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Review article

Neuroadaptations to antipsychotic drugs: Insights from pre-clinical and human *post-mortem* studies

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ABSTRACT

Antipsychotic drugs, all of which block the dopamine D2 receptor to a greater or lesser extent, are the mainstay for the pharmacological treatment of schizophrenia. Engaging in a deeper understanding of how antipsychotics act on the brain and body, at the cellular, molecular and physiological level is vital to comprehend both the beneficial and potentially harmful actions of these medications and stimulate development of novel therapeutics. To address this, we review recent advances in our understanding of neuroadaptations to antipsychotics, focusing on (1) treatment efficacy, (2) impact on brain volume and (3) evidence from human *post-mortem* studies that attempt to dissect neuropathological effects of antipsychotic drugs from organic schizophrenia neurobiology and (4) cardio-metabolic side effects. Our aim is to stimulate discussion on these highly clinically relevant topics and consider how we might use current and evolving knowledge and new methodologies in the fields of neuropharmacology and neuroscience, to advance our understanding of the long-term impact of antipsychotic treatment. Ultimately, this may inform the clinical use of these drugs.

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1. Prologue

Schizophrenia is a debilitating disease, ranked among the top 20 causes of disability worldwide (van Os and Kapur, 2009). The precise burden to society is difficult to estimate with precision, due to the diversity of data available and the manner in which it has been collected, nevertheless, large-scale studies examining indicators of the cost-of-illness generally suggest a disquieting picture of substantial human and economic costs. The lifetime prevalence of schizophrenia has been estimated at 0.25% in North America and 0.52% in Europe (Simeone et al., 2015). Indeed, in the European Union alone, a 2011 estimate suggested up to 5 million citizens suffer from schizophrenia and related psychoses (Wittchen et al., 2011). Schizophrenia is not purely a disease of mental health; patients have higher mortality rates and die 12–15 years (on average) earlier than the general population (Saha et al., 2007). It may surprise some then, that schizophrenia leads to more loss of life than several cancers and other physical illnesses (van Os and Kapur, 2009). Whilst many of these deaths reflect suicide, the primary reason for increased mortality is physical causes, including cardiovascular disease (Hennekens et al., 2005; Saha et al., 2007).

After diagnosis of schizophrenia, for which there is still no objective diagnostic test (Fond et al., 2015; Prata et al., 2014), the clinical management of this devastating disorder is very much grounded in the use of antipsychotic drugs (APD) (Kapur and Mamo, 2003), all of which act at dopamine D2 receptors. Unfortunately, these drugs do not effectively treat all symptom dimensions, particularly negative and cognitive symptoms. Furthermore they are associated with numerous side effects, decrease in efficacy over time, and a substantial proportion of patients fail to respond to multiple courses of APD, leaving a significant unmet medical need (Kapur and Mamo, 2003). Now more than 50 years since the introduction of these medications, little real progress has been made in advancing towards novel, non-dopaminergic therapeutics, despite decades of research effort and spending (Millan et al., 2015). In part, this reflects our emerging understanding of the complex, multi-factorial nature of schizophrenia pathophysiology, driven by advances in psychiatric genetics (Anon, 2014, 2015; Fromer et al., 2014), *post-mortem* brain tissue studies, and neuroimaging, particularly in prodromal individuals who have yet to transition to psychosis (Bloomfield et al., 2015; Crossley et al., 2015; Demjaha et al., 2014; Howes et al., 2015; Kambeitz et al., 2014; Selvaraj et al., 2014; van Erp et al., 2015). Combined, these approaches are beginning to paint a picture that schizophrenia is a complex syndrome, with likely multiple aetiologies and potentially distinct neurobiological phenotypes that may have profound implications for clinical treatment strategies. These insights will undoubtedly, in the fullness of time, provide the key pieces of information that will unlock novel drug treatments for schizophrenia, beyond dopamine and the D2 receptor.

