, collaborative, person first and respectful approach needs to be taken to understand what recovery means for the individual as well as the intention underpinning the wish to discontinue neuroleptic drugs (Breggin, 2013; Gibson et al, 2013). Similarly, it is argued that "many discontinuation attempts, historically interpreted by clinicians as reflecting a lack in insight, may be understood and anticipated if the person in recovery is asked about their perspective on psychotropic treatment" (Salomon & Hamilton, 2013, p. 163).

In response to the dearth of clinical guidelines, written information and support from clinical staff on discontinuation of neuroleptic drugs, consumers and their allies have produced material on withdrawal, and these are discussed under the section 'Alternative responses'. To avoid "distressing and dangerous withdrawal reactions" (Breggin, 2013, p. xxiii) it is proposed that discontinuation is framed within a harm reduction framework (Hall, 2013; Salomon & Hamilton, 2013) and this is discussed further in the "Alternative responses" section which follows. Of relevance here is that harm reduction promotes person-centred responses, puts the service user in the driving seat, is non-judgemental and respects the individual's right to choose to continue or cease using neuroleptic drugs. Will Hall proposes that when balanced information is provided to people about the risks and benefits of neuroleptic drugs, informed choice is possible, yet this sits in contrast to the current common state of denial of a "basic medical right" (2012, p. 5) to be provided with full information in an impartial manner.

When people do withdraw from neuroleptic drugs, they can "expect a roller-coaster ride of emotions that require considerable support" (Breggin, 2013, p. 124) and while many people may be unable to secure this support from clinicians, family or friends, it does appear to make the journey of discontinuation much easier (Larsen-Barr, 2016; Le Geyt et al., 2016).

Other elements which can improve the discontinuation process include:

- Monitoring and responding to withdrawal responses
- Believing in the self
- Quality sleep and nutrition
- Developing other strategies like exercise, meditation and mindfulness
- Preparing for the first attempt to be unsuccessful
- Framing the challenges as part of the recovery journey

(Hall 2012; Larsen-Barr 2016; Le Geyt et al, 2016; Mind, 2016)

Summary and Discussion — Withdrawal and Discontinuation

While at least 50% of consumers attempt to discontinue neuroleptic drugs and 80% do not use them in the prescribed manner, very little guidance or information is available to consumers, families or clinicians on the topic. This is despite withdrawal and discontinuation inducing a wide range of direct effects, some of which present significant risks to the individual's health and wellbeing. With a lack of guidelines and information on the subject, it is fair to assume that few (if any) clinicians have been trained in conversations about discontinuing neuroleptic drugs. This situation alone is worthy of critical reflection on why clinical guidance is absent and that consumers have responded by developing guidelines (covered under 'Harm Reduction Approach' in the next section).

While this area is not heavily researched, most of the work undertaken is from a clinical perspective and the representation of consumer experiences is minimal. Discussions about discontinuation between clinicians and consumers are usually problematic; particularly if practitioners frame a consumer's request to reduce or discontinue neuroleptic drugs as 'a lack of insight into the illness' and 'evidence of the illness'. This stance is problematic from a consumer and family perspective as it denies the unique meanings made by the individual around their lived experience of mental distress or psychosis. As with concepts like the dopamine hypothesis, ideas about why people appear to develop psychosis after discontinuing neuroleptic drugs are also hypothetical and not grounded in robust, empirical evidence. In conclusion, this is an area requiring urgent clinical and policy attention.

Alternative Responses

In this section we provide overview information on five approaches which offer an alternative to neuroleptic drugs. Most of the approaches would provide support and services to individuals with or without medication, and they are not anti-medication in their stance. Rather, they seek to expand understanding and responsiveness to individuals who experience mental distress.

THE SOTERIA APPROACH

Soteria, from Greek meaning deliverance or salvation.

Developed by psychiatrist Loren Mosher and colleagues, the Soteria approach is a residential alternative to hospitalisation for people with early episode psychosis that involves the delivery of an intensive, interpersonal intervention by non-professional staff, typically without the use of neuroleptics, in a safe and supportive home-like environment (Mosher, 1999; Mosher, Menn & Matthew, 1975). The original Soteria-California project (1971-1976), was an experimental study whereby two matched cohorts of patients newly diagnosed with schizophrenia received either treatment as usual at an in-patient community mental health centre with neuroleptics, or an interpersonally focused intervention at Soteria House generally without neuroleptic drugs. In instances where drugs were used it was done so from a position of choice and without coercion (Mosher et al., 1975). There were no scheduled therapy sessions at Soteria house, instead the role of staff was to existentially be with residents and stand by attentively, without being intrusive, as residents navigated their way through altered states of consciousness (Mosher, 1999). The experiences of residents were unconditionally accepted as understandable given the historical context of each person's life.

Mosher and Bola (2004) noted that it was crucial that the power and autonomy of residents be preserved, and as such, there was minimal hierarchy and role differentiation between residents and staff. Residents graduated from Soteria once there was informal group consensus that they had got themselves "together" (Mosher et al., 1975, p. 459), and they were encouraged to maintain their relationships with staff and other residents after leaving the house (Mosher & Bola, 2004).

At the end of the original two year study, Soteria residents had lower psychopathology scores, greater global adjustment scores and fewer hospital readmissions when compared to those participants who received conventional treatment in a hospital setting, despite only 24% of Soteria residents receiving any drugs in the first six weeks of treatment, compared to 100% of participants in the treatment as usual group (Mosher et al., 1975). These compelling results prompted the establishment of a replication facility (Emanon) and other residential alternatives based on the minimal medication Soteria approach (Mosher, 1999). Calton, Ferriter, Huband and Spandler (2008) conducted a systematic review to evaluate the efficacy of the approach and concluded that Soteria was at least as effective as conventional hospital-based treatment, with this being achieved without a reliance on neuroleptics as the primary intervention.

Mosher and Bola (2004) pointed to similarities in the supportive and collectivist social processes in Soteria and developing countries, where more favourable course and outcomes for patients with first episode schizophrenia have been reported in the context of minimal neuroleptic use (Jablensky et al., 1992).

Summary and Discussion — The Soteria Approach

The Soteria approach is a residential alternative to hospitalisation for people with psychosis that involves the delivery of an intensive, interpersonal intervention in a safe and supportive home-like environment. Central to this approach is the view that psychosis is a temporary experience and recovery not only possible but probable and to be expected. Soteria enacted cautious use of neuroleptics, and research has shown that this approach is at least as effective as conventional hospital-based treatment for psychosis.

THE OPEN DIALOGUE APPROACH

Developed in Finnish Western Lapland in the 1980s, Open Dialogue is a network based, language approach to treatment for people experiencing psychosis. Central to the Open Dialogue approach is the establishment of a consistent treatment team and the creation of a joint space where the consumer, their family and other key members of the social network can engage in respectful, deliberative dialogue throughout the treatment process. The main forum for the dialogue is team meetings where the network collectively works together to gather information and explore different perspectives about the crisis at hand, develop a treatment plan, make decisions about ongoing therapy, hospitalisation and medication, and generate a new dialogue for the problem.
The core principles of the Open Dialogue approach are listed below:

1. ***Immediate help.***
   The professional team arrange the first meeting within 24 hours of the first contact by the consumer, their family, or a referring agency. A 24-hour crisis service is also set-up.

2. ***Social network perspective.***
   The consumer, key members of their social network (including family, friends, neighbours and work colleagues), and key workers from other agencies are always invited to the first meeting with the aim of mobilising support for the consumer and their family.

3. ***Flexibility and mobility.***
   The treatment response is adapted to suit the specific and changing needs of each consumer and their family. Often meetings are held at the consumer's home.

4. ***Responsibility and Psychological Continuity.***
   The practitioner who was first contacted by the consumer and/or their family is responsible for organising the first meeting. A consistent treatment team is established which takes responsibility for the entire treatment sequence (irrespective of how long that may be), in both inpatient and community settings.

5. ***Tolerance of uncertainty.***
   It is acknowledged that there are many unknowns and that a rapid solution to the problem is unlikely, therefore, the focus is on creating safe and trusting relationships needed for the joint recovery process. Daily meetings are held during the period of initial crisis, and to avoid premature conclusions and hasty treatment decisions, no detailed therapeutic contract is made during this phase. Seikkula et al. (2001a) recommend that the use of neuroleptics should be discussed in at least three team meetings before being implemented.

6. ***Dialogism.***
   The primary focus is to create a joint space for respectful, deliberate dialogue where new language can be generated and a new understanding among the different participants can emerge. All issues are openly acknowledged and discussed. (Seikkula, Alakara, & Aaltonen, 2001a; 2001b)

Open Dialogue is vastly different to traditional psychiatric practices in many ways, but most notably the symptoms of psychosis are not immediately suppressed using neuroleptics when the consumer first presents in crisis. Instead, psychosis is conceptualised as an important and meaningful experience, often reflective of severely frayed social relationships or traumatic experiences, and attempts are made to understand the experience and generate a new narrative which enables healing to occur (Seikkula et al., 2001a). The use of neuroleptics is delayed with the hope that with support and therapeutic dialogue, consumers can come to make sense of their experience and get through their first crisis without ever needing to use these drugs. In Open Dialogue, the decision to use neuroleptics is case-specific, and all conversations, (personal and professional) involve the consumer and their network. Benzodiazepines may be selectively used in the beginning to help with sleep and anxiety, and eventually a low-dose neuroleptic may be prescribed; yet there is always a plan to taper from these drugs (Whitaker, 2010). This approach is very different to traditional practices which maintain consumers on neuroleptics indefinitely following their first episode of psychosis.

By considering the experience of psychosis from a psychological and systems viewpoint, the treatment team is more oriented toward the changing needs of the consumer and their network and can respond flexibly (Whitaker, 2010). Viewing psychosis in this way rather than as a fixed, clinical reality also creates the space for hope, as Birgitta Alakare, one of the founders of Open Dialogue explains: "The message we give is that we can manage this crisis. We have experience that people can get better, and we have trust in this kind of possibility" (as cited by Whitaker, 2010, p. 342). The possibility of Open Dialogue has been bolstered by research suggesting that this approach may be significantly superior to normal treatment of acute psychosis (Seikkula et al., 2006). After five years, 82% of patients treated with Open Dialogue therapy had no remaining psychotic symptoms and 76% had returned to their work or studies with just 14% living on the disability allowance (Seikkula et al., 2006). Two thirds of the patients in this study had never taken neuroleptics and at follow-up 17% of the patents in the Open Dialogue group used these drugs regularly. In Australia almost all patients with a diagnosis of schizophrenia or psychosis receive neuroleptics, and as highlighted previously, few could expect to be symptom free and living active lives in the community after five years.

