Antipsychotic medication in schizophrenia: a review

John Lally†,* and James H. MacCabe‡

†Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience (IoPPN), King’s College London, London, United Kingdom, and ‡National Psychosis Service, South London and Maudsley NHS Foundation Trust, London, United Kingdom

*Correspondence address. Department of Psychosis Studies, PO63, Institute of Psychiatry, Psychology & Neuroscience (IoPPN), King’s College London, De Crespigny Park, London SE5 8AF. Tel: +(0044) (0)20 7848 0216; Fax: +(0044) 020 7848 0287; E-mail john.lally@kcl.ac.uk

Accepted 1 April 2015

Abstract

Introduction: Antipsychotic medications are mainstays in the treatment of schizophrenia and a range of other psychotic disorders.

Sources of data: Recent meta-analyses of antipsychotic efficacy and tolerability have been included in this review, along with key papers on antipsychotic use in schizophrenia and other psychotic illnesses.

Areas of agreement: The heterogeneity in terms of individuals’ response to antipsychotic treatment and the current inability to predict response leads to a trial-and-error strategy with treatment choice. Clozapine is the only effective medication for treatment-resistant schizophrenia.

Areas of controversy: There are a significant number of side effects associated with antipsychotic use. With a reduction in the frequency of extrapyramidal side effects with the use of second-generation antipsychotics, there has been a significant shift in the side effect burden, with an increase in the risk of cardiometabolic dysfunction.

Growing points: There exist small and robust efficacy differences between medications (other than clozapine), and response and tolerability to each antipsychotic drug vary, with there being no first-line antipsychotic drug that is suitable for all patients.

Areas timely for developing research: A focus on the different symptom domains of schizophrenia may lead to endophenotypic markers being identified, e.g. for negative symptoms and cognitive deficits (as well as for positive symptoms) that can promote the development of novel therapeutics, which
will rationally target cellular and molecular targets, rather than just the dopamine 2 receptor. Future developments will target additional processes, including glutamatergic, cholinergic and cannabinoid receptor targets and will utilize personalized medicine techniques, such as pharmacogenetic variants and biomarkers allowing for a tailored and safer use of antipsychotics.

**Key words:** schizophrenia, antipsychotic medication, psychotic disorders

### Introduction

Antipsychotic medications are primarily indicated for the treatment of schizophrenia and other psychotic disorders [including schizoaffective disorder, delusional disorder and bipolar affective disorder (BPAD)]. They have traditionally been categorized as first-generation (formerly known as ‘typical’ or ‘conventional’) antipsychotics (FGAs) or second-generation antipsychotics (SGAs) (formerly ‘atypical’ antipsychotics). The burden of side effects associated with FGAs, in particular debilitating extrapyramidal side effects (EPSEs), led to the introduction of the SGA medications in the 1990s. The SGAs have a lower propensity to cause EPSEs (i.e. acute dystonias, akathisia, parkinsonism and tardive dyskinesia) compared with the FGAs, and these properties, aligned with their differentiating receptor profiles, led them to be labelled as ‘atypical’. The 8 SGAs that are currently licensed for use in the UK (12 in total are licensed in Europe) were modelled on the pharmacological profile of clozapine, due to its low propensity to cause EPSEs and superior effectiveness in refractory schizophrenia. The SGAs are associated with a lesser burden of EPSEs at moderate doses (though they are not free from inducing EPSEs, with some such as aripiprazole carrying a risk of akathisia of ~10%), but many are associated with increased risk of cardiometabolic abnormalities, including weight gain, dyslipidaemia and glucose dysregulation.

### Mechanism of antipsychotic action

D2 receptor antagonism in the brain is a general pharmacodynamic property of all antipsychotics; this has given rise to the hypothesis that schizophrenia involves a dysregulation of dopaminergic circuits with excess dopaminergic activity in the mesolimbic pathway (leading to positive symptoms of psychosis) and reduced dopaminergic signalling in the mesocortical pathway (leading to negative symptoms). Evidence for the dopamine hypothesis comes from not only the efficacy of D2 receptor antagonists, but also through the effects of D2 agonists such as amphetamine in precipitating psychosis and the effects of dopamine-depleting drugs such as reserpine in reducing psychotic symptoms.

