In this context, I would also like to underscore the difficulties in reliably documenting psychosocial outcomes, starting by pointing to the difficulties in assessing quality of life from either a subjective or an objective perspective in patients suffering from reality distortion. This becomes even more challenging when considering the influence of sociocultural and geopolitical diversity in larger scale multicenter, often international, clinical trials. The same holds true when considering other relevant psychosocial outcomes, such as employment rates, which differ tremendously based on regional specifics. Even within the same country, recruiting patients from diverse socioeconomic backgrounds renders the interpretation of the obtained results very difficult.

Lastly, I would like to underscore the importance of stigma and discrimination from two different points of view, namely those caused by a psychotic relapse and by the side effects of medication. Starting with the latter, those of us with enough experience in the field to still remember heavily parkinsonized and akathisic patients on antipsychotics do appreciate the fact that these side effects, albeit not totally eliminated, are, in the true sense of the word, considerably less visible with new generation antipsychotics. Apart from the subjective discomfort that patients with motor side effects experience, this also considerably lessens the stigma caused by medication, as patients are less obviously "disturbed" in their motor appearance.

On a different but related note, stigma and discrimination can also be among the sequelae of psychotic symptoms, and the negative impact that unusual, odd and sometimes dangerous behaviour can have on psychosocial (re-)integration cannot be appreciated enough. It has been well documented that reducing antipsychotic dose below a critical level, or discontinuing medication altogether, enhances the risk for residual symptoms and/or relapse[9]. In an ideal world, society may find a certain level of symptom acceptable, if the patient does not subjectively suffer, yet, unfortunately, we do not live in this ideal world, and symptoms such as those experienced by schizophrenia patients still lead to a considerable amount of stigma and discrimination, which must not be underestimated.

All in all, I fully agree with Correll et al that the bulk of the available evidence still supports the judicious evidence-based use of maintenance antipsychotic treatment in most patients suffering from schizophrenia. Involving patients and, if available, significant others in treatment considerations is a *conditio sine qua non*. In addition, regular risk/benefit assessments, as well as medication adjustments based on a monitoring of symptom and safety/tolerability levels, are an obvious requirement. Although we may not yet have the tools to provide predictive personalized medicine, individualized care based on these considerations allows to optimize management options for every person affected with this serious mental disorder.

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DOI:10.1002/wps.20542

Antipsychotic drugs: challenges and future directions

Some sixty years on from the first use of chlorpromazine to treat schizophrenia, it is worth reflecting on where we have come from. Back in the 1950s, it was not known that dopamine was a neurotransmitter, how antipsychotics worked, what symptoms they worked on, or indeed if they worked at all[1]. Now we know that dopamine is a neurotransmitter, antipsychotics are all dopamine receptor blockers and, as Correll et al[2] nicely review, large randomized, double-blind placebo-controlled trials have unequivocally demonstrated that they work both to treat acute psychotic episodes and to reduce relapse rates over the short to medium term.

Recent meta-analytic data generated from over sixty years of placebo-controlled trials estimate the standardized mean difference (SMD) between antipsychotics and placebo to be 0.38, with a greater effect seen on positive symptoms (SMD= 0.45) than negative symptoms (SMD= 0.35), quality of life (SMD=0.35) or depression (SMD=0.27)[3]. Such effect sizes are comparable to or larger than those found for treatments used for many common physical health conditions, including angiotensin-converting enzyme (ACE) inhibitors for reducing cardiac events and mortality due to hypertension (SMD= 0.16) and statins for reducing the risk of cardiac disease and stroke (SMD=0.15)[4]. Clearly, we have come a long way from the 1950s, but, despite these robust data on antipsychotics, many fundamental gaps in knowledge remain.

One glaring gap highlighted in this Forum is that as of yet we are unable to say conclusively what the optimum length of treatment with antipsychotic medication should be, once a patient has recovered from an acute episode. In current practice, many patients are treated with antipsychotic medication long-term if not lifelong, in an attempt to prevent the frequency and severity of relapses that can be so disruptive to a person's life.