Summary and Discussion — The Open Dialogue Approach

Open Dialogue brings together the person experiencing psychosis with their network of friends, family and support people to engage in a therapeutic dialogue with the aim of creating a shared understanding of the problem, through a shared language. The use of neuroleptics is case-specific, and if it is used there is a protocol for tapering off these drugs. Research exploring the effectiveness of Open Dialogue suggests promising outcomes for consumers, without or with the limited use of neuroleptics.

HEARING VOICES APPROACH

Psychiatrist, Professor Marius Romme and journalist, Dr Sandra Escher, are credited with developing what is now known as the hearing voices approach (Parker, Georgaca, Harper, McLaughlin and Stowell-Smith, 1995). In particular, Romme noticed that some patients, and one in particular, Patsy Hage, continued to hear voices, despite taking neuroleptic drugs (Romme & Escher, 2000). This led to Romme's appearance on a television program in 1987 with Patsy Hage where voice hearing was discussed and people with these experiences were invited to contact the television station. The response to the program was much greater than expected with Romme and Escher reporting: "It was quite shocking at first to meet ordinary healthy people who were telling us that they could hear voices ... it questioned our assumption that auditory hallucinations were a symptom of a psychiatric disorder" (2000, p. 18).

As a result, Romme and Escher undertook research with 18 people diagnosed with schizophrenia, 15 diagnosed with dissociative disorders, and 15 who heard voices and had no involvement with mental health services. The research used a tool now known as the Maastricht Interview which was developed by Romme and Escher. This tool comprehensively investigates the construct (or psychological formulation) of who and what the voices represent. The research found that while participants reported both positive and negative voices, those who had not been involved in services were more likely to hear positive voices. The majority of people involved in mental health services reported a fearful relationship with their voices which contrasted the experience of those who did not receive services and who had less fear of their voices. In relation to being able to control voices, those not involved in services were more likely to report they could manage the voices. Regardless of involvement in mental health services, 70% of people reported at least one traumatic life event. This led to a hypothesis that a relationship existed between voice hearing and trauma; and consequently a critical questioning of bio-medical explanations of voice hearing. Romme and Esher's work was furthered in 2013 by Eleanor Longden (a psychologist and voice hearer with a PhD) and Dirk Corstens (psychiatrist and PhD candidate) who examined the voice constructs of 100 people, again using the Maastricht Interview. They found that the majority of people heard between two and five voices, 89% of people reported adverse experiences from childhood, and 94% of the sample could link their voices with difficult emotions (Corstens & Longden, 2013).

These findings gave rise to a range of ways of responding to voices. Romme and Escher (2000) suggest that education and awareness raising on voices, their function and who/what they represent (via the Maastricht Interview process and tool) can provide significant benefit. They also propose that there may be a place for neuroleptics to reduce the intensity of the emotional reactions to the voices. However, they also say "hearing voices in itself, is no reason to take medication" (Romme & Escher, 2000, p. 62). Some who have lived experience of voices would argue that a "clear head" (Longden, 2010, p. 257), free of neuroleptic drugs, is needed to begin to make sense of the voices. Furthermore, Romme and Escher (2000) suggest that peer and self-help support may be of substantial benefit as "people's own input is the most powerful tool for change, and ... self-help is an important means of giving clients practice in developing a new relationship to their voices and to their problems" (2000, p. 115). Further, Romme, Hage and Escher's work paved the way for the development of the Hearing Voices Network (Parker, Georgaca, Harper, McLaughlin and Stowell-Smith, 1995).

The Hearing Voices Network approach frames voice hearing as "significant, decipherable and intimately connected to a person's life story" (Dillon & Hornstein, 2013, p. 289). Across the world, hearing voices peer support groups can be found and these groups privilege the unique lived experience of voice hearers, adopting a stance which accepts voices as a common part of human existence. Such groups can be found in community, inpatient and more recently, correctional settings (Dillon & Hornstein, 2013). In this approach, voice hearing experiences are accepted, welcomed and explored. This is counter to traditional psychiatric system responses, where the bio-medical framework of understanding dominates and utilises labels such as psychosis and schizophrenia to explain voice hearing.

Hearing voices approaches aim to centre the voice hearer and their unique experiences, meanings and attachments and respond in partnership orientated and respectful ways. Some authors critique the bio-medical approach, practices and discourses:

> ***Mainstream biomedical psychiatry's account of auditory verbal hallucinations we regard as phenomenologically impoverished, actively disempowering, over-invested in unsupportable distinctions between "normal" and "pathological" voices and ill-equipped to investigate or make sense of what is now known about the link between voice-hearing and people's life experiences*** *(Woods, Romme, McCarthy-Jones, Escher & Dillon, 2013, p. 213)*

Furthermore, some argue that the hearing voices approach requires "a radical revision of psychiatric theory and practice" (Parker et al., 1995, p. 126).

It is argued that hearing voices peer support groups have "profound effects" on participants, yet "these effects cannot easily be quantified or studied with traditional research paradigms", as each group has a unique structure and approach (Dillon & Hornstein, 2013, p. 286). However, central to each group is the acceptance of diverse experiences of voices, visions and other perceptual phenomenon. Importantly:

> ***"People are free to share and explore their experiences in detail, including the content of what their voices say, without the threat of censorship, loss of liberty or forced medication"*** *(Dillon & Hornstein, 2013, p. 289).*

While the groups emphasise peer support, non-voice hearers who subscribe to this framework of understanding are welcomed and invited to partner with consumers. Typically, group members are invited to share their voice hearing experiences and other group members commonly enquire about the nature, content, impact, and form of the voices, triggers and changes to the voices over time (Dillon & Hornstein, 2013). This approach creates the conditions for voice hearers to understand factors, events and people which may trigger voices, along with developing deeper understanding and appreciation for the role, purpose and function of the voices in their life. Consequently, many people report a changed relationship and set of responses to their voices, including greater capacity to cope.

While similar explorations could occur in a counselling or therapeutic context, Dillon and Hornstein (2013) argue that hearing voices groups reflect different power relations, and individual voice hearers are less likely to be concerned about the potential for abuse of trust which could occur in a one to one relationship, such as in counselling. Another impact of hearing voices groups is the potential to renegotiate and expand identities beyond illness (Dillon & Hornstein, 2013).

As noted earlier, undertaking evaluation and comparative research on hearing voices groups is difficult, given the unique structure and approach taken in each group. However, some Australian researchers have undertaken research with a small number (n=29) of hearing voices group participants. Overall, the research found that the experience is positive, and participants reported that they felt better understood and less isolated, and that they had increased understanding of voices and more hope (Beavan, de Jager, & dos Santos, 2016).

Summary and Discussion — Hearing Voices Approach

The Hearing Voices approach positions voices and visions as meaningful experiences which are commonly a manifestation of trauma or distressing experiences. In this, the approach offers a distinct alternative to the dominant bio-medically informed understanding of voices and visions, as products of brain or genetic dysfunction. While the evidence base on the effectiveness of these approaches is limited, it would appear from small-scale research projects that participants report a positive experiences. Given that many consumers and their families report that traditional and dominant psychiatric treatment responses are unhelpful, approaches like Hearing Voices may offer a real alternative.

HARM REDUCTION APPROACH

Consumers, advocates and allies have responded to the dearth of clinical guidelines, written information and support from clinical staff on discontinuation of antipsychotic drugs by producing freely available material on withdrawal. In particular, a harm reduction approach has been applied to discontinuation of neuroleptic drugs, taking into account the adverse effects reported associated with withdrawal. This approach promotes person-centred responses, puts the service user in the driving seat, is non-judgemental and respects the individual's right to choose to cease using neuroleptic drugs. Harm reduction frameworks originate from the drug and alcohol field and can be applied across a range of areas. It has two key principles (Marsh & Dale, 2006):

1. People have the right to enact self-determination
2. Services and professional staff have a responsibility to ensure that consumers have access to information on harm reduction principles and methods

In order to promote self-determination, practitioners need to reflexively suspend judgements about the consumer's choices. This means exploring and unpacking ideas, intentions and aspirations for recovery — from both the consumer and their supporters (Le Geyt et al., 2016). Additionally, harm reduction lends itself to peer and reciprocal support frameworks (Hall, 2012).

Will Hall has developed a body of work on harm reduction when discontinuing psychiatric drugs. Hall argues that when minimal or no information is provided to consumers and families there is a denial of a "basic medical right" (2012, p. 5). He also asserts that informed choice is underpinned by the provision of balanced information which considers both risks and benefits. Specifically, Hall argues: "The decision to take psychiatric drugs should be based on the usefulness of the drug's effects relative to the risks involved, not any false belief that the person 'must' be on the drug because of biology or genes" (2012, p. 16). Hall's work, published by The Icarus Project and The Freedom Centre, does not provide medical advice and was developed in collaboration with 61 advisors who represent consumer, medical, psychological and academic interests. The "Harm Reduction Guide to Coming off Psychiatric Drugs" (2012) situates itself between pro-medication and anti-medication stances; arguing that individuals can make good decisions about psychiatric medications when provided with sufficient information from a range of viewpoints.

Harm reduction approaches take into account the range of risks and benefits associated with neuroleptic drug use, and seek to balance risks and lifestyle choices while promoting improvements in wellbeing. Specifically, a harm reduction approach acknowledges:

> ***People are already taking psychiatric drugs, already trying to come off them, and already living with symptoms — and that in this complicated reality people need true help, not judgement. It encourages balancing the different risks involved: the harm from extreme states, as well as the harm from treatments such as adverse drug effects, disempowering labels, and traumatic hospitalization*** *(Hall, 2012, p. 7).*

In relation to the processes and steps involved in a harm reduction approach to discontinuing psychiatric drugs, Hall (2012, pp. 35-36) suggests that consumers and their supporters consider the following (many of which are also suggested by authors such as Breggin, 2013; British Psychological Society, n.d.; Gardos et al., 1978; Livingston, 2012; Mind, 2016; Taylor et al., , 2009):

- Taper and slowly reduce the dosage
- Reduce one drug at a time if more than one is prescribed
- Withdraw from anti-Parkinson's drugs last
- Plan how the tapering will occur and review it regularly
- Consider the length of time on the drug and the safest way to withdraw
- Carefully monitor all direct effects of withdrawing, noting that some can be especially serious, such as neuroleptic malignant syndrome
- Consider using a compound pharmacy if tapering requires "small or irregular doses" (2012, p. 36)
- Be aware that non-psychiatric medical drugs may interact with the withdrawal process
- Pay particular attention to benzodiazepine withdrawal as abrupt discontinuation is a risk to health
- If the withdrawal process creates the conditions for crisis, see this as learning; rather than failure
- Keep in mind that it may not be possible to completely withdraw, but reduction may be a better outcome.

In addition to these suggestions the guide offers a range of other information on keeping well and preparing for challenges during the withdrawal process. The resource can be found at: **google.com.au/search?q=harm+reduction+guide+to+coming+off+psychiatric+drugs&ie=utf-8&oe=utf-8&client=firefox-b-ab&gfe_rd=cr&ei=OzuIWPXrMoyEogP-8LTIDg**

Summary and Discussion — Harm Reduction Approach

The principles for, and practice of, harm reduction are well established in the alcohol and other drugs field. While no evidence of the effectiveness of this approach is available in the mental health field, it would appear to provide a useful framework for guiding people when discontinuing neuroleptic drugs. This is particularly important in light of the absence of either clinical guidelines or information for consumers and their families when it comes to withdrawal and discontinuation of neuroleptic drugs. As has been discussed in other areas of this review, at least 50% of consumers will attempt to withdraw from neuroleptic drugs and the emphasis of reducing harm and promoting in depth knowledge of the drugs as found in harm reduction approaches could be of significant benefit to individuals and their families.

SHARED DECISION MAKING

The use of neuroleptics is complex, dynamic and involves consumers carefully attempting to balance the costs and benefits of treatment. Shared decision making is a person-centred, recovery-oriented alternative to traditional notions of compliance that recognise that an individual's personal attitudes, preferences, explanatory models and cultural context influence their medication choices (Deegan, 2007; Deegan & Drake, 2007; Roe & Swarbrick, 2007). Shared decision making involves the redistribution of power and is founded on the premise that there are two experts in the consultation room; the consumer and the clinician. The consumer has lived experience expertise of psychosis and an intimate knowledge of what gives their life meaning and purpose. Medication is seen as just one tool among many that people may use in their recovery and it is recognised that consumers often have a whole host of self-care strategies and activities that they use to enhance their overall sense of wellbeing (also known as personal medicine). The clinician, on the other hand, has technical knowledge about 'schizophrenia' and 'psychosis' and its clinical treatment. Shared decision making involves these two forms of expertise coming together and emphasises an explicit negotiation and discussion concerning options and preferences to arrive at a mutually acceptable plan for moving forward in the treatment process (Charles, Gafni, & Whelan, 1997; Deegan & Drake, 2006). The principles underpinning shared decision making proposed by Deegan (2007) are outlined below:

1. The goal of using psychiatric medication is personal recovery. 'Maintenance in the community' is not an acceptable outcome.
2. Psychiatric medicine must support personal medicine, or the things that give one's life purpose and meaning.
3. The purpose of the treatment team is to support consumers through decisional conflict when it arises to ensure the optimal use of both personal medicine and psychiatric medicine in the recovery process.

The practice of shared decision making is uncommon in psychiatric settings despite healthcare reform aligning policies with the principle of person-centred care and mental health consumers expressing a strong desire to actively participate in the health care decisions that impact them (Chan & Mak, 2012; Goossensen, Zijlstra, & Koopmanschap, 2007). Shared decision making is often viewed as unfeasible for patients diagnosed with schizophrenia and psychosis due to poor 'insight' or reduced decisional capacity, however, studies have shown that with the right support shared decision making is possible (Chan & Mak, 2012; Hamann et al., 2006). Of the handful of studies that have explored shared decision making practice in mental health settings, this approach was found to be associated with many positive outcomes including greater knowledge about schizophrenia and its treatment, more favourable attitudes towards medication, and an increased sense of control and involvement in decision making process (Hamann et al., 2006; Hamann et al., 2011; Malm, Ivarsson, Allebeck, & Falloon, 2003).

Currently, there are a number of programs and projects underway to promote shared decision making in mental health. One such project, led by Pat Deegan involves the use of CommonGround, a software program that helps consumers to identify their preferences, personal medicine and treatment goals and effectively communicate these to clinicians (Deegan, 2010). Consumers access the software in peer-run decision support centres with the assistance of certified peer support specialists who provide technical and emotional support. The CommonGround software converts consumer responses into a one page health report that can then be used in their appointment to ensure that their questions, concerns and goals are addressed. More information about this project can be found at: **patdeegan.com/commonground**

Summary and Discussion — Shared Decision Making

Shared decision making encourages a movement away from paternalistic notions of compliance towards the creation of a therapeutic alliance. This enables the empowered use, rather than the passive taking, of medication in the recovery process. Shared decision making involves the patient and the clinician coming together and exchanging knowledge, deliberating and discussing treatment options, and arriving at a joint agreement on the recovery plan. Research has shown that shared decision making is possible for people diagnosed with schizophrenia and psychosis and increases the quality of decisions.

Conclusion

This review of the range of adverse effects associated with neuroleptic drugs has shown that since their introduction, and to the current day, their use is based on the hypothesis that psychosis is caused by excessive dopamine, and ergo, neuroleptic drugs supress dopamine.

While the dopamine hypothesis has changed since first postulated, it remains speculative and is not accepted as conclusive or empirical evidence. This is contrary to most of the medical professions which rest their practice on scientific principles and reasoning. Importantly, we can see that this hypothetical stance underpins the majority of psychiatric responses to psychosis today.

We have demonstrated that the range of evidence and literature indicates that the efficacy of neuroleptic drugs is inconclusive, and the benefits of these drugs may have been overestimated. Similarly, claims that second generation neuroleptics are more efficacious and cause fewer direct effects when compared to older compounds are not supported within the literature. This sits alongside emerging evidence to suggest that the postponement of treatment with neuroleptics and the tapering/discontinuation of these drugs may be associated with better outcomes. Despite this, psychiatry continues to use neuroleptic drugs as the frontline response to psychosis, with four out of five Australians diagnosed with psychosis or schizophrenia prescribed the drugs. A major concern is the increasing prescription of neuroleptics and the trend for neuroleptic drugs to be used in off-label prescribing, meaning the population exposed to these drugs extends beyond those diagnosed with psychosis or schizophrenia. While polypharmacy is not recommended, it is common practice.

While some studies show modest improvements from neuroleptics (typically limited to a reduction in positive symptoms), this is rarely balanced with the serious, debilitating and disabling direct effects of these drugs. Significantly, many lives are lost, with a much higher mortality gap for people diagnosed with schizophrenia and psychosis when compared to the general population.

The direct effects of neuroleptics including diabetes, sedation and tardive dyskinesia are far ranging and rarely experienced singularly; instead people report numerous direct effects, concurrently. It has been argued that the adverse effects associated with neuroleptics would result in most drugs in general medicine being removed from the market.

Overall, it would seem that consumers and their families are far more concerned with the adverse direct effects of neuroleptics than clinicians. It appears as though there is an 'on balance' decision making process occurring, where for clinicians, the desire to eradicate or control symptoms overrides the real and debilitating direct effects that people report. We are curious about the sorts of mechanisms that support the decision to not engage with the lived experience of people who are negatively impacted by direct effects. For example, if psychiatry engaged more deeply and critically with the lived experience of the direct effects of neuroleptic drugs, we wonder what sorts of claims to knowledge and expertise it may be able to make. We say this in the spirit of understanding that it is challenging and unsettling to have a profession's knowledge base and practices questioned. Yet, we believe that the knowledge and expertise of consumers and families has much to offer a range of professions involved in psychiatry. Importantly, an open and inquisitive stance to emerging evidence and the lived experience of consumers and their families is more likely to give rise to personal recovery.

Another area which reflects significant incongruence between the positions of practitioners and consumers and their families relates to withdrawal and discontinuation of neuroleptic drugs. It is established that many people will discontinue neuroleptics, yet there is a distinct lack of clinical guidance or information for people on how to safely withdraw.

This seems to reflect an unwillingness by practitioners to engage in conversations with people about withdrawal, and resonates with ideas about consumer 'insight'. Such a position is not reflective of personal recovery stances or Australian policy frameworks, and constitutes the denial of a basic medical right. Again, we are left wondering what barriers exist to addressing this gap between practices within psychiatry and the reality of consumers' lived experience and choices.

Recognising the importance of choice and informed consent, this review has also highlighted a number of approaches that may be used as an alternative to, or in conjunction with, neuroleptic drugs. Common to Soteria, Open Dialogue, Hearing Voices Network, harm reduction and shared decision making approaches is the centering of lived experience and the conceptualisation of the individual as an active agent in their own recovery. We note that despite emerging research demonstrating positive outcomes, these approaches remain on the periphery and inaccessible to many consumers and families. This has implications for the ability of consumers and families to make fully informed decisions regarding treatment. We are curious as to the mechanisms that support the dominance of neuroleptics as a response to psychosis where safer and potentially more effective alternatives exist.

Finally, we reiterate that the majority of the literature we have reviewed fails to incorporate or privilege the fundamental and crucial lived experience testimonies of consumers and their families. Instead, the material is dominated by the views and work of researchers, clinicians and the professions. We suggest that the inclusion of lived experience in research is long overdue and argue that embedding the voice of those whose lives are critically impacted by neuroleptic drugs is crucial to forming a balanced viewpoint on the most effective and least harmful avenue to recovery.

References

Adams, C. E., Awad, G. A., Rathbone, J., Thornley, B., & Soares-Weiser, K. (2014). Chlorpromazine versus placebo for schizophrenia. *Cochrane Database of Systematic Reviews*, *1(1).* doi:10.1002/14651858.CD000284.pub3

Adams, C. E., Bergeman, H., Irving, C. B., & Lawrie, S. (2013). Haloperidol versus placebo for schizophrenia. *Cochrane Database of Systematic Reviews*, (11). doi:10.1002/14651858.CD003082.pub3

Adler, L. A., Angrist, B., Reiter, S., & Rotrosen, J. (1989). Neuroleptic-induced akathisia: A review. *Psychopharmacology*, *97,* 1-11.

Alexander, G. C., Gallagher, S. A., Mascola, A., Moloney, R. M., & Stafford, R. S. (2011). Increasing off-label use of antipsychotic medications in the United States, 1995–2008. *Pharmacoepidemiology and Drug Safety, 20(2),* 177-184. doi:10.1002/pds.2082

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

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders:* DSM-IV-TR. Washington, DC: Author.

