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NEWER ATYPICAL ANTIPSYCHOTICS IN SPECIAL POPULATIONS

SUMMARY

-  There is no one definitive antipsychotic switching method, however certain strategies may be more appropriate in individual cases.
-  By definition, atypical antipsychotics are associated with a lower incidence of extrapyramidal effects.
-  Atypical antipsychotic drugs should be used with caution in patients with cardiovascular disease.
-  The lower propensity of the atypical antipsychotics to cause adverse effects is of particular benefit in the elderly.



Weight gain is associated, to varying degrees, with all the atypical antipsychotics, but may be managed by appropriate strategies.

SWITCHING TO AN ATYPICAL ANTIPSYCHOTIC

There are situations where it may be appropriate to switch a patient's therapy from a 'typical' or 'conventional' antipsychotic to an atypical antipsychotic, or from one atypical to another. These include persistent positive or negative symptoms, relapse despite compliance, severe adverse effects, non-compliance due to adverse effects, non-compliance with clozapine monitoring requirements, or patient request. The greatest concern in changing the medication of a stable patient is the potential risk of exacerbation of psychotic symptoms during the crossover process. It would be inadvisable to switch to an atypical antipsychotic if the patient has had an excellent response to a conventional agent, if the patient has recently recovered from an acute psychotic episode and is on the same medication successfully used to treat that episode, or if the patient was recently noncompliant with oral medication and is now compliant with a depot antipsychotic.^{1,2,3}

Various strategies have been suggested for switching a patient from a typical antipsychotic to an atypical antipsychotic, or from one atypical to another. There is no one definitive switching method, however certain strategies may be more appropriate in individual cases.^{1,2} Ultimately the method used must be individualised to the patient, and should include appropriate monitoring for effectiveness, adverse reactions, withdrawal symptoms and drug interactions.^{1,2,4} The timing of the switch is important and should not coincide with major life stress events.^{1,2} Switching medications at a time of relapse and rehospitalisation may be appropriate, as the additional monitoring needed during the switching process is already in place.²

One approach to switching oral medications is to discontinue the previous drug before the new drug is started. The switch may be immediate, or there may be a drug-free interval (which reduces the risks of combined adverse effects and drug interactions). In order to reduce the risk of relapse, an alternative strategy is to temporarily overlap the two drugs in either a partial or a full overlap. In the former method, the new drug is added while slowly tapering the previous drug; in the latter, the new drug is added to the therapeutic dose of the previous drug, and the previous drug is then slowly tapered. The disadvantages of an overlap are an increased risk of combined adverse effects, drug interactions, and medication errors due to the complexity of the regimen.^{1,2,4}

It is preferable to gradually taper the dose when discontinuing an oral antipsychotic, irrespective of which switching method is used. This is in order to minimise withdrawal symptoms and to reduce the risk of psychotic relapse.^{2,4,5,6} Depot medication may be stopped abruptly, since the plasma concentration of the drug declines very slowly and withdrawal reactions have not been reported.^{1,4} The atypical replacement medication can be commenced on the date the next depot would otherwise be due.^{1,6}

Anticholinergic medication is sometimes used to treat the extrapyramidal side-effects of conventional antipsychotics. It is not usually needed once the switch to an atypical antipsychotic is complete, but continued use for a short period may be necessary to prevent cholinergic rebound.^{4,6,7} When discontinuing the anticholinergic drug, slow tapering of the dose is recommended.^{1,2,4}

EXTRAPYRAMIDAL SYMPTOMS

One of the defining characteristics of atypicality is a reduced tendency, compared to conventional antipsychotics, to cause extrapyramidal symptoms (EPS).⁸ Acute EPS include dystonic reactions, akathisia, and pseudoparkinsonism.¹ Tardive dyskinesia (TD) is a delayed EPS that causes particular concern, as, unlike the acute EPS, it is potentially irreversible. *Acute* EPS have been identified as risk factors for (TD), so it is postulated that the atypical antipsychotics with their diminished risk of EPS, should also have a reduced risk of TD.^{9,10} Atypical antipsychotics appear

to cause less TD than typical antipsychotics, although longer-term studies are needed to confirm this.^{9,10,11,12,13}

Neuroleptic Malignant Syndrome is an infrequent but potentially fatal extrapyramidal adverse effect of antipsychotic drugs.¹⁴ Rare cases have been reported with all atypical antipsychotics.^{15,16,17,18,19,20}