On the other hand, such success is unlikely to be immediate. Given the medical need, there is another view, which suggests that engaging in a deeper understanding of how currently used APD act on the brain and the body, by dissecting their cellular, molecular and physiological effects in relevant model systems, is of paramount importance to speed the quest for new and improved medications. Such a systematic approach is likely to yield crucial insights into the mechanisms underlying the beneficial and potentially harmful effects of these drugs. This can provide logical routes to adjunct treatments, some of which, particularly anti-inflammatory drugs, are already showing encouraging signs of success in the clinic (Sommer et al., 2014). Furthermore, if one can better understand the cellular, molecular and physiological basis of the positive and negative effects of APDs, there is the potential to use rational drug design to develop novel antipsychotic agents that retain the beneficial effects, without the adverse ones (Cohen et al., 2013). In this review, we address this issue, by combining information from different, but parallel, research lines, with a common goal – to understand at the cellular and molecular level, the effects of long-term APD treatment on the brain and body, which ultimately, may inform the clinical use of these drugs and the development of new APD. In doing so, we first briefly introduce the history of the development and current application of modern antipsychotics. We then present evidence from parallel lines of research into APD, focussing in particular on three key areas: (1) treatment efficacy and failure, (2) potential impact on brain structure and (3) metabolic side effects. We also review the evidence from human *post-mortem* studies to dissect neuropathological effects of antipsychotics from schizophrenia neurobiology. Our overall aim is to stimulate a critical discussion on these highly clinically relevant topics. In particular, we aim to inspire debate on how we might use current and evolving knowledge and new methodologies in the fields of neuropharmacology and neuroscience to advance our understanding of the long-term impact of APD treatment, which ultimately, may inform the clinical use of these drugs.

1.1. Clinical use of antipsychotic drugs for the treatment of schizophrenia: concerns and controversies

Antipsychotics remain the mainstay of pharmacological treatment of schizophrenia (Kapur and Mamo, 2003; Samara et al., 2014). These drugs are classified into First Generation Antipsychotics (FGA), also referred to as typical antipsychotics, of which haloperidol and chlorpromazine are the prototypical examples, and the newer Second Generation Antipsychotics (SGA), or atypical antipsychotics, examples of which include risperidone, olanzapine, quetiapine, ziprasidone, and most recently aripiprazole and brexpiprazole (sometimes referred to as Third Generation Antipsychotics). FGAs were discovered serendipitously in the 1950′s and remain effective in the treatment of psychotic symptoms. However, based on initial optimism that SGA are more effective in improving negative and cognitive symptoms of schizophrenia, as well as their more favourable side effect profiles, these agents have largely supplanted the use of FGA in clinical practice and treatment guidelines. Without question, SGA are effective in treating positive symptoms and are associated with significantly less motor side effects. However, the initial promise of efficacy in other domains remains controversial (Leucht et al., 2013).

The use of APD has dramatically increased over the past decade and more than 50 million prescriptions are dispensed annually (Snyder and Murphy, 2008). Importantly, in addition to psychosis, antipsychotics are increasingly being prescribed for use, under certain circumstances, in the treatment of depression, bipolar disorder and behavioural sedation in autism spectrum disorder (ASD) (Domino and Swartz, 2008; Kaye et al., 2003). In addition, there is increasing “off-label” prescription for anxiety disorders, insomnia and behavioural sedation in dementia patients (Maher et al., 2011). This increasing use, particularly of SGA, assumes that these drugs have few long-term adverse effects or other clinical issues. However, it has long been known that FGA are associated with a higher prevalence of extra-pyramidal symptoms (EPS), including tardive dyskinesia and akathasia, resulting in cautious use clinically (Lerner et al., 2015). Whilst the newer SGA have a much lower EPS liability (Rummel-Kluge et al., 2012), they come with different risks and challenges for patients and physicians alike. In particular, these drugs are associated with a high incidence of metabolic side effects including weight gain, metabolic syndrome and elevated risk for type-II diabetes (Mitchell et al., 2013a,b). Moreover, in recent years increasing evidence has emerged from both clinical studies and basic research to suggest a link between the dose and duration of APD treatment and a progressive loss of grey matter, which if true, may have significant clinical implications (Vita et al., 2015). Aside from the adverse effects of these medications, another