Australian Institute of Health and Welfare. (2014). *Mortality and life expectancy of Indigenous Australians 2008 to 2012*. Canberra: AIHW.

Awad, A. G., & Voruganti, L. N. P. (2004). Impact of atypical antipsychotics on quality of life in patients with schizophrenia. *CNS Drugs*, *18(13),* 877-893. doi:10.2165/00023210-200418130-00004

Baggaley, M. (2008). Sexual dysfunction in schizophrenia: Focus on recent evidence. *Human Psychopharmacology: Clinical and Experimental*, *23(3*), 201-209. doi:10.1002/hup.924

Ban, T. (2007). Fifty years of chlorpromazine: A historical perspective. *Neuropsychiatric Disease and Treatment*, *3(4)*, 495-500.

Barnes, T. R. E., & Paton, C. (2012). Antipsychotic polypharmacy in schizophrenia. *CNS Drugs*, *25(5)*, 383-399. doi:10.2165/11587810-000000000-00000

Baxter, K. (Ed.). (2010). Stockley's drug interactions: *A source book of interactions, their mechanisms, clinical importance and management* (9th ed.). London: Pharmaceutical Press.

Beavan, V., de Jager, A., & dos Santos, B. (2016). Do peer-support groups for voice-hearers work? A small scale study of Hearing Voices Network support groups in Australia. *Psychosis,* 1-10. doi:10.1080/17522439.2016.1216583

Bennett, C., Sundram, S., Farhall, J., Fossey, E., Grigg, M., Terese, M., . . . Singh, B. S. (2012). Schizophrenia and related disorders. In G. Meadows, J. Farhall, E. Fossey, M. Grigg, F. McDermott, & B. S. Singh (Eds.), *Mental Health in Australia: Collaborative Community Practice* (3rd ed., pp. 741-788). Melbourne, Australia: Oxford University Press.

Berezin, R. (2013). Psychotherapy of character: *The play of consciousness in the theater of the brain*. Arizona: Wheatmark Publications.

Bleakley, S. (2012). Identifying and reducing the risk of antipsychotic drug interactions. *Progress in Neurology and Psychiatry, March/April,* 20-24. Retrieved from www.progressnp.com

Bola, J. R., Kao, D., Soydan, H., & Adams, C. E. (2011). Antipsychotic medication for early episode schizophrenia. *Cochrane Database of Systematic Reviews*, *(6)*. doi:10.1002/14651858.CD006374.pub2.

Bola, J. R., Lehtinen, K., Aaltonen, J., Räkköläinen, V., Syvälahti, E., & Lehtinen, V. (2006). Predicting medication-free treatment response in acute psychosis: Cross-validation from the Finnish need-adapted project. *The Journal of Nervous and Mental Disease*, *194(10),* 732-739. doi:10.1097/01.nmd.0000243080.90255.88

Bola, J. R., Lehtinen, K., Cullberg, J., & Ciompi, L. (2009). Psychosocial treatment, antipsychotic postponement, and low-dose medication strategies in first-episode psychosis: A review of the literature. *Psychosis, 1(1),* 4-18. doi:10.1080/17522430802610008

Bola, J. R., & Mosher, L. R. (2003). Treatment of acute psychosis without neuroleptics: Two-year outcomes from the Soteria project. *Journal of Nervous and Mental Disease*, *191(4)*, 219-229. doi:10.1097/00005053-200304000-00002

Boyle, M. (2002). Schizophrenia: *A scientific delusion?* (2nd ed.). London: Routledge.

Breggin, P. R. (2008). *Brain-disabling treatments in psychiatry: Drugs, electroshock, and the role of the FDA* (2nd ed.). New York, NY: Springer Publishing Company.

Breggin, P. R. (2011). Psychiatric drug-induced chronic brain impairment (CBI): Implications for long-term treatment with psychiatric medication. *International Journal of Risk & Safety in Medicine*, *23(4)*, 193-200.

Breggin, P. R. (2013). *Psychiatric Drug Withdrawal: A Guide for Prescribers, Therapists, Patients, and Their Families.* New York: Springer Publishing Company.

Breggin, P. R. (2016). Rational principles of psychopharmacology for therapists, healthcare providers and clients. *Journal of Contemporary Psychotherapy*, *46(1),* 1-13. doi:10.1007/s10879-015-9307-2

Breggin, P. R., & Cohen, D. (2007). *Your drug may be your problem: How and why to stop taking psychiatric medications.* Philadelphia, PA: Da Capo Press.

British Psychological Society. (n.d.). *Understanding psychosis and schizophrenia: Why people sometimes hear voices, believe things that others find strange, or appear out of touch with reality, and what can help:* British Psychological Society, Retrieved from www.bps.org.uk/system/files/.../rep03_understanding_psychosis.pdf

Brown, S., Kim, M., Mitchell, C., & Inskip, H. (2010). Twenty-five year mortality of a community cohort with schizophrenia. *The British Journal of Psychiatry, 196(2)*, 116-121. doi:10.1192/bjp.bp.109.067512

Bushe, C., & Holt, R. (2004). Prevalence of diabetes and impaired glucose tolerance in patients with schizophrenia. *The British Journal of Psychiatry, 184(47),* 67-71. doi:10.1192/bjp.184.47.s67

Calton, T., Ferriter, M., Huband, N., & Spandler, H. (2008). A systematic review of the Soteria paradigm for the treatment of people diagnosed with schizophrenia. *Schizophrenia Bulletin, 34(1),* 181-192. doi:10.1093/schbul/sbm047

Carrick, R., Mitchell, A., Powell, R. A., & Lloyd, K. (2004). The quest for well-being: A qualitative study of the experience of taking antipsychotic medication. *Psychology and Psychotherapy: Theory, Research and Practice, 77(1),* 19-33. doi:10.1348/147608304322874236

Chakos, M., Lieberman, J., Hoffman, E., Bradford, D., & Sheitman, D. (2001). Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia: A review and meta-analysis of randomized trials. *American Journal of Psychiatry, 158(4)*, 518-526. doi:10.1176/appi.ajp.158.4.518

Chan, K. K. S., & Mak, W. W. S. (2012). Shared decision making in the recovery of people with schizophrenia: The role of metacognitive capacities in insight and pragmatic language use. *Clinical Psychology Review*, *32,* 535-544. doi:10.1016/j.cpr.2012.06.001

Charles, C., Gafni, A., & Whelan, T. (1997). Shared decision-making in the medical encounter: What does it mean? (or it takes at least two to tango). *Social Science & Medicine, 44(5),* 681-692. Retrieved from http://www.sciencedirect.com/science/article/pii/S0277953696002213

Chiang, Y. L., Klainin-Yobas, P., Ignacio, J., & Chng, C. M. (2011). The impact of antipsychotic side effects on attitudes towards medication in people with schizophrenia and related disorders. *Journal of Clinical Nursing, 20*, 2172-2182. doi:10.1111/j.1365-2702.2010.03659.x

Chouinard, G., Jones, B., & Annable, L. (1978). Neuroleptic-induced supersensitivity psychosis. *American Journal of Psychiatry*, *135(11)*, 1409-1410.

Commonwealth of Australia Therapeutic Goods Association. (n.d.). Various factsheets retrieved from https://www.tga.gov.au/

Corstens, D., & Longden, E. (2013). The origins of voices: Links between life history and voice hearing in a survey of 100 cases. *Psychosis, 5(3),* 270-285. doi:10.1080/17522439.2013.816337

Cutler, A. J. (2003). Sexual dysfunction and antipsychotic treatment. *Psychoneuroendocrinology*, *28, Supplement 1,* 69-82. doi:10.1016/S0306-4530(02)00113-0

Daumit, G. L., Goff, D. C., Meyer, J. M., Davis, V. G., Nasrallah, H. A., McEvoy, J. P., . . . Lieberman, J. A. (2008). Antipsychotic effects on estimated 10-year coronary heart disease risk in the CATIE schizophrenia study. *Schizophrenia Research*, *105,* 175-187. doi:10.1016/j.schres.2008.07.006

Day, J. C., Kinderman, P., & Bentall, R. (1998). A comparison of patients' and prescribers' beliefs about neuroleptic side-effects: prevalence, distress and causation. *Acta Psychiatrica Scandinavica, 97(1)*, 93-97. doi:10.1111/j.1600-0447.1998.tb09969.x

Deegan, P. E. (2007). The lived experience of using psychiatric medication in the recovery process and a shared decision-making program to support it. Psychiatric Rehabilitation Journal, 31(1), 62-69. doi:10.2975/31.1.2007.62.69

Deegan, P. E., & Drake, R. E. (2006). Shared decision making and medication management in the recovery process. *Psychiatric Services, 57(11)*, 1636-1639. doi:10.1176/ps.2006.57.11.1636

De Hert, M., Detraux, J., van Winkel, R., Yu, W., & Correll, C. U. (2012). Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. *Nature Reviews Endocrinology, 8(2)*, 114-126. doi:10.1038/nrendo.2011.156

De Hert, M., Dockx, L., Bernagie, C., Peuskens, B., Sweers, K., Leucht, S., . . . Peuskens, J. (2011). Prevalence and severity of antipsychotic related constipation in patients with schizophrenia: A retrospective descriptive study. *BMC Gastroenterology*, *11(1).* doi:10.1186/1471-230x-11-17

De Hert, M., Schreurs, V., Vancampfort, D., & Van Winkel, R. (2009). Metabolic syndrome in people with schizophrenia: A review. *World Psychiatry*, *8,* 15-22. doi:10.1002/j.2051-5545.2009.tb00199.x

De Hert, M., Van Winkel, R., Silic, A., Van Eyck, D., & Peuskens, J. (2010). Physical health management in psychiatric settings. *European Psychiatry, 25,* 22-28. doi:10.1016/s0924-9338(10)71702-8

Department of Health. (2013). *DUSC review on the utilisation of antipsychotics* Retrieved from http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2013-08/antipsychotics

Devon Partnership NHS Trust (n.d). *Recovery orientated prescribing & medicines management project: Putting recovery at the heart of everything.* Retrieved from https://recoverydevon.co.uk/resources/

DiBonaventura, M., Gabriel, S., Dupclay, L., Gupta, S., & Kim, E. (2012). A patient perspective of the impact of medication side effects on adherence: Results of a cross-sectional nationwide survey of patients with schizophrenia. *BMC Psychiatry*, *12 (20).* doi:10.1186/1471-244X-12-20

Dillon, J., & Hornstein, G. A. (2013). Hearing voices peer support groups: a powerful alternative for people in distress. *Psychosis, 5(3),* 286-295. doi:10.1080/17522439.2013.843020

Divac, N., Prostran, M., Jakovcevski, I., & Cerovac, N. (2014). Second-generation antipsychotics and extrapyramidal adverse effects. *BioMed Research International, 2014*, 1-6. doi:10.1155/2014/656370

Dold, M., & Leucht, S. (2014). Pharmacotherapy of treatment-resistant schizophrenia: A clinical perspective. *Evidence Based Mental Health*, *17(2)*, 33-37. doi:10.1136/eb-2014-101813

Drake, R. E., & Ehrlich, J. (1985). Suicide attempts associated with akathisia. *American Journal of Psychiatry*, *142*, 499-501.