Clozapine and quetiapine have a minimal risk of EPS across their therapeutic dose ranges.^{7,19,21,22,23} The incidence of EPS with risperidone and amisulpride is dose-related; however it is low at usual therapeutic doses.^{24,11,19,25} Olanzapine is also associated with a lower incidence of EPS than conventional antipsychotics.²⁶ Clozapine is potentially useful for treating EPS caused by previous conventional antipsychotic therapy.²⁷ In particular, it has been shown to improve pre-existing TD in some cases.^{11,10,19,27} There is limited evidence to suggest that olanzapine, and possibly risperidone, may be useful treatment options in patients at risk of TD.¹¹ Case reports suggest that olanzapine may also improve pre-existing TD.^{19,26,28}

CARDIOVASCULAR ADVERSE EFFECTS

Interest in the cardiovascular adverse effects of antipsychotic agents has increased in recent years, particularly since the restriction of thioridazine to second-line treatment in adult schizophrenia only. This was due to reports of QTc interval (heart-rate-corrected QT interval) prolongation with thioridazine use.^{29,30} Lengthening of the QTc interval can be associated with various ventricular arrhythmias, syncope and sudden death, and with a potentially fatal ventricular tachycardia known as torsade de pointes (TdP).^{31,32,33} QTc prolongation has been reported for all atypical antipsychotics, with varying incidences and degrees of severity.³⁴ The atypical antipsychotics can also cause other cardiovascular adverse effects, e.g. orthostatic hypotension.³²

Risk factors for cardiovascular adverse effects with the atypical antipsychotics include known cardiovascular disease, electrolyte disturbances (particularly hypokalaemia and hypomagnesaemia), genetic characteristics, increasing age, female sex (for QTc lengthening and TdP), autonomic dysfunction, high doses, the use of interacting drugs, and psychiatric illness itself.^{11,35,36,31,32} Atypical antipsychotics should be used with caution in patients with cardiovascular disease, or other conditions or medications which pre-dispose to hypotension, or who are being treated with drugs that prolong the QTc interval (e.g. erythromycin, clarithromycin, antiarrhythmic drugs etc.).^{37,38,39} In any patient with pre-existing cardiac disease, a pre-treatment ECG with routine follow-up is recommended.¹² Rapid dose escalation of antipsychotics should be avoided in cardiac disease.⁴⁰

Clozapine is contra-indicated in cardiac failure. In patients suffering from cardiovascular disorders, the initial dose should be 12.5mg given once on the first day, and dosage increase should be slow and in small increments.¹⁷ Cardiovascular adverse effects associated with clozapine include tachycardia, postural hypotension, with or without syncope, and less commonly hypertension. These are most common early in treatment and are related to rapidity of titration.^{41,42} Patients generally develop tolerance, although hypotension can persist in some patients.⁴² ECG changes may occur and there have been rare cases of cardiac arrhythmias, pericarditis, cardiomyopathy, myocarditis, thromboembolism and circulatory collapse (with cardiac and respiratory arrest).^{17,31,40,32}

Risperidone can occasionally cause orthostatic dizziness, hypotension including orthostatic hypotension, tachycardia including reflex tachycardia, and hypertension. Orthostatic hypotension can occur, especially during the initial dose-titration period. Dose reduction should be considered if hypotension occurs. Trials have also reported palpitations and rarely ECG changes (including QTc interval prolongation).^{32,37,43,8,44}

Olanzapine was not associated with a persistent increase in absolute QT intervals in clinical trials. An increase in the QTc interval has been seen rarely. Orthostatic hypotension and oedema are

common side effects with olanzapine. Bradycardia, with or without hypotension or syncope, has occurred less commonly.^{1,18}

Amisulpride can occasionally cause hypotension and bradycardia. Isolated cases of QT prolongation have been reported.^{45,46,47}

Quetiapine may commonly induce orthostatic hypotension, associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period. A dose reduction or more gradual titration should be considered if orthostatic hypotension occurs. In clinical trials, quetiapine was associated with a small mean decrease in QTc. However, QTc prolongation was also reported for a small number of patients. None of these changes were associated with any clinical sequelae. Quetiapine should be used with caution in patients with known cardiovascular or cerebrovascular disease.^{16,20}