Where patients are symptom free but experiencing side effects, such as weight

gain, that may shorten life as well as affect its quality, the risk-benefit balance for relapse prevention is finely poised. Yet, as Correll et al highlight, there is little evidence from randomized, double blind controlled studies to support prophylactic treatment beyond two-three years. Whilst some naturalistic studies do provide support for treatment beyond this term, the inherent limitations of these designs mean that the question remains unresolved, and guidelines cannot be conclusive.

This is a challenge to the field which needs to be met. We will need longer and, crucially, larger randomized controlled studies. This will not be easy, but other fields have risen to the challenge. For instance, in the case of the examples discussed above, statins and ACE inhibitors, there are now a number of randomized placebo-controlled trials with several thousand patients. These studies are roughly two orders of magnitude larger and five to ten times longer than the typical long-term randomized controlled study in schizophrenia. These large sample sizes give the power to have extended follow-up and account for treatment changes and drop-out. It is likely that we will need new ways of working, including international academic consortia as well as partnership with the pharmaceutical industry and governments, to achieve such large-scale studies.

Correll et al also highlight heterogeneity in schizophrenia, something that is increasingly becoming apparent in the neurobiology underlying the disorder as well as its clinical manifestations, course and treatment response[5].

Treatment resistance is probably the most clinically important manifestation of heterogeneity in patients with schizophrenia, and remains a major issue that continues to provoke debate over its pathophysiology, diagnosis and clinical management[6]. About a third of patients are thought to have treatment resistant illnesses, and around 15% show treatment resistance from illness onset[7]. Moreover, we have no way to identify the individuals whose illness will benefit from antipsychotic treatment.

Thus, large numbers of patients currently receive antipsychotic treatment although their illness is unlikely to respond to dopamine antagonists. The solutions to this will likely be found in part through identifying biomarkers that allow disease stratification, for example by the likelihood of response to dopamine receptor antagonists and, in the future, novel non-dopamine receptor blocking medication.

As both trial data and clinical experience show, current antipsychotic treatment works most effectively in reducing the positive symptoms of schizophrenia, whereas the negative and cognitive symptoms often remain problematic. Cognitive symptoms in particular are associated with poor functional outcomes in schizophrenia[8], yet our current treatments do nothing for them. In fact, there is evidence to suggest that dopamine antagonists may cause secondary negative and cognitive symptoms in people with schizophrenia[9]. Put simply, taking an antipsychotic may be unpleasant for some patients, and lead to secondary symptoms. This highlights the third challenge to the field: the need to develop treatments that are more than just antipsychotic and that patients are happy to take in the long term if necessary.

The final challenge is that our current antipsychotic medications are not disease modifying. Pre-synaptic striatal dopamine dysfunction is thought to drive the symptoms of schizophrenia[10], yet all of our current antipsychotic drugs act post-synaptically. Thus, they block the consequences of pre-synaptic dopamine dysfunction but do not address the underlying dopamine dysfunction, which remains present even after long-term treatment. This provides a neurobiological explanation for why patients may relapse on stopping antipsychotic treatment.

Targeting the upstream abnormality and/or the factors that lead to it is an alternative approach that could both be better tolerated and more effective in the long term. Broadly speaking, the glutamatergic and GABAergic systems have excitatory and inhibitory effects, respectively, on the dopamine system. Genetic studies measuring copy number variants in patients with schizophrenia[11] suggest that abnormalities in both neurotransmitter systems may be critical to the upstream regulation of dopamine. Findings like these suggest that targeting GABA and glutamate control of subcortical dopamine function could modify the pathophysiology, and potentially even be disease modifying. The interaction between psychosocial factors and biological changes[12] also highlights the potential for psychological treatments to be disease modifying.

It is clear that we have come a long way from the 1950s in terms of both understanding of the pathophysiology of schizophrenia and its treatment, and this has thrown up new questions and issues. Antipsychotic drugs are likely to remain a crucial part of our therapeutic arsenal for years to come, so it behoves us to address the questions that remain.

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DOI:10.1002/wps.20522