Drug. (n.d.). In Oxford online dictionary. Retrieved from https://en.oxforddictionaries.com/definition/drug

Fakhoury, W. K. H., Wright, D., & Wallace, M. (2001). Prevalence and extent of distress of adverse effects of antipsychotics among callers to a United Kingdom national mentalhealth helpline. *International Clinical Psychopharmacology, 16(3)*, 153-162. Retrieved from http://link.lis.curtin.edu.au/cgi-bin/ezproxy/ezpgateway.cgi?url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed5&AN=2001165753

Faulkner, A. (2015). *Randomised controlled trials: The straightjacket of mental health research?* Retrieved from http://mcpin.org/wp-content/uploads/talking-point-paper-1.pdf

Gaebel, W., Weinmann, S., Sartorius, N., Rutz, W., & McIntyre, J. S. (2005). Schizophrenia practice guidelines: international survey and comparison. *The British Journal of Psychiatry*, *187(3)*, 248-255. doi:10.1192/bjp.187.3.248

Gallego, J. A., Bonetti, J., Zhang, J., Kane, J. M., & Correll, C. U. (2012). Prevalence and correlates of antipsychotic polypharmacy: A systematic review and meta-regression of global and regional trends from the 1970s to 2009. *Schizophrenia Research*, *138(1)*, 18-28. doi:10.1016/j.schres.2012.03.018

Gallego, J. A., Nielsen, J., De Hert, M., Kane, J. M., & Correll, C. U. (2012). Safety and tolerability of antipsychotic polypharmacy. *Expert Opinion on Drug Safety, 11(4),* 527-542. doi:10.1517/14740338.2012.683523

Galletly, C., Castle, D., Dark, F., Humberstone, V., Jablensky, A., Killackey, E., . . . Tran, N. (2016). Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders. *Australian and New Zealand Journal of Psychiatry, 50(5)*, 410-472. doi:10.1177/0004867416641195

Galletly, C., Foley, D. L., Waterreus, A., Watts, G. F., Castle, D., McGrath, J. J., . . . Morgan, V. A. (2012). Cardiometabolic risk factors in people with psychotic disorders: The second Australian national survey of psychosis. *Australian and New Zealand Journal of Psychiatry, 46,* 753-761. doi:10.1177/0004867412453089

Gardos, G., Cole, J., & Tarsy, D. (1978). Withdrawal syndromes associated with antipsychotic drugs. *American Journal of Psychiatry, 135(11)*, 1321-1324.

Gibson, S., Brand, S., Burt, S., Boden, Z., & Benson, O. (2013). Understanding treatment non-adherence in schizophrenia and biploar disorder: A survey of what service users do and why. *BMC Psychiatry, 13(153),* 1-12. Retrieved from http://www.biomedcentral.com/1471-244X/13/153

Gilbert, P., Harris, M., McAdams, L., & Jeste, D. (1995). Neuroleptic withdrawal in schizophrenic patients: A review of the literature. *Archives of General Psychiatry, 52,* 173-186.

Goff, D. C., Sullivan, L. M., McEvoy, J. P., Meyer, J. M., Nasrallah, H. A., Daumit, G. L., . . . Lieberman, J. A. (2005). A comparison of ten-year cardiac risk estimates in schizophrenia patients from the CATIE study and matched controls. *Schizophrenia Research, 80(1)*, 45-53. doi:10.1016/j.schres.2005.08.010

Goossensen, A., Zijlstra, P., & Koopmanschap, M. (2007). Measuring shared decision making processes in psychiatry: Skills versus patient satisfaction. *Patient Education and Counselling, 67,* 50-56. doi:10.1016/j.pec.2007.01.017

Gur, R. E., Maany, V., Mozley, P. D., Swanson, C., Bilker, W., & Gur, R. C. (1998). Subcortical MRI volumes in neuroleptic-naive and treated patients with schizophrenia. *American Journal of Psychiatry, 155,* 1711-1717.

Haddad, P. M., & Anderson, I. M. (2002). Antipsychotic-related QTc prolongation, Torsade de Pointes and sudden death. *Drugs, 62,* 1649-1671. doi:10.2165/00003495-200262110-00006

Haddad, P. M., & Sharma, S. G. (2012). Adverse effects of atypical antipsychotics. *CNS Drugs, 21(11),* 911-936. doi:10.2165/00023210-200721110-00004

Hall, W. (2012). *Harm Reduction Guide to Coming off Psychiatric Drugs.* The Icarus Project and The Freedom Center. Retrieved from www.freedom-center.org

Hamann, J., Langer, B., Winkler, V., Busch, R., Cohen, R., Leucht, S., & Kissling, W. (2006). Shared decision making for in-patients with schizophrenia. *Acta Psychiatrica Scandinavica, 114(4),* 265-273. doi:10.1111/j.1600-0447.2006.00798.x

Hamann, J., Mendel, R., Meier, A., Asani, F., Pausch, E., Leucht, S., & Kissling, W. (2011). "How to speak to your psychiatrist": Shared decision-making training for inpatients with schizophrenia. *Psychiatric Services, 62(10),* 1218-1221.

Hamilton, B., & Roper, C. (2006). Troubling 'insight': Power and possibilities in mental health care. *Journal of Psychiatric and Mental Health Nursing, 13(4),* 416-422. doi:10.1111/j.1365-2850.2006.00997.x

Harrow, M., & Jobe, T. H. (2007). Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications: A 15-year multifollow-up study. *The Journal of Nervous and Mental Disease, 195(5)*, 406-414. doi:10.1097/01.nmd.0000253783.32338.6e

Harrow, M., & Jobe, T. H. (2013). Does long-term treatment of schizophrenia with antipsychotic medications facilitate recovery? *Schizophrenia Bulletin, 39(5),* 962-965. doi:10.1093/schbul/sbt034

Harrow, M., Jobe, T. H., & Faull, R. N. (2014). Does treatment of schizophrenia with antipsychotic medications eliminate or reduce psychosis? A 20-year multi-follow-up study. *Psychological Medicine, 44(14),* 3007-3016. doi:10.1017/S0033291714000610

Hasan, A., Falkai, P., Wobrock, T., Lieberman, J., Glenthoj, B., Gattaz, W. F., . . . Möller, H.-J. (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),* 318-378. doi:10.3109/15622975.2012.696143

Healy, D., Le Noury, J., Harris, M., Butt, M., Linden, S., Whitaker, C., . . . Roberts, A. P. (2012). Mortality in schizophrenia and related psychoses: Data from two cohorts, 1875–1924 and 1994–2010. *BMJ Open, 2(5).* doi:10.1136/bmjopen-2012-001810

Hellewell, J. S. E. (2002). Patients' subjective experiences of antipsychotics: Clinical relevance. *CNS Drugs, 16(7),* 457-471.

Ho, B., Andreasen, N. C., Nopoulos, P., Arndt, S., Magnotta, V., & Flaum, M. (2003). Progressive structural brain abnormalities and their relationship to clinical outcome: A longitudinal magnetic resonance imaging study early in schizophrenia. *Archives of General Psychiatry, 60(6),* 585-594. doi:10.1001/archpsyc.60.6.585

Ho, B., Andreasen, N. C., Ziebell, S., Pierson, R., & Magnotta, V. (2011). Long-term antipsychotic treatment and brain volumes: A longitudinal study of first-episode schizophrenia. *Archives of General Psychiatry, 68(2),* 128-137. doi:10.1001/archgenpsychiatry.2010.199

Hoffmann, T. C., Légaré, F., Simmons, M. B., McNamara, K., McCaffery, K., Trevena, L. J., . . . Del Mar, C. B. (2014). Shared decision making: What do clinicians need to know and why should they bother. *The Medical Journal of Australia, 201(1),* 35-39.

Howes, O. D., & Kapur, S. (2009). The dopamine hypothesis of schizophrenia: version III--the final common pathway. *Schizophrenia Bulletin, 35(3),* 549-562. doi:10.1093/schbul/sbp006

Howes, O. D., & Murray, R. M. Schizophrenia: an integrated sociodevelopmental-cognitive model. *The Lancet, 383(9929),* 1677-1687. doi:10.1016/S0140-6736(13)62036-X

Howland, R. (2010). Potential adverse effects of discontinuing psychotropic drugs: Part 3: Antipsychotic, dopaminergic, and mood-stabilizing drugs. *Journal of Psychosocial Nursing, 48(8),* 11-14. Retrieved from http://www.healio.com/psychiatry/journals/jpn

Hutton, P., Weinmann, S., Bola, J. R., & Read, J. (2013). Antipsychotic drugs. In J. Read & J. Dillon (Eds.), *Models of madness: Psychological, social and biological approaches to psychosis* (2nd ed., pp. 105-124). East Sussex, UK: Routledge.

Ilyas, S., & Moncrieff, J. (2012). Trends in prescriptions and costs of drugs for mental disorders in England, 1998–2010. *The British Journal of Psychiatry, 200(5),* 393-398. doi:10.1192/bjp.bp.111.104257

Iseger, T. A., & Bossong, M. G. (2015). A systematic review of the antipsychotic properties of cannabidiol in humans. *Schizophrenia Research, 162(1–3),* 153-161. doi:10.1016/j.schres.2015.01.033

Jablensky, A., & Sartorius, N. (2008). What Did the WHO Studies Really Find? *Schizophrenia Bulletin, 34(2),* 253-255. doi:10.1093/schbul/sbm151

Jablensky, A., Sartorius, N., Ernberg, G., Anker, M., Korten, A., Cooper, J. E., . . . Bertelsen, A. (1992). Schizophrenia: Manifestations, incidence and course in different cultures. A World Health Organization ten-country study. *Psychological Medicine. Monograph Supplement, 20,* 1-97. doi:10.1017/S0264180100000904

Jackson, S. L. (2006). Research methods and statistics: *A critical thinking approach* (2nd ed.). Belmont, CA: Thomson Wadsworth.