ELDERLY

The development of atypical antipsychotics, with their lower propensity to cause adverse effects and cognitive impairment, offers potential benefits to older patients. The use of antipsychotics in the elderly deserves special mention as the elderly present particular clinical challenges, and antipsychotics are among the most frequently prescribed medications in this age group. The elderly have increased sensitivity to all medications as a consequence of age-related changes in pharmacokinetics, and altered hepatic and renal metabolism. The elderly patient with psychosis or behavioural problems with symptoms of dementia is also likely to have comorbid illnesses, and potential drug interactions need to be carefully considered.^{48,49} Side-effects that need to be especially considered in the elderly include EPS, in particular TD and pseudoparkinsonism, anticholinergic effects, orthostatic hypotension (with risk of falls), cardiac conduction defects, reduced bone mineral density secondary to hyperprolactinaemia, sedation and cognitive slowing.⁴⁸

The general advice regarding prescribing in this population is to start low, usually one half to one third of the usual adult dose, to titrate slowly and to monitor clinical response and any potential adverse effects closely, both in the short and long term.⁴⁰ Non-essential medication should be avoided where possible, and patients with comorbid conditions should be monitored closely to avoid drug interactions. Additional clinical trials are needed to determine which agents are most efficacious and best tolerated in this age group.

ANTIPSYCHOTICS FOR AGITATION

In clinical practice, antipsychotic medications are frequently used to control severe behavioural disturbances such as agitation. Agitation can be broadly defined as a combination of symptoms including aggressiveness, hyperactivity, disinhibition, wandering and restlessness. It is interesting to note that in the US until 1999, it was estimated that more than 70% of prescriptions for the atypical antipsychotics were for conditions other than schizophrenia.⁵⁰ The optimal treatment of agitation is a combination of behavioural and pharmacological intervention, with the ideal agent having a rapid onset of action and minimal somatic and cognitive side-effects.⁵¹ Traditional antipsychotics have been the mainstay of treatment for agitation and behavioural disturbances in patients with dementia, however they are limited by their lack of efficacy and high risk of adverse effects, which include worsening of already poor cognitive function.⁵²

Thioridazine previously was a common treatment for anxiety, agitation and restlessness in the elderly, although is no longer indicated in this setting. When choosing a suitable drug as an alternative to thioridazine, it is important first to re-evaluate the patient, as non-drug measures may be more appropriate. If thioridazine was being used primarily for its antipsychotic properties, then another antipsychotic agent would be appropriate. No one specific antipsychotic is recommended as choice will depend on the individual patient and the likelihood of adverse effects. Psychomotor agitation and restlessness can be managed with low doses of the typical antipsychotic haloperidol. More recent experience suggests that the atypical antipsychotics olanzapine, risperidone and quetiapine are also useful for the short-term management of agitation

and aggression, and for the psychotic manifestations of dementia.^{51,53,54} Alternative agents include trazodone and the anticonvulsant valproate in severe agitation (unlicensed). The benzodiazepines have a limited place in this setting as they can lead to tolerance, dependence and worsening of memory and cognition.⁵²

BODY WEIGHT

The tendency of the newer antipsychotics to induce weight gain needs to be considered in all patients. Antipsychotic-induced weight gain has been shown to affect compliance with subsequent relapse rates, in addition to the known long term effects of obesity on mortality and morbidity (e.g. hypertension, heart disease, diabetes mellitus, stroke, osteoarthritis, sleep apnoea and certain cancers). It is also important to question how much of the weight gain is attributable to medication. There is evidence that patients with schizophrenia, especially women, are more likely to be obese than individuals without schizophrenia.^{55,56} When assessing the impact of medication on weight, it is necessary to consider other causes such as thyroid dysfunction, hyperphagia associated with depression, polydipsia, pregnancy, oedema or recent smoking cessation. The patient may also be on other medications such as lithium, the anticonvulsants valproate or carbamazepine, or tricyclic antidepressants which are all known to affect weight.

Both the traditional and newer antipsychotics are associated with weight gain. A meta-analysis of 81 studies involving over 30,000 patients looked at weight changes associated with antipsychotic medication at standard doses. Of the newer agents, clozapine was associated with the greatest potential to induce weight gain, followed by olanzapine. Risperidone had intermediate risk for inducing weight gain and there was insufficient information to evaluate quetiapine. Amisulpride was not included in the analysis.⁵⁷ Another paper reviewing reports of weight gain with the different antipsychotics concluded that based on available evidence, quetiapine is the antipsychotic which is least likely to induce weight gain.⁵⁸ Clozapine and olanzapine treated patients tend to gain weight over a more prolonged period of time (~20 weeks), whereas risperidone treated patients have a more limited period of weight gain.⁵⁹

The underlying pathophysiology of weight gain with antipsychotics remains unclear. Proposed mechanisms are their antihistaminergic, serotonergic, dopaminergic or anticholinergic effects. Studies have shown that clozapine,^{60,61} and olanzapine⁶² may induce an increase in serum triglyceride levels, although there is no substantial evidence showing an association between serum cholesterol and triglyceride levels and body weight. An increase in the adipocyte-derived hormone leptin, which correlates positively with body fat, has been shown to be associated with olanzapine and clozapine administration.⁶³

Prevention should be the main aim of managing antipsychotic induced weight gain. Medical and psychiatric examinations should include periodic monitoring for weight change, with assessments made for individual risk factors for obesity-related medical illness. Treatment strategies may be either behavioural or pharmacological, with the importance of healthy diet and exercise advised in all patients. Unlicensed pharmacological agents that have been used include topiramate, H2 antagonists and serotonin reuptake inhibitors, although the evidence supporting their use in this setting is limited.⁶⁴ Sibutramine is contraindicated in patients with psychiatric illness.⁶⁵ Further clinical studies are needed before orlistat can be recommended in this patient population.⁶⁶ Switching to a different atypical antipsychotic that is less likely to produce weight gain should also be considered.

TREATING CHILDHOOD AND ADOLESCENT SCHIZOPHRENIA

Approximately 10-30% of patients with schizophrenia develop psychosis before 18 years of age, and it is therefore understandable that despite being **unlicensed** for this age group, antipsychotics are frequently prescribed to younger patients for schizophrenia and other

neuropsychiatric conditions. Characteristics of early onset schizophrenia are a male predominance (2:1 ratio), a high prevalence of premorbid expression and often poor outcome. Onset of schizophrenia is rare before 13 years but rises sharply in adolescents. Important differentials to exclude are mood disorders, developmental disorders, non-psychiatric emotional and behavioural disturbances, organic brain disorder and substance abuse.

Atypical antipsychotics, compared to traditional agents, are particularly suited to younger patients because of their tolerability profiles and efficacy.⁷³ Most of the studies to date have been open, uncontrolled and of short duration in small patient populations and hence limit the conclusions that can be made in this age group. Of the atypical agents, clozapine, risperidone and olanzapine have been the most widely studied. The American Academy of Child and Adolescent Psychiatry has released a practice parameter for the assessment and treatment of children and adolescents with schizophrenia.⁶⁷ Their treatment strategies incorporate antipsychotic medication with psychoeducational, psychotherapeutic and social and educational support programmes.

Clozapine was the first of the atypical agents to be used in the treatment of early onset schizophrenia. In one of the few double-blind controlled studies published, clozapine was superior to haloperidol for the positive and negative symptoms in treatment-refractory childhood-onset schizophrenia.⁶⁸ Side-effects may be more prevalent in the paediatric population as in this study, although numbers were small: 5 of the 10 patients treated with clozapine developed significant neutropenia, and 2 had a seizure. Of the other atypicals, risperidone remains the most widely studied and has been used in treating children and adolescents with schizophrenia as well as other neuropsychiatric disorders such as Tourette's syndrome, conduct disorder and aggressive behaviour.^{69,70,71,72} A 6-week open-label pilot study was conducted in 10 children between 11 and 18 years with schizophrenia. In all patients, risperidone produced clinical improvement. Olanzapine⁷⁴ and quetiapine⁷⁵ have also been found to improve symptoms in children with schizophrenia. Sedation was the most frequent side-effect but was transient in most patients.

For details of the individual atypical antipsychotics in elderly patients, in patients with cardiovascular disease, renal or hepatic impairment, in pregnancy and lactation, and switching guidelines, refer to the manufacturers' Summary of Product Characteristics.

References for the bulletins "Newer Atypical Antipsychotics" and "Newer Atypical Antipsychotics in Special Populations" are available on request.

Every effort has been made to ensure that this information is correct and is prepared from the best available resources at our disposal at the time of issue. Prescribers are recommended to refer to the drug data sheet or summary of product characteristics (SPC) for specific information on drug use.