Antipsychotic action has consistently been shown to occur when the occupation of striatal D2 receptors is more than 65%, but further increases in the level of D2 blockade are not associated with improved antipsychotic efficacy; rather, it leads to the onset of side effects such as EPSEs and hyperprolactinaemia. A threshold dose for EPSEs occurs when ~80% of the D2 receptors are occupied and for hyperprolactinaemia when D2 blockade exceeds 72%. Despite the association of striatal dopamine blockade with the risk of EPSEs, it is important to note that this is not the critical site of action for therapeutic effect, which occurs most prominently in the mesolimbic brain system.

### Clozapine: a special case

Clozapine is unique among antipsychotic medications and can be viewed as a standalone ‘third class’ of antipsychotic. It is the only antipsychotic medication that has proven effectiveness in treatment-resistant schizophrenia (TRS). The precise mechanism of clozapine’s superior effectiveness in TRS has not been established, but some 50–60% of patients with schizophrenia refractory to other antipsychotics will respond to clozapine. Clozapine produces robust antipsychotic effect at <65% threshold of striatal D2
receptor blockade, suggesting that beyond D2 receptor blockade in the striatum, other receptors or mechanisms also contribute to its therapeutic effect.

Clozapine and TRS are considered in greater detail in the following text.

**Clinical efficacy of FGA versus SGA**

The introduction of SGAs was thought to be a revolution in the treatment of schizophrenia. Initially, claims were made that the SGAs had better efficacy for positive and negative symptomatology and cognitive deficits as well as improved tolerability. However, over time, this initial enthusiasm and optimism for therapeutic advantages for the SGAs as a class have diminished.

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) and the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS), which compared FGAs and SGAs, failed to show a difference between FGAs and SGAs in rates of treatment discontinuation, improvement in psychotic symptoms or quality of life. CATIE further failed to demonstrate that SGAs were more effective in the reduction of negative or cognitive symptoms than FGAs. The results of CATIE and CUtLASS demonstrated similarities in treatment response, though with SGAs carrying a lower risk of tardive dyskinesia. Further evidence for clozapine’s unique position among antipsychotics was provided, with it found to be superior to other SGAs in both CATIE and CUtLASS.

In 2012, a multi-treatment meta-analysis assessing the efficacy of antipsychotic medication in randomized controlled trials (RCTs) in patients with schizophrenia demonstrated that all antipsychotic medications were significantly more effective than placebo. This showed that antipsychotics had a relapse rate of 28% compared with a relapse rate of 64% for placebo over a 7-12-month follow-up period. The effect size is comparable with that seen for many treatments for non-psychiatric disorders, such as hypertension, hypercholesterolaemia and type 2 diabetes. This indicates that antipsychotic medications are not less effective when prescribed for their target conditions, than those used by other medical specialties.

In a more recent meta-analysis, the separation of antipsychotic medications into FGA and SGA groupings has been further called into question, with similar efficacy between the groups seen. The most efficacious antipsychotics in this meta-analysis were the SGAs that were first developed, with small but robust differences seen in efficacy for amisulpride, olanzapine and risperidone (and for clozapine, but the effect for clozapine was diminished by the exclusion of studies with TRS patients).

**Antipsychotic medication and adverse effects**

In Leuchts’ meta-analysis, amisulpride proved to be the best in terms of tolerability, with less discontinuation due to side effects compared with placebo. Haloperidol was the worst drug for discontinuation rates compared with placebo. Haloperidol was identified as the medication most likely to cause EPSEs, while weight gain and metabolic dysfunction were most notably identified with the use of olanzapine and clozapine (and to a lesser extent with risperidone and quetiapine), findings that have been consistently replicated in other studies.