Jeste, D. V., Caligiuri, M. P., & Paulsen, J. S. (1995). Risk of tardive dyskinesia in older patients: A prospective longitudinal study of 266 outpatients. *Archives of General Psychiatry, 52(9),* 756-765. doi:10.1001/archpsyc.1995.03950210050010

John, A. P., Gee, T., Alexander, S., Ramankutty, P., & Dragovic, M. (2014). Prevalence and nature of antipsychotic polypharmacy among inpatients with schizophrenia spectrum disorders at an Australian mental health service. *Australasian Psychiatry, 22(6),* 546-550. doi:10.1177/1039856214546672

Johnstone, L. (2011). Can traumatic events traumatize people? Trauma, madness and 'psychosis'. In M. Rapley, J. Moncrieff & J. Dillon (Eds.), *De-medicalizing misery: Psychiatry, psychology and the human condition* (pp. 99-109). Hampshire: Palgrave Macmillan.

Jones, P. B., Barnes, T. E., Davies, L., Dunn, G., Lloyd, H., Hayhurst, K. P., . . . Lewis, S. W. (2006). Randomized controlled trial of the effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost utility of the latest antipsychotic drugs in schizophrenia study (CUtLASS 1). *Archives of General Psychiatry, 63(10)*, 1079-1087. doi:10.1001/archpsyc.63.10.1079

Kelly, D. L., & Conley, R. R. (2004). Sexuality and schizophrenia: A review. *Schizophrenia Bulletin, 30(4),* 767-779. Retrieved from http://schizophreniabulletin.oxfordjournals.org/content/30/4/767.abstract

Kennedy, W. K., Jann, M. W., & Kutscher, E. C. (2013). Clinically significant drug interactions with atypical antipsychotics. *CNS Drugs, 27(12),* 1021-1048. doi:10.1007/s40263-013-0114-6

Kisely, S. (2016). No mental health without oral health. *Canadian Journal of Psychiatry, 61(5),* 277-282. doi:10.1177/0706743716632523

Khin, N. A., Chen, Y. F., Yang, Y., Yang, P., & Laughren, T. P. (2012). Exploratory analyses of efficacy data from schizophrenia trials in support of new drug applications submitted to the US Food and Drug Administration. *The Journal of clinical psychiatry, 73(6),* 856-864. doi:10.4088/JCP.11r07539

Lambert, M., Conus, P., Eide, P., Mass, R., Karow, A., Moritz, S., . . . Naber, D. (2004). Impact of present and past antipsychotic side effects on attitude toward typical antipsychotic treatment and adherence. *European Psychiatry, 19(7),* 415-422. doi:10.1016/j.eurpsy.2004.06.031

Larsen-Barr, M. (2016). *Experiencing Antipsychotic Medication: From First Prescriptions to Attempted Discontinuation*. Doctor in Clinical Psychology. University of Auckland Retrieved from https://www.researchgate.net/publication/309485009_Experiencing_Antipsychotic_Medication_From_First_Prescriptions_to_Attempted_Discontinuation

Laursen, T. M. (2011). Life expectancy among persons with schizophrenia or bipolar affective disorder. *Schizophrenia Research, 131(1–3),* 101-104. doi:10.1016/j.schres.2011.06.008

Laursen, T. M., Munk-Olsen, T., & Vestergaard, M. (2012). Life expectancy and cardiovascular mortality in persons with schizophrenia. *Current Opinion in Psychiatry, 25(2),* 83-88. doi:10.1097/YCO.0b013e32835035ca

Lawrence, D., Holman, C. D. J., & Jablensky, A. V. (2001). *Duty to care: Preventable physical illness in people with mental illness.* Perth: The University of Western Australia.

Lazarus, A., Mann, S. C., & Caroff, S. N. (1989). *The neuroleptic malignant syndrome and related conditions.* Washington, DC: American Psychiatric Press.

Le Geyt, G., Awenat, Y., Tai, S., & Haddock, G. (2016). Personal accounts of discontinuing neuroleptic medication for psychosis. *Qualitative Health Research*, 1-16. doi:10.1177/1049732316634047

Le Noury, J., Khan, A., Harris, M., Wong, W., Williams, D., Roberts, T., . . . Healy, D. (2008). The incidence and prevalence of diabetes in patients with serious mental illness in North West Wales: Two cohorts, 1875–1924 & 1994–2006 compared. *BMC Psychiatry, 8*. doi:10.1186/1471-244x-8-67

Lepping, P., Sambhi, R. S., Whittington, R., Lane, S., & Poole, R. (2011). Clinical relevance of findings in trials of antipsychotics: Systematic review. *The British Journal of Psychiatry, 198,* 341–345. doi:10.1192/bjp.bp.109.075366

Leucht, S., Cipriani, A., Spineli, L., Mavridis, D., Örey, D., Richter, F., . . . Davis, J. M. (2013). Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: A multiple-treatments meta-analysis. *The Lancet, 382(9896),* 951-962. doi:10.1016/S0140-6736(13)60733-3

Leucht, S., Corves, C., Arbter, D., Engel, R. R., Li, C., & Davis, J. M. (2009). Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *The Lancet, 373(9657),* 31-41. doi:10.1016/S0140-6736(08)61764-X

Leucht, S., Kane, J. M., Etschel, E., Kissling, W., Hamann, J., & Engel, R. R. (2006). Linking the PANSS, BPRS, and CGI: Clinical Implications. *Neuropsychopharmacology, 31(10),* 2318-2325. doi:10.1038/sj.npp.1301147

Leucht, S., Komossa, K., Rummel-Kluge, C., Corves, C., Hunger, H., Schmid, F., . . . Davis, J. M. (2009). A meta-analysis of head-to-head comparisons of second-generation antipsychotics in the treatment of schizophrenia. *American Journal of Psychiatry, 166,* 152-163. doi:10.1176/appi.ajp.2008.08030368

Leucht, S., Tardy, M., Komossa, K., Heres, S., Kissling, W., & Davis, J. M. (2012). Maintenance treatment with antipsychotic drugs for schizophrenia. *Cochrane Database of Systematic Reviews(5)*. doi:10.1002/14651858.CD008016.pub2.

Lieberman, J. A. (2004). Managing anticholinergic side effects. *Primary Care Companion to The Journal of Clinical Psychiatry, 6*(suppl 2), 20-23. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC487008/

Lieberman, J. A., & Stroup, T. S. (2011). The NIMH-CATIE Schizophrenia Study: What did we learn? *American Journal of Psychiatry, 168(8),* 770-775. doi:10.1176/appi.ajp.2011.11010039

Lieberman , J. A., Stroup , T. S., McEvoy , J. P., Swartz , M. S., Rosenheck , R. A., Perkins , D. O., . . . Hsiao , J. K. (2005). Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *New England Journal of Medicine, 353(12),* 1209-1223. doi:10.1056/NEJMoa051688

Livingston, M. (2012). Guide to when and how to safely withdraw antipsychotics. *Prescriber, 19*, 37-40. Retrieved from www.prescriber.co.uk

Llorca, P., Chereau, I., Bayle, F., & Lancon, C. (2002). Tardive dyskinesias and antipsychotics: A review. *European Psychiatry, 17(3),* 129-138. doi:10.1016/S0924-9338(02)00647-8

Longden, E., & Read, J. (2016). Assessing and reporting the adverse effects of antipsychotic medication: a systematic review of clinical studies, and prospective, retrospective, and cross-sectional research. *Clinical Neuropharmacology, 39(1)*, 29-39. doi:10.1097/wnf.0000000000000117

Malm, U., Ivarsson, B., Allebeck, P., & Falloon, I. R. H. (2003). Integrated care in schizophrenia: A 2-year randomized controlled study of two community-based treatment programs. *Acta Psychiatrica Scandinavica, 107(6),* 415-423. doi:10.1034/j.1600-0447.2003.00085.x

Mann, S. C., Caroff, S. N., Keck, P. E., & Lazarus, A. (2003). *The neuroleptic malignant syndrome and related conditions* (2nd ed.). Washington, DC: American Psychiatric Press.

Marsh, A., & Dale, A. (2006). *Addiction counselling: content and process.* Melbourne: IP Communications Pty Ltd.

Marston, L., Nazareth, I., Petersen, I., Walters, K., & Osborn, D. P. J. (2014). Prescribing of antipsychotics in UK primary care: a cohort study. *BMJ Open, 4(12).* doi:10.1136/bmjopen-2014-006135

McCance-Katz, E. F., Sullivan, L. E., & Nallani, S. (2010). Drug interactions of clinical importance among the opioids, methadone and buprenorphine, and other frequently prescribed medications: a review. *Am J Addict, 19(1),* 4-16. doi:10.1111/j.1521-0391.2009.00005.x

McCann, T. V., & Clark, E. (2004). Embodiment of severe and enduring mental illness: Finding meaning in schizophrenia. *Issues in Mental Health Nursing, 25(8)*, 783-798. doi:10.1080/01612840490506365

Medication. (n.d.). In Oxford online dictionary. Retrieved from https://en.oxforddictionaries.com/definition/medication

Mind. (2016). *How to: Coming off psychiatric drugs: Mind.* Retrieved from http://www.mind.org.uk/information-support/drugs-and-treatments/medication-stopping-or-coming-off/#.WIbQ9UbpqSo

Moncrieff, J. (2006). Does antipsychotic withdrawal provoke psychosis? Review of the literature on rapid onset psychosis (supersensitivity psychosis) and withdrawal-related relapse. *Acta Psychiatrica Scandinavica, 114(1),* 3-13. doi:10.1111/j.1600-0447.2006.00787.x

Moncrieff, J. (2007). *The myth of the chemical cure: A critique of psychiatric drug treatment.* New York, NY: Palgrave Macmillan.

Moncrieff, J. (2009). *A straight talking introduction to psychiatric drugs* (R. Bentall & P. Sanders Eds.). Herefordshire, UK: PCCS Books.

Moncrieff, J. (2013). Magic bullets for mental disorders: The emergence of the concept of an "antipsychotic" drug. Journal of the History of the Neurosciences, 22(1), 30-46. http://dx.doi.org/10.1080/0964704X.2012.664847

Moncrieff, J. (2013). *The bitterest pills: The troubling story of antipsychotic drugs.* Hampshire, UK: Palgrave MacMillan.

Moncrieff, J., & Leo, J. (2010). A systematic review of the effects of antipsychotic drugs on brain volume. *Psychological Medicine, 40(9),* 1409-1422. doi:10.1017/S0033291709992297

Morgan, V., Waterreus, A., Jablensky, A., Mackinnon, A., McGrath, J., Carr, V., . . . Saw, S. (2011). *People living with psychotic illness 2010: Report on the second Australian national survey.* Commonwealth of Australia. Retrieved from https://www.health.gov.au/internet/main/publishing.nsf/content/.../psych10.pdf

Morgenstern, H., & Glazer, W. M. (1993). Identifying risk factors for tardive dyskinesia among long-term outpatients maintained with neuroleptic medications: Results of the Yale tardive dyskinesia study. A*rchives of General Psychiatry, 50(9),* 723-733. doi:10.1001/archpsyc.1993.01820210057007

Morrison, P., Meehan, T., & Stomski, N. J. (2015). Living with antipsychotic medication side-effects: The experience of Australian mental health consumers. *International Journal of Mental Health Nursing, 24(3)*, 253-261. doi:10.1111/inm.12110

Mosher, L. R. (1999). Soteria and other alternatives to acute psychiatric hospitalization: A personal and professional review. *Journal of Nervous and Mental Disease, 187(3),* 142-149. doi:10.1097/00005053-199903000-00003

Mosher, L. R., & Bola, J. R. (2004). Soteria-California and its American successors: Therapeutic ingredients. *Ethical Human Psychology and Psychiatry: An International Journal of Critical Inquiry, 6(1)*, 7-23.

Mosher, L. R., Menn, A., & Matthews, S. M. (1975). Soteria: Evaluation of a home-based treatment for schizophrenia. *American Journal of Orthopsychiatry, 45(3),* 455-467. doi:10.1111/j.1939-0025.1975.tb02556.x

Murphy, A. L., Gardner, D. M., Kisely, S., Cooke, C., Kutcher, S. P., & Hughes, J. (2015). A qualitative study of antipsychotic medication experiences of youth. *Journal of the Canadian Academy of Child and Adolescent Psychiatry, 24(1),* 61-69.

Nasrallah, H. (2007). The roles of efficacy, safety, and tolerability in antipsychotic effectiveness: Practical implications of the CATIE schizophrenia trial. *Journal of Clinical Psychiatry, 68,* 5-11.

Nasrallah, H. A., & Mulvihill, T. (2001). Iatrogenic disorders associated with conventional vs. atypical antipsychotics. *Annals of Clinical Psychiatry, 13(4)*, 215-227. doi:10.3109/10401230109147385

National Health and Clinical Excellence NICE. (2014). *Do not offer adherence therapy (as a specific intervention) to people with psychosis or schizophrenia.* Retrieved from https://www.nice.org.uk/donotdo/do-not-offer-adherence-therapy-as-a-specific-intervention-to-people-with-psychosis-or-schizophrenia

National Health and Medical Research Council. (2009). *NHMRC levels of evidence and grades for recommendations for developers of guidelines.* Retrieved from https://www.nhmrc.gov.au/guidelines-publications/information-guideline-developers/resources-guideline-developers

NSW Government Health. (n.d.). *Clozapine and smoking cessation NSW.* Retrieved from www.health.nsw.gov.au/tobacco/Publications/tool-03-clozapine-smoking-cessation.pdf

Ogino, S., Miyamoto, S., Miyake, N., & Yamaguchi, N. (2014). Benefits and limits of anticholinergic use in schizophrenia: Focusing on its effect on cognitive function. *Psychiatry and Clinical Neurosciences, 68(1),* 37-49. doi:10.1111/pcn.12088

Ozbilen, M., & Adams, C. E. (2009). Systematic overview of Cochrane reviews for anticholinergic effects of antipsychotic drugs. *Journal of Clinical Psychopharmacology, 29(2)*, 141-146. doi:10.1097/JCP.0b013e31819a91f1

Ozbilen, M., & Rattehalli, R. (2012). Systematic review and meta-analysis of anticholinergic side effects of long-acting antipsychotics. *The Open Conference Proceedings Journal, 3(1),* 18-23.

Parker, I., Georgaca, E., Harper, D., McLaughlin, T., & Stowell-Smith, M. (1995). *Deconstructing psychopathology.* London: Sage.

Pelonero, A. L., Levenson, J. L., & Pandurangi, A. K. (1998). Neuroleptic malignant syndrome: A review. *Psychiatric Services, 49(9),* 1163-1172. doi:10.1176/ps.49.9.1163

Perlis, R. H., Perlis, C. S., Wu, Y., Hwang, C., Joseph, M., & Nierenberg, A. A. (2005). Industry sponsorship and financial conflict of interest in the reporting of clinical trials in psychiatry. *American Journal of Psychiatry, 162(10),* 1957-1960. doi:10.1176/appi.ajp.162.10.1957

Peuskens, J., Sienaert, P., & De Hert, M. (1998). Sexual dysfunction: The unspoken side effect of antipsychotics. *European Psychiatry, 13(1)*, 23-30. doi:10.1016/S0924-9338(97)89490-4

Piat, M., Sabetti, J., & Bloom, D. (2009). The importance of medication in consumer definitions of recovery from serious mental illness: A qualitative study. *Issues in Mental Health Nursing, 30(8),* 482-490. doi:10.1080/01612840802509452

Ray , W. A., Chung , C. P., Murray , K. T., Hall , K., & Stein , C. M. (2009). Atypical antipsychotic drugs and the risk of sudden cardiac death. *New England Journal of Medicine, 360(3)*, 225-235. doi:10.1056/NEJMoa0806994

Read, J. (2013). Does 'schizophrenia' exist? Reliability and validity. In J. Read & J. Dillon (Eds.), Models of madness: Psychological, social and biological approaches to psychosis (2nd ed., pp. 47-61). East Sussex: Routledge.

Read, J., Goodman, L., Morrison, A., Ross, C., & Aderhold, V. (2004). Childhood trauma, loss and stress. In J. Read, R. Mosher & R. Bentall (Eds.), *Models of madness: Psychological, social and biological approaches to schizophrenia* (pp. 223-254). London, UK: Routledge.

Robertson, M. (2012). *Acute psychiatric management* (2nd ed.). Gladesville, NSW: Health Education and Training Institute. Retrieved from http://www.heti.nsw.gov.au/Resources-Library/Acute-Psychiatric-Management/

Roe, D., & Swarbrick, M. (2007). A recovery-oriented approach to psychiatric medication: guidelines for nurses. *Journal of Psychosocial Nursing & Mental Health Services, 45(2),* 35-51.

Rogers, A., Day, J. C., Williams, B., Randall, F., Wood, P., Healy, D., & Bentall, R. P. (1998). The meaning and management of neuroleptic medication: a study of patients with a diagnosis of schizophrenia. *Social Science & Medicine, 47(9),* 1313-1323. doi:10.1016/S0277-9536(98)00209-3

Romme, M., & Escher, S. (2000). *Making Sense of Voices - A guide for professionals who work with voice hearers* London: MIND Publications.

Rummel-Kluge, C., Komossa, K., Schwarz, S., Hunger, H., Schmid, F., Lobos, C. A., . . . 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)*, 225-233. doi:10.1016/j.schres.2010.07.012

Saha, S., Chant, D., & McGrath, J. (2007). A systematic review of mortality in schizophrenia: Is the differential mortality gap worsening over time? *Archives of General Psychiatry, 64(10),* 1123-1131. doi:10.1001/archpsyc.64.10.1123

Salomon, C., & Hamilton, B. (2013). "All roads lead to medication?" Qualitative responses from an Australian first-person survey of antipsychotic discontinuation. *Psychiatric Rehabilitation Journal, 36(3),* 160-165. doi:10.1037/prj0000001

Schaffer, S. D., Yoon, S., & Zadezensky, I. (2009). A review of smoking cessation: Potentially risky effects on prescribed medications. *Journal of Clinical Nursing, 18(11),* 1533-1540. doi:10.1111/j.1365-2702.2008.02724.x

Seale, C., Chaplin, R., Lelliott, P., & Quirk, A. (2007). Antipsychotic medication, sedation and mental clouding: An observational study of psychiatric consultations. *Social Science & Medicine, 65(4)*, 698-711. doi:10.1016/j.socscimed.2007.03.047

Seikkula, J., Alakare, B., & Aaltonen, J. (2001a). Open dialogue in psychosis i: An introduction and case illustration. *Journal of Constructivist Psychology, 14(4)*, 247-265. doi:10.1080/10720530125965

Seikkula, J., Alakare, B., & Aaltonen, J. (2001b). Open dialogue in psychosis ii: A comparison of good and poor outcome cases. *Journal of Constructivist Psychology, 14(4)*, 267-284. doi:10.1080/10720530126129

Seikkula, J., Aaltonen, J., Alakare, B., Haarakangas, K., Keränen, J., & Lehtinen, K. (2006). Five-year experience of first-episode nonaffective psychosis in open-dialogue approach: Treatment principles, follow-up outcomes, and two case studies. *Psychotherapy Research, 16(2)*, 214-228. doi:10.1080/10503300500268490

Sengupta, S., Parrilla-Escobar, M. A., Klink, R., Fathalli, F., Ying Kin, N., Stip, E., . . . Joober, R. (2008). Are metabolic indices different between drug-naïve first-episode psychosis patients and healthy controls? *Schizophrenia Research, 102, 329-336.* doi:10.1016/j.schres.2008.02.013

Serretti, A., & Chiesa, A. (2011). Sexual side effects of pharmacological treatment of psychiatric diseases. *Clinical Pharmacology & Therapeutics, 89(1),* 142-147. doi:10.1038/clpt.2010.70

Sin, J., & Roberts, C. (2006). Managing medication. In C. Gamble & G. Brennan (Eds.), Working with serious mental illness: A manual for clinical practice (pp. 317-339). Edinburgh: Elsevier.

Slade, M. (2009). *Personal recovery and mental illness: A guide for mental health professionals.* Cambridge, UK: Cambridge University Press.

Slade, M., & Priebe, S. (2001). Are randomised controlled trials the only gold that glitters? *The British Journal of Psychiatry, 179(4)*, 286-287. doi:10.1192/bjp.179.4.286

Song, F., Hooper, L., & Loke, Y. (2013). Publication bias: What is it? How do we measure it? How do we avoid it? *Open Access Journal of Clinical Trials, 2013(5),* 71-81. doi:10.2147/OAJCT.S34419

Spina, E., & de Leon, J. (2007). Metabolic drug interactions with newer antipsychotics: A comparative review. *Basic and Clinical Pharmacology & Toxicology, 100,* 4-22. Retrieved from http://onlinelibrary.wiley.com/journal/10.1111/%28ISSN%291742-7843

Stahl, S. M. (1999). Antipsychotic polypharmacy, Part 1: Therapeutic option or dirty little secret? *The Journal of Clinical Psychiatry, 60(7),* 425-426.

Stahl, S. M. (2004). Focus on antipsychotic polypharmacy: Evidence-based prescribing or prescribing-based evidence? *International Journal of Neuropsychopharmacology, 7(2),* 113. doi:10.1017/S1461145704004146

Stephenson, C. P., Karanges, E., & McGregor, I. S. (2013). Trends in the utilisation of psychotropic medications in Australia from 2000 to 2011. *Australian and New Zealand Journal of Psychiatry, 47(1)*, 74-87. doi:10.1177/0004867412466595

Suzuki, T., Kanahara, N., Yamanaka, H., Takase, M., Kimura, H., Watanabe, H., & Iyo, M. (2015). Dopamine supersensitivity psychosis as a pivotal factor in treatment-resistant schizophrenia. *Psychiatry Research, 227(2-3)*, 278-282. doi:10.1016/j.psychres.2015.02.021

Taylor, D., Paton, C., & Kapur, S. (2009). *The South London and Maudsley NHS Foundation Trust and Oxleas NHS Foundation Trust: Prescribing Guidelines.* London: Informa Healthcare.

Tyrer, P., & Kendall, T. The spurious advance of antipsychotic drug therapy. *The Lancet, 373(9657),* 4-5. doi:10.1016/S0140-6736(08)61765-1

Üçok, A., İncesu, C., Aker, T., & Erkoç, Ş. (2007). Sexual dysfunction in patients with schizophrenia on antipsychotic medication. *European Psychiatry, 22(5),* 328-333. doi:10.1016/j.eurpsy.2007.01.001

van Putten, T. (1975). The many faces of akathisia. *Comprehensive Psychiatry, 16(1),* 43-47.

Verdoux, H., Tournier, M., & Bégaud, B. (2010). Antipsychotic prescribing trends: a review of pharmaco-epidemiological studies. *Acta Psychiatrica Scandinavica, 121(1),* 4-10. doi:10.1111/j.1600-0447.2009.01425.x

Wahlbeck, K., Westman, J., Nordentoft, M., Gissler, M., & Laursen, T. M. (2011). Outcomes of Nordic mental health systems: Life expectancy of patients with mental disorders. *The British Journal of Psychiatry, 199(6),* 453-458. doi:10.1192/bjp.bp.110.085100

Waterreus, A., Morgan, V. A., Castle, D., Galletly, C., Jablensky, A., Di Prinzio, P., & Shah, S. (2012). Medication for psychosis — consumption and consequences: The second Australian national survey of psychosis. *Australian & New Zealand Journal of Psychiatry, 46(8),* 762-773. doi:10.1177/0004867412450471

Weinmann, S., & Aderhold, V. (2010). Antipsychotic medication, mortality and neurodegeneration: The need for more selective use and lower doses. *Psychosis, 2(1),* 50-69. doi:10.1080/17522430903501999

Weinmann, S., Read, J., & Aderhold, V. (2009). Influence of antipsychotics on mortality in schizophrenia: Systematic review. *Schizophrenia Research, 113(1)*, 1-11. doi:10.1016/j.schres.2009.05.018

Weiss, M., & Britten, N. (2009). What is concordance? The Pharmaceutical Journal, (271), 493. Retrieved from http://www.pharmaceutical-journal.com/learning/learning-article/what-is-concordance/10988929.article

Whitaker, R. (2010). *Anatomy of an epidemic: Magic bullets, psychiatric drugs, and the astonishing rise of mental illness in America.* Westbury, NY: Broadway Paperbacks.

Woods, A., Romme, M., McCarthy-Jones, S., Escher, S., & Dillon, J. (2013). Special edition: Voices in a Positive Light. *Psychosis, 5(3),* 213-215. doi:10.1080/17522439.2013.843021

Wunderink, L., Nienhuis, F. J., Sytema, S., Slooff, C. J., Knegtering, R., & Wiersma, D. (2007). Guided discontinuation versus maintenance treatment in remitted first-episode psychosis: Relapse rates and functional outcome. *Journal of Clinical Psychiatry, 68(5),* 654-661.

Wunderink, L., Nieboer, R. M., Wiersma, D., Sytema, S., & Nienhuis, F. J. (2013). Recovery in remitted first-episode psychosis at 7 years of follow-up of an early dose reduction/discontinuation or maintenance treatment strategy: Long-term follow-up of a 2-year randomized clinical trial. *JAMA Psychiatry, 70(9)*, 913-920. doi:10.1001/jamapsychiatry.2013.19

Appendix 1: Methods

As discussed in the background, the project scope and parameters were produced by members of the NMHCCF with input from the research team.

The scope of the project, as proposed by the NMHCCF members was substantial, covering a wide range of topics related to the overall aim of articulating the adverse and iatrogenic effects of neuroleptic drugs. It was clear through our discussions with the NMHCCF representative who led negotiations that there was a strong desire to include literature which valued the lived experience of both consumers and families. Given this, our initial aim was to undertake a critical scoping review of the literature on adverse effects of neuroleptic drugs and a narrative review of the other nine sections.

We started by examining the literature on frameworks and tools which measure or assess quality across both qualitative and quantitative methods. This led us to conclude that the types of quality criteria used in other studies such as transparency in reporting research design, clarity in representing both methods and findings, sample size and analytic methods did not bring the level of nuanced understanding to the topic as requested by the NMHCCF. This highlighted the significant disconnect between the realities of people living with the issues (in this case the adverse effects of neuroleptic drugs) and those researching and writing in the area. Similarly, the concerns, questions and motivations for each group vary considerably, and this is shown throughout the review where we have highlighted that there is a significant gap in that the voice of consumers and families are missing in the research.

Consequently, we felt that the usual measures of quality in research would not meet the scope as established by the NMHCCF. We then engaged in dialogue with the NMHCFF and collaboratively developed a set of nine core values which would be used to assess the quality of the literature on adverse effects.

As researchers, we see this stance of redefining 'quality' as one which values and privileges lived experience. However, our approach would not be considered methodologically valid when compared to usual, positivist standards for academic research. The co-produced values reflect a commitment to privileging the lived experience of individuals taking neuroleptics and their families as well as a critical questioning of psychiatry and the assumptions underpinning the use of neuroleptic drugs. They include:

1. The lived experience of individuals and families is included and/or privileged.
2. The assertion that the benefits of neuroleptics outweigh the adverse effects is critically examined.
3. The idea that neuroleptics form an 'integral' component of recovery or treatment is critically examined.
4. The idea that professionals know what is in the consumer's best interests is critically examined.
5. The idea that clinicians are educated/informed in terms of side effects and purported efficacy and limitations of neuroleptics is critically examined.
6. The idea that all 'symptoms' are intolerable and must be eradicated is critically examined.
7. Endorses the idea that people can (and should, where possible) make informed decisions about medication.
8. The limits of the scientific approach in psychiatry are considered.
9. An endorsement of a wide range of treatment and support responses is evident.

We then examined the peer-reviewed literature for evidence of some or all of these values in relation to the impacts of neuroleptic drugs. Grey literature (non-peer reviewed) including reports, books, and other documents were not included. Examples of the search terms used included:

Neuroleptic Drugs	Adverse Effects
Neuroleptic	Adverse effects
Anti-psychotic	Adverse effect burden
Antipsychotic	Side effects
	Iatrogenic effects
	Iatrogenic disorders
	Direct effects
	Non-therapeutic effects
	Mortality
	Life expectancy
	Psychosocial effects
	Psycho-social effects

Electronic searches of PsychInfo, Embase, Medline, Proquest, and Scopus databases were undertaken. Synonyms were searched using the OR operator and results were combined using the AND operator. Qualitative and quantitative studies were included and no date limits were placed on the search. Additional sources of interest were identified through purposive examination of cited references. One hundred and forty nine abstracts were identified and screened for relevance. Studies were considered relevant if they included an exploration or discussion of the impact of neuroleptics. Studies were ineligible if they exclusively reflected clinical, biomedical or pharmaceutical treatment paradigms given the emphasis within the project on valuing lived experience and personal recovery. Studies were also excluded if they had a specific focus on children (under 18 years) or older adults (65 and over) and populations with dementia, Alzheimer's disease, intellectual disability, or autism.

As a result, 33 articles were identified that included an exploration or discussion of the impact of taking neuroleptics and which appeared to incorporate some or all of the nine values. These articles were read in full and rated independently by two researchers according to how well they aligned with each of the nine project values listed above.

A score of zero indicated no evidence of alignment to the project value, a score of one indicated partial evidence, and a score of two was awarded if there was comprehensive evidence that the value was reflected in the article. Articles could receive a maximum total score of 18. The two researchers met to cross-check their scoring of the articles against the project values, and deliberated until a unanimous decision was reached.

Overall, there was great variation in the extent to which the 33 articles met the values guiding this piece of work, with total scores ranging from two to 16. Only one third of the articles reviewed were awarded a score of 10 or more, highlighting significant limitations in the literature. Most obviously, the voices of those directly impacted by neuroleptics; the consumers who take these drugs and their family members, were missing and clinician researcher perspectives dominated.

Given the limited number of articles which privileged lived experience the research team decided it needed to rethink its approach to assessing and including literature on the adverse effects of neuroleptic drugs. After consultation with the NMHCFF, we changed our approach to include literature which had some alignment with the nine core values and was classified as 'gold standard' research evidence (as explained under the section titled 'What is the Efficacy of Neuroleptic Drugs'). We have adopted a critical narrative review approach, with all readings examined using critical thinking concepts such as:

- In what ways are lived experiences represented and valued?
- How has the lived experience of consumers and families informed the design, operationalisation and findings of the research?
- What sorts of interests do the authors represent and in what ways do they reflexively account for this in their research?
- What power relations can be traced in the project, and how were they managed or accounted for?
- How have contradictions, gaps and assumptions been considered and addressed?
- How have the philosophical frameworks and values of the authors been discussed?

As a result a wide range of articles of both qualitative and quantitative orientation are included and used to narrate the story of the effects of neuroleptic drugs across a wide range of areas.

In line with our commitment to learn from and value lived experience, we employed a Lived Experience Consultant with considerable professional and personal experience in the use of neuroleptic drugs. The Consultant has reviewed the first draft of this report and will be involved in incorporating feedback from the NMHCCF members and the development of the information sheets (stage 2).

National Mental Health
Consumer & Carer Forum