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PrescQIPP Community Interest Company

Antipsychotic drugs

This bulletin reviews the appropriateness of antipsychotic prescribing for the management of psychosis (including schizophrenia and bipolar disorder) and offers guidance and support material for organisations considering reviewing the prescribing of antipsychotic drugs as a QIPP project.

Please note: This bulletin focuses on drugs for psychosis only. It does not include prescribing antipsychotic drugs for patients with dementia (they should not be used long- term in this group of patients). Please refer to the PrescQIPP reducing antipsychotic prescribing in dementia toolkit for more information on this: https://www.prescqipp.info/our-resources/bulletins/t7-reducing-antipsychotic-prescribing-in-dementia/

Recommendations

- Do not start antipsychotic medication for a first presentation of sustained psychotic symptoms in primary care unless it is done in consultation with a consultant psychiatrist. For children and young people (under the age of 18), this should be a consultant psychiatrist with training in child and adolescent mental health.
- Only consider the use of antipsychotic medication during periods of relapse or symptom exacerbation on an 'as required' or prn basis for people with psychosis or schizophrenia who are unwilling to accept a continuous maintenance regimen or if there is another contraindication to maintenance therapy, such as side-effect sensitivity.
- Where a patient is taking an antipsychotic intermittently, clinical indications, frequency of administration, therapeutic benefits and side effects should be reviewed each week or as appropriate.
- The secondary care team should maintain responsibility for monitoring the patients physical health and the effects of antipsychotic medication for at least the first 12 months or until the person's condition has stabilised, whichever is longer.
- Responsibility for prescribing and monitoring antipsychotics in primary care should always be done under formal shared care arrangements if the primary care prescriber is willing to take this on.
- Refer to the relevant National Institute for health and Care Excellence (NICE) guidance for further information on prescribing antipsychotics for people with depression or bipolar disorder.
- Toxicity in overdose should be taken into account when prescribing psychotropic medication during periods of high suicide risk. The need to limit the quantity of medication supplied to reduce the risk to life if the patient overdoses should be assessed.
- In the absence of more available evidence of the risks versus the benefits of long-term treatment, it would seem prudent for the patient's psychiatrist to regularly review the benefit to each patient of continuing prophylactic antipsychotics against the risk of side-effects.
- The lowest effective dose that prevents the return of distressing symptoms should be used for prophylaxis of psychosis. A trial of a slow withdrawal may be undertaken once the patient is sufficiently stabilised if the patient and the consultant psychiatrist deems this appropriate.

Recommendations

- Any withdrawal of antipsychotic medication should be undertaken gradually and the patient monitored regularly for signs and symptoms of relapse. This monitoring should continue for at least two years after withdrawal.
- Consider switching all patients prescribed quetiapine modified release (MR) to an equivalent dose of the immediate release (IR) formulation unless there is a clinical reason for an MR preparation (e.g. patients who do not tolerate quetiapine IR but are able to tolerate MR or where adherence with twice daily dosing may be an issue).
- Patients prescribed a more costly orodispersible preparation (aripiprazole, olanzapine or risperidone), where this is not clinically indicated (e.g. for swallowing difficulties, patients who are PEG fed or for patients with compliance issues), should be reviewed to determine the appropriateness of switching to a more cost-effective formulation.
- Patients still requiring an orodispersible formulation of olanzapine, should be switched to the same dose of generic orodispersible sugar free tablets as these are more cost-effective.
- Patients requiring a liquid formulation of an antipsychotic should be reviewed to determine their appropriateness for switching to a more cost-effective formulation.
- All switches of formulations of antipsychotic drugs should be on specialist advice only with the appropriate shared care agreement updated accordingly, with the exception of switching olanzapine orodispersible to a more cost-effective orodispersible formulation, and quetiapine MR to IR if agreed locally.
- As always, switches should be tailored to the individual patient.

National guidance

Background

Psychotic symptoms include:[1,2]

- Hallucinations - hearing voices and sometimes seeing things that are not really there.
- Delusions - believing that something is real or true when it is not, such as believing they are being watched or having their thoughts monitored.
- Negative symptoms such as emotional apathy, lack of drive, poverty of speech, social withdrawal and self-neglect.

For most people, the symptoms start when they are young adults, but they can happen at any age. The first time a person has these symptoms is called a 'first episode of psychosis'. Some people only ever have one episode of psychosis, but others may have more than one.[1]

There are different types of psychosis; schizophrenia is one type, but psychosis can also sometimes occur in people with bipolar disorder or depression.[2-6]

Antipsychotic medication, alongside cognitive behavioural therapy (CBT) and family intervention, are the mainstays of treatment for new onset, an acute exacerbation or recurrence of psychosis or schizophrenia[1-3]

Treatment choice

For adults, the choice of antipsychotic medication should be made by the person with schizophrenia, bipolar disorder or depression and the healthcare professional together, taking into account the views of the carer if the person agrees.[2,4,6]

For children, the choice of antipsychotic medication should be made by the parents or carers of younger children, or jointly with the young person and their parents or carers, and healthcare professionals.[3,5,6]

Baseline investigations

Before starting antipsychotic medication, the following baseline investigations should be undertaken and the results recorded:[2,3]

- Weight (and height for children and young people) plotted on a chart.
- Waist (and hip for children and young people) circumference.
- Pulse and blood pressure.
- Fasting blood glucose, glycosylated haemoglobin (HbA1c), blood lipid profile and prolactin levels.
- Assessment of any movement disorders.
- Assessment of nutritional status, diet and level of physical activity.
- Electrocardiogram (ECG), if indicated – see below.

Before starting antipsychotic medication, the person with psychosis or schizophrenia should be offered an ECG if:[2,3]

- Specified in the summary of product characteristics (SPC) – for children and young people this includes if it is specified in the SPC for adults and/or children.
- A physical examination has identified specific cardiovascular risk (such as diagnosis of high blood pressure).
- There is a personal history of cardiovascular disease.
- For children and young people, if there is a family history of cardiovascular disease such as premature sudden cardiac death or prolonged QT interval.
- The person is being admitted as an inpatient.

Treatment initiation

Antipsychotic medication should not be started for a first presentation of sustained psychotic symptoms in primary care unless it is done in consultation with a consultant psychiatrist.[2] For children and young people (under the age of 18), this should be a consultant psychiatrist with training in child and adolescent mental health.[3]

Treatment with antipsychotic medication should be considered an explicit individual therapeutic trial.[2,3]

The following should take place at treatment initiation:[2,3]

- Discussion and recording of the side effects that the person is willing to tolerate.
- Recording of the indications and expected benefits and risks of oral antipsychotic medication, and the expected time for a change in symptoms and appearance of side effects.

Any non-prescribed therapies that the service user wishes to use (including complementary therapies), along with the use of alcohol, tobacco, prescription and non-prescription medication and illicit drugs should be discussed with the person, and carer if appropriate. The safety and efficacy of other therapies, and possible interference with the therapeutic effects of prescribed medication and psychological treatments should be discussed.[2]

At the start of treatment, the dose given should be at the lower end of the licensed range for adults. If the treatment is for a child or young person and it is not licensed for their age group, give a dose below the lower end of the licensed range for adults, or at the lower end of the licensed range if the drug is licensed for children and young people.

Titrate slowly upwards within the dose range given in the British National Formulary (BNF), the British National Formulary for Children (BNFC) or SPC. Any reasons for dosages outside the range given in the BNF, BNFC or SPC must be justified and recorded.[2,3]

Once the optimum dosage is reached, after titration of the dose, a trial of the medication should be carried out for four to six weeks.[2,3] The rationale for continuing, changing or stopping medication, and the effects of such changes should be recorded.[2,3]

Antipsychotic medication should not be offered to people considered to be at increased risk of developing psychosis or with the aim of decreasing the risk of or preventing psychosis.[2,3]

Antipsychotic medication should also not be offered to children or young people for psychotic symptoms or mental state changes that are not sufficient for a diagnosis of psychosis or schizophrenia.[3]

A loading dose of antipsychotic medication (often referred to as 'rapid neuroleptisation') should not be used.[2,3]

Although the mainstay of treatment for psychosis and schizophrenia has been antipsychotic medication, there is limited evidence of its efficacy in children and young people.[3]

In addition, most antipsychotic medication does not have a UK marketing authorisation specifically for children and young people.[3] The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's (GMC) Prescribing guidance: prescribing unlicensed medicines and 0-18 years: guidance for all doctors for further information.[7,8]

Intermittent dosage strategies

Targeted, intermittent dosage maintenance strategies (the use of antipsychotic medication only during periods of incipient relapse or symptom exacerbation on an 'as required' or prn basis) should not be routinely used. They can, however, be considered for people with psychosis or schizophrenia who are unwilling to accept a continuous maintenance regimen or if there is another contraindication to maintenance therapy, such as side-effect sensitivity.[2]

Where a patient is taking an antipsychotic intermittently, clinical indications, frequency of administration, therapeutic benefits and side effects should be reviewed each week or as appropriate. It is important to check whether 'prn' prescriptions have led to a dosage above the maximum specified in the BNF or SPC.[2]

Depot/long-acting injectable antipsychotics

Depot/long-acting injectable antipsychotic medication can be considered for the following people with psychosis or schizophrenia:[2]

- Those who would prefer such treatment after an acute episode.
- Where avoiding covert non-adherence (either intentional or unintentional) to antipsychotic medication is a clinical priority within the treatment plan.

When initiating depot/long-acting injectable antipsychotic medication, a small test dose should be used initially as set out in the BNF or SPC and the following should be taken into account:[2]

- The person's preferences and attitudes towards the mode of administration (regular intramuscular injections) and organisational procedures (for example, home visits and location of clinics).
- The same criteria recommended for the use of oral antipsychotic medication in relation to the risks and benefits of the drug regimen.

Psychological interventions without an antipsychotic

Advise people who want to try psychological interventions alone that these are more effective when delivered in conjunction with antipsychotic medication.[2,3]

If the person still wants to try psychological interventions alone:[2,3]

- Offer family intervention and CBT.

- Agree a time (one month or less) to review treatment options, including introducing antipsychotic medication.
- Continue to monitor symptoms, distress, impairment and level of functioning (including education, training and employment) regularly.

Review and ongoing monitoring

The secondary care team should maintain responsibility for monitoring the person's physical health and the effects of antipsychotic medication for at least the first 12 months or until the person's condition has stabilised, whichever is longer. Thereafter, the responsibility for this monitoring may be transferred to primary care under shared care arrangements.[2,3]

The following should be regularly and systematically monitored and recorded throughout treatment, but especially during titration:[2,3]

- Response to treatment or efficacy, including changes in symptoms and behaviour.
- Side effects of treatment, taking into account overlap between certain side effects and clinical features of schizophrenia (for example, the overlap between akathisia and agitation or anxiety) and impact on functioning.
- The emergence of movement disorders.
- Weight, weekly for the first six weeks, then at 12 weeks, at one year and then annually (plotted on a chart or growth chart for children).
- For children and young people, height every six months (plotted on a growth chart).
- Waist circumference annually for adults (plotted on a chart) and every six months for children and young people (plotted on a percentile chart).
- Pulse and blood pressure at 12 weeks, at one year and then annually for adults and every six months for children and young people (plotted on a percentile chart).
- Fasting blood glucose, HbA1c and blood lipid levels at 12 weeks, at one year and then annually for adults and every six months for children and young people also including prolactin levels.
- Adherence.
- Overall physical health.

Antipsychotic medication should be reviewed annually, including observed benefits and any side effects.[2,3]

Shared care

People with psychosis or schizophrenia whose symptoms have responded effectively to treatment and remain stable should be offered the option to return to primary care for further management under a shared care arrangement.[2,3] Children and young people with psychosis or schizophrenia who are being treated in an early intervention in psychosis service should have access to that service for up to three years (or until their 18th birthday, whichever is longer) whatever the age of onset of psychosis or schizophrenia.[3]

As previously mentioned, the secondary care team should maintain responsibility for monitoring the person's physical health and the effects of antipsychotic medication for at least the first 12 months or until the person's condition has stabilised, whichever is longer.[2,3]

This does not include clozapine, which should be prescribed in secondary care only.

The shared care arrangements set out how responsibilities, particularly for ongoing monitoring, will be shared between the specialist and the primary care prescriber. If the primary care prescriber does not feel comfortable taking this on, for whatever reason, there is no obligation to do so but this should be

communicated to the specialist as soon as possible. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist.[7]

Depression and antipsychotics

For depression unresponsive to treatment, for recurrent depression or psychotic depression, combining or augmenting an antidepressant with an antipsychotic such as aripiprazole, olanzapine, quetiapine or risperidone can be considered as an option if a person with depression is informed about, and prepared to tolerate, the increased side-effect burden.[4]

This is an off-label use of the antipsychotics, with the exception of quetiapine which is licensed as an add-on treatment of major depressive episodes in patients with major depressive disorder (MDD) who have had sub-optimal response to antidepressant monotherapy.[9,10]

For children and young people with psychotic depression, augmenting the current treatment plan with a second-generation antipsychotic medication should be considered, although the optimum dose and duration of treatment are unknown.[5]

Refer to the NICE clinical guidelines Depression in adults: recognition and management [CG90] and Depression in children and young people: identification and management [CG134] for further information.[4,5]

Bipolar disorder and antipsychotics

For mania or hypomania, haloperidol, olanzapine, quetiapine or risperidone can be offered if an antipsychotic or mood stabiliser is not being taken already, taking into account any advance statements, the person's preference and clinical context (including physical comorbidity, previous response to treatment and side effects).[6]

If the first antipsychotic is poorly tolerated at any dose (including rapid weight gain) or ineffective at the maximum licensed dose, an alternative antipsychotic may be offered.[6]

Toxicity in overdose should be taken into account when prescribing psychotropic medication during periods of high suicide risk. The need to limit the quantity of medication supplied to reduce the risk to life if the person overdoses should be assessed.[6]

Refer to the NICE clinical guideline on Bipolar disorder: assessment and management [CG185] for further information.[6]

For young people with mania or hypomania

Aripiprazole is recommended as an option for treating moderate to severe manic episodes in adolescents with bipolar I disorder, within its marketing authorisation (that is, up to 12 weeks of treatment for moderate to severe manic episodes in bipolar I disorder in adolescents aged 13 and older).[11]

Prescribers should refer to the BNF for Children to modify drug treatments and be aware of the increased potential for a range of side effects. Antipsychotic treatment should not be routinely continued for longer than 12 weeks in this patient group. At 12 weeks, a full multidisciplinary review of mental and physical health should be carried out, and further management of depression or long-term management considered.[6]

Recurrence of psychosis

For people with schizophrenia whose illness has not responded adequately to pharmacological or psychological treatment, the following should be reviewed:[2,3]

- The diagnosis.
- Whether there has been adherence to antipsychotic medication, prescribed at an adequate dose and for the correct duration.

- Engagement with and use of psychological treatments and ensure that these have been offered according to the NICE guidelines. If family intervention has been undertaken suggest CBT; if CBT has been undertaken suggest family intervention for people in close contact with their families.
- Other potential causes of non-response, such as comorbid substance misuse (including alcohol), the concurrent use of other prescribed medication or physical illness.

For people with an acute exacerbation or recurrence of psychosis or schizophrenia, oral antipsychotic medication should be offered or their existing medication reviewed. The choice of drug should be influenced by the same criteria recommended for starting treatment, taking into account the clinical response and side effects of the service user's current and previous medication.[2,3]

Regular combined antipsychotic medication should only be initiated for short periods (for example, when changing medication).[2,3]

Side effects of antipsychotics

Common or very common side effects of antipsychotics listed in the BNF include:[10]

- Agitation
- Amenorrhoea
- Arrhythmias
- Constipation
- Dizziness
- Drowsiness
- Dry mouth
- Erectile dysfunction
- Galactorrhoea
- Gynaecomastia
- Hyperprolactinaemia
- Hypotension (dose-related)
- Insomnia
- Leucopenia
- Movement disorders
- Neutropenia
- Parkinsonism
- QT interval prolongation
- Rash
- Seizure
- Tremor
- Urinary retention
- Vomiting
- Weight increase.

Although uncommon, the following side effects are also noted:[10]

- Agranulocytosis
- Embolism and thrombosis
- Neuroleptic malignant syndrome*

**Discontinue - potentially fatal. Symptoms include hyperthermia, fluctuating level of consciousness, muscle rigidity, and autonomic dysfunction with fever, tachycardia, labile blood pressure and sweating.*

Rarely or very rarely: sudden death can occur; neonatal withdrawal syndrome.[10]

Information should be provided and a discussion had on the likely benefits and possible side effects of each drug (age-appropriate for children and young people).[2,3]

Potential side effects that should be discussed with patients (or their parents or carers, as appropriate) prior to commencement of treatment include:[2,3]

- Metabolic side effects (including weight gain and diabetes)
- Extrapyramidal side effects (including akathisia, dyskinesia and dystonia)