**Cardiometabolic adverse effects**

Higher rates of modifiable cardiovascular risk factors are seen in schizophrenia, with 33% of patients with schizophrenia meeting the criteria for metabolic syndrome throughout the course of the illness. The increased risk for cardiometabolic risk factors is multifactorial with genetic factors and the cumulative long-term effect of poor health behaviours and long-term exposure to antipsychotic drug postulated as causes.

SGAs are associated with higher rates of metabolic dysfunction compared with FGAs (though FGAs such as chlorpromazine are associated with increased cardiometabolic risk and it remains the case that the cardiometabolic risk associated with FGAs has not been as extensively studied as with SGAs). Clozapine and olanzapine both have the greatest affinity for 5-HT2C and Histamine (H) 1 receptors and the greatest weight gain potential, which can
occur early in the course of treatment, before plateauing as the treatment continues. The most dramatic weight gain is seen in antipsychotic naïve patients over the first 6 weeks of treatment and for the majority, those with initial weight gain did not lose that weight thereafter, even after switching to more weight-neutral antipsychotics. SGAs such as aripiprazole, lurasidone and asenapine have a more neutral metabolic side effect profile.

Physical health monitoring

It is recommended that all patients while treated with antipsychotics are monitored regularly for cardiometabolic risk factors. Despite this, and the cumulative cardiometabolic risk factors, monitoring of physical health parameters in those treated with schizophrenia continues to be poor. For an individual starting an antipsychotic for the first time (and for any future antipsychotic changes), the following are recommended to be monitored: weight, at baseline, then weekly for the first 6 weeks, then at 12 weeks, at 1 year, and then annually (plotted on a chart) (more frequently at the start of treatment as rapid early weight gain may predict severe weight gain in the longer term); waist circumference at baseline and then annually (plotted on a chart) (waist size or BMI have been suggested as a simple screening test for metabolic syndrome in schizophrenia); and blood pressure, fasting blood glucose, HbA1c, and blood lipid and serum prolactin levels at baseline, at 12 weeks, at 1 year, and then at least annually. Further, pharmacological and non-pharmacological interventions for weight loss and cardiometabolic dysfunction should be initiated when required.

Choice of antipsychotic

At present, there are no specific biomarkers or pharmacogenetic tests to guide the choice of treatment. According to the National institute for health and care excellence guidelines, a person presenting with a first episode of schizophrenia or a first episode of psychosis (FEP) should be offered treatment with an antipsychotic. The onset of the response to treatment is highly variable, but meta-analysis has indicated that the largest part of antipsychotic medication effect takes place within the first week (excluding the use of clozapine), and thereafter the improvements are more marginal.

If a patient does not have a response to antipsychotic treatment at 4–6 weeks, then the recommendation is to switch to an antipsychotic medication with a different receptor-binding profile. It is important to ensure that the patient is adherent to treatment and that it is not a case of medication intolerability that has led to a poor response. Antipsychotic medications should be titrated to a therapeutic dose (e.g. olanzapine 5–10 mg daily or risperidone 2–4 mg daily in the first episode of schizophrenia) in order to assess treatment response. It is only a small proportion of patients with an FEP (~15–20%) that will not have a further episode of psychosis, but at this stage of the illness, it is not possible to predict who will not relapse once maintenance treatment is discontinued.

How long to continue?

Maintenance treatment is recommended for all, with first-episode patients treated for at least 1 year, while those with multi-episodes should have treatment for at least 5 years. Further, the severity of the acute episode, namely the degree of symptomatology that somebody presents with and the risk of violence and suicidality, which may be associated with the acute episode, will increase the likelihood that longer-term maintenance treatment be recommended. The discontinuation of antipsychotic medication has been shown to be associated with a fivefold increased risk of relapse over a 5-year follow-up period compared with maintenance therapy. It is standard practice to continue the medication that was effective in the acute phase as long as it is well tolerated.

Switching antipsychotics

There are different methods for switching antipsychotic medications, if required for clinical ineffectiveness or intolerability. This may involve a crossover where one medication is gradually tapered while the second medication is concurrently titrated to its full dose. Another approach is to abruptly stop
the first drug with the introduction of the new drug at a therapeutic dose (most appropriately used in cases of acute psychosis in an inpatient setting), or the original medication is slowly discontinued and only when it is stopped will the next medication be started (best used for those with a low risk of relapse). With any switch of antipsychotic medication, the individual is at heightened risk of a deterioration and psychotic relapse or exacerbation, necessitating a close monitoring of the individuals mental state during this switching process.

**Treatment-resistant schizophrenia** (TRS) and clozapine

Approximately 30% of patients with schizophrenia will not respond to the use of FGAs or SGAs. The failure to respond to two different antipsychotics, at therapeutic doses and for a sufficient duration (generally taken to be 6-8 weeks of antipsychotic therapy) means that a person meets the criteria for treatment resistance. The only medication with proven effectiveness in this subgroup of patients with TRS is clozapine. In the UK, some 50–60% of patients will respond to clozapine, with a 30% response rate achieved at 6 weeks of clozapine treatment and a higher response rate achieved over longer treatment periods with up to 60–70% responding at 1 year. This prolonged period of ongoing clinical response over the first year of treatment is unique to clozapine among antipsychotic medications. It has been shown that clozapine does not have superior efficacy in comparison with other antipsychotics in the treatment of first-episode psychosis, reinforcing the hypothesis that TRS constitutes a subgroup schizophrenia patient population, with differences in pathological processes.

However, clozapine use varies widely depending on geography, with the prevalence of clozapine use being lower in most countries than the ~30% of patients who are likely to benefit from clozapine, and substantial evidence exists that it is only used after a delay of several years. This is partly due to the nature and degree of side effects that it can cause, including agranulocytosis, which affects some 0.8% of patients prescribed clozapine and is associated with a mortality of 1 in 10 000 of clozapine-treated patients in the UK. In the UK, clozapine is only prescribed in conjunction with the weekly measurement of the white cell count for the first 18 weeks of treatment, followed by a fortnightly white cell count measurement for the next 34 weeks and then followed by monthly white cell counts for as long as the patient is maintained on clozapine. It is likely that the fear of adverse medication reactions (by clinicians and patients alike) and the inconvenience of therapeutic monitoring of full blood counts (FBCs) so early in the course of clozapine use are factors contributing to this delay.

Clozapine is relatively free of EPSEs, though it carries a heavy burden of other adverse reactions. In addition to haematological adverse reactions, it can also cause sedation, weight gain, constipation, hypersalivation and rarely myocarditis and cardiomyopathy. However, despite the high rate of adverse effects associated with clozapine, there is evidence that it is associated with reduced mortality compared with other antipsychotics, with this reduction in mortality not entirely explained by a reduction in suicide risk.

**Medication non-adherence**

Non-adherence to medication is more common in any chronic illness, though rates of non-adherence are higher in schizophrenia than other chronic illnesses. Non-adherence with antipsychotic treatment is high, with up to 75% of patients at 2 years post hospital discharge being non-adherent with antipsychotic medication. It can occur due to intolerable side effects, lack of insight, the persistence of residual psychotic symptoms and poor therapeutic alliance. The discontinuation of antipsychotics is associated with a worse prognosis, with increased rates of relapse, rehospitalization and suicide. Partial adherence with antipsychotics is similarly associated with an increased risk of relapse and rehospitalization, when compared with complete medication adherence. Strategies to support individual adherence with medication are important to ensure that medication gaps are limited in order to improve long-term prognosis. These interventions can be particularly important in the early stages of the illness, where medication partial or non-adherence...
can have devastating effects on the longer-term illness course. Interventions include psychoeducation, motivational interviewing techniques, integration of the importance of antipsychotic use into a relapse prevention and recovery model, and a pharmacy-based intervention consisting of easy-use packaging, refill reminders and medication education.26

**Long-acting injection (depot) medications and combination/high-dose therapy**

The use of antipsychotic long-acting injections (LAIs) (also known as depots) is recommended when a patient expresses a preference for this treatment or when there is evidence of non-adherence with oral medications. The use of LAIs ensures that clinicians know when a patient has taken medication or when they stop it. It remains to be clearly established that LAIs are more effective than oral antipsychotic medication, though a recent meta-analysis indicated that LAIs had reduced rates of relapse compared with oral antipsychotics,8 with specific study designs tending to more consistently support the effectiveness of LAIs. A Finnish naturalistic study showed that the use of LAIs led to a threefold reduction in the rates of rehospitalization compared with the oral formulation of the same antipsychotic.27 However, a recent large RCT did not show superiority of risperidone LAI versus oral medications.28

Pipotiazine palmitate (Piportil®) may be associated with less-frequent EPSEs18 but is scheduled to be withdrawn from the UK market and discontinued in March 2015 (due to a global shortage of an active ingredient of the compound).

There are four LAI formulations of SGAs, namely risperidone, paliperidone, olanzapine embonate and aripiprazole; and four FGAs depot medications, namely haloperidol decanoate, flupentixol decanoate, zuclopenthixol decanoate and fluphenazine decanoate.

**Antipsychotic polypharmacy**

Combination antipsychotic treatment (i.e. two or more different antipsychotics), which is also known as antipsychotic polypharmacy, is a frequently used practice. The reported prevalence of antipsychotic polypharmacy ranges from 7 to 50%.29 There is often a lack of clear pharmacological rationale for combining antipsychotics that provide the same putative antipsychotic dopamine D2 receptor blockade and little information to know what the mechanism of action of multiple antipsychotics in the brain is. Further, combining antipsychotics can lead to high overall dose and an increased burden of adverse effects, along with an increased risk for drug–drug interactions, as well as variability in serum levels and increased difficulty for patients in remaining adherent to the treatment regimen. There is no clear evidence to support combination antipsychotics,29 and it is best to reserve the use of combination treatments for those who have a documented lack of response to antipsychotic monotherapy and who may be intolerant of clozapine, thus restricting their access to this medication. If clinicians decide to use combination antipsychotics, they should be guided by the pharmacodynamic profiles of the combined antipsychotics, with the aim of using antipsychotics with differing receptor-binding profiles.

**High-dose antipsychotic use**

The majority of side effects associated with antipsychotic treatments are dose related, and the use of high-dose antipsychotics [i.e. above British National Formulary (BNF)-licensed maximum doses] is associated with a higher rate of adverse effects (such as sedation, constipation, postural hypotension, EPSEs, QTc prolongation and sudden cardiac death). The use of high-dose antipsychotic treatment should only be used in exceptional circumstances, and care should be taken if combination antipsychotics are used, to ensure that the combined dose equivalence is not >100% of the BNF-licenced maximum dose. High-dose antipsychotic therapy is defined by the Royal College of Psychiatrists (RCPsych) as a total daily dose of a single antipsychotic that exceeds the upper limit stated in the BNF, or a total daily dose of two or more antipsychotics that exceeds the BNF maximum as calculated by percentages using the antipsychotic dose ready reckoner [example calculation: fluphenazine depot 100 mg monthly (50%) and olanzapine 15 mg daily (75%) =

\[
50\% + 75\% =
\]
125% (>100% therefore ‘high dose’)). For all those treated with high-dose antipsychotics, it is important to regularly monitor for metabolic abnormalities and for evidence of ECG changes, especially QTc prolongation.

Clinical indications for antipsychotics
Antipsychotic medications are effective in a range of disorders other than schizophrenia. In addition to their antipsychotic effects, antipsychotics may also have mood-stabilising, antimanic, antidepressant and anxiolytic effects.

Bipolar affective disorder (BPAD)
Multiple international guidelines recommend the use of antipsychotic medication in the treatment of all stages of BPAD. For acute mania, antipsychotics (particularly olanzapine, risperidone and quetiapine) along with mood stabilisers are consistently identified as primary treatment options. A recent meta-analysis identified that antipsychotics are more effective than mood stabilisers in the treatment of acute mania. Olanzapine and quetiapine are recommended first-line treatments for bipolar depression. Both quetiapine and olanzapine are associated with a rapid onset of action in bipolar depression, with efficacy demonstrated from the first week of treatment onwards. In clinical practice, quetiapine is now considered more for its mood-stabilising properties than for its antipsychotic effects. Similarly, the antipsychotics that are indicated for acute mania are generally recommended for maintenance therapy in BPAD. Clozapine has evidence of effectiveness in refractory mania and should be considered for this.

Anxiety disorders
Antipsychotic medications have long been used as augmentation strategies for anxiety disorders, with the best evidence for their use as selective serotonin reuptake inhibitor augmentation strategies in obsessive compulsive disorder (OCD) and for the use of quetiapine in generalized anxiety disorder (GAD).

Update on new antipsychotics
In the UK, several SGAs are now off patent, including risperidone, olanzapine, amisulpride and quetiapine (instant-release formulation). However, given the heterogeneous patient response to and tolerability of antipsychotics, there remains a need to improve the therapeutic efficacy of available agents and to aid choice in improving treatment tolerability for patients. The newer branded SGAs, asenapine and lurasidone, have less impact on weight and metabolic parameters than older agents such as olanzapine.
treatment of psychotic and manic symptoms of schizoaffective disorder. Its adverse effect profile is similar to that of the parent compound risperidone, with increased weight gain, hyperprolactinaemia and EPSEs at higher doses, along with case reports of tardive dyskinesia. At doses of 9–12 mg of oral paliperidone (equivalent to risperidone 4–6 mg daily), the risk of EPSEs is increased. The therapeutic dose range is 6–9 mg once daily (equivalent to risperidone 3–4 mg daily).

Paliperidone palmitate is the LAI formulation, which achieves active serum levels within days of initiation and allows deltoid, rather than gluteal muscle administration.

**Asenapine**

Asenapine has demonstrated efficacy in the acute and maintenance phases of schizophrenia treatment and in the treatment of acute mania in BPAD, but it is only currently licensed for the treatment of mania in the UK. Asenapine has high affinity for multiple serotonin receptors, with antagonism at 5-HT2A, 5-HT2C and 5-HT7 and 5-HT1A agonism, along with potent D2 and D3 antagonism and some histamine (H) 1 antagonism.

Asenapine is subject to first-pass metabolism and thus inactive if swallowed. It is, therefore, available only as an orally disintegrating tablet, meaning that it is absorbed via oral mucosa. This is in contrast to the other antipsychotic orodispersible tablets of olanzapine, risperidone and aripiprazole, all of which must be swallowed to be effective. This means that patients must be informed that asenapine cannot be swallowed and that food or drink must be avoided for at least 10 min after administration.

Asenapine does not require dose titration and can be dosed at 5 mg bd for acute schizophrenia with doses of up to 10 mg twice daily shown efficacy in preventing relapses in schizophrenia. Asenapine has a half-life of 24 h and as such could theoretically be prescribed as a once-daily medication, but the efficacy of a once-daily prescription remains to be studied in trials. It appears to be a metabolically neutral antipsychotic with low propensity to cause weight gain (though some evidence for a higher propensity for weight gain in acute mania exists) and has little effect on prolactin levels. It can cause akathisia (increased occurrence at 10 mg twice-daily dosing compared with 5 mg twice daily), sedation and taste disturbance.

**Lurasidone**

Lurasidone is licensed for the treatment of schizophrenia and has shown efficacy as an adjunctive treatment for bipolar depression, and it is a licensed therapy for bipolar depression in the USA.

Lurasidone has full D2 antagonism and is an antagonist at 5HT2A and 5HT7 receptors, with partial agonism at 5-HT1A receptors, and with low affinity for 5HT2C, H1 and muscarinic receptors. Lurasidone is a once-daily prescription, simplifying its administration. It is dosed in adults at 37 mg once daily initially and increased if necessary to a maximum of 148 mg once daily. For schizophrenia, a dose range of 37–148 mg daily is recommended, with a lower dose range of 18.5–120 mg daily, recommended for bipolar depression (lurasidone at lower doses of 20–60 mg daily has been shown to be as clinically efficacious in bipolar depression, as at the higher dose range of 80–100 mg/day). Lurasidone is metabolized by CYP3A4 enzymes, meaning that its dose should be reduced when used with concomitant CYP3A4 inhibitors (e.g. diltiazem, erythromycin).

Lurasidone is generally well tolerated, with low incidences of weight gain and metabolic dysfunction. It is associated with akathisia (increased incidence at doses of 120 mg or greater), sedation and nausea, but similarly to asenapine, despite being a full D2 antagonist, it is not associated with higher incidences of EPSEs (excluding akathisia) and hyperprolactinaemia.

**Conclusions**

**Maintaining the status Quo in antipsychotic treatment**

It remains the case that there has been no fundamental innovation in psychopharmacology for schizophrenia since the discovery of clozapine in the late 1950s. This is further exacerbated by the recent retreat of the pharmaceutical industry away from
research and development in psychiatric disorders. For all the benefits bought by antipsychotics and the initially perceived advantages of SGAs, we are still working with medications that are not fully effective and often carry significant adverse effect burdens.

SGAs or FGAs?

Despite the lack of clear-cut differences in clinical efficacy between SGAs and FGAs (with the exception of clozapine), the introduction of the SGAs from the early 1990s onwards represented meaningful steps in attempting to improve pharmacotherapy for patients with schizophrenia. While we are improving our knowledge of what different treatments can and cannot do, we still remain a long way from being able to recommend with precision, specific treatments for individual patients, in terms of the clinical response and lack of adverse events. There is also no longitudinal evidence to support attempts to identify those patients who will and who will not require long-term antipsychotic medication with FGAs or SGAs.

Change in approach to medication development

There is a growing consensus in academic psychiatry, acknowledging that schizophrenia is not a single disease entity and that the positive symptoms of psychosis (delusions, hallucinations) which antipsychotics work best to treat, are only one aspect of the disorder’s pathology. We need to focus future pharmaceutical development on symptoms domains of schizophrenia, with a particular need for treatments to target negative symptoms and cognitive impairments in schizophrenia. A more concentrated focus on the different symptom domains may lead to endophenotypic markers being identified for negative symptoms and cognitive deficits (as well as for positive symptoms) that can promote novel medication discovery. If medications are discovered for separate symptom domains of schizophrenia, then we could expect to be able to develop concurrent medication strategies, with antipsychotics used in combination with medications for negative symptoms or along with those that have cognitive enhancing effects.

Novel therapeutic strategies

Our current level of knowledge regarding the pathogenesis of schizophrenia continues to improve, leading to the hope that in future novel therapeutics that will rationally target cellular and molecular targets, rather than just the D2 receptor, can be developed. All antipsychotic medications that have been developed over the past six decades have been based on the targeting of D2 receptors, and later the characteristic 5-HT2A antagonism of SGAs. Future developments will target additional processes, including glutamatergic, cholinergic and cannabinoid receptor targets, and the emerging field of pharmacogenetics will aim for treatments to be tailored to individual patients in terms of efficacy and tolerability.

Conclusion

The heterogeneity in terms of individuals’ response to antipsychotic treatment and the current inability to predict response leads to a trial-and-error strategy with treatment. It remains the case that we are no closer to mirroring the effects of clozapine in TRS, with its mechanism of action proving elusive to identify and replicate in other antipsychotic therapies for schizophrenia.

Funding

Dr Lally and Dr MacCabe are both supported by CRESTAR (CRESTAR project, http://www.crestar-project.eu/) EU-FP7 grant number 279227; Dr MacCabe is supported by STRATA (MRC grant no. MR/L011794/) and by the National Institute for Health Research (NIHR), Biomedical Research Centre for Mental Health at the South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, Psychology and Neuroscience, Kings College London.

The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Conflict of Interest statement

None declared.


29. Correll CU, Rummel-Kluge C, Corves C, et al. Antipsychotic combinations vs monotherapy in schizophrenia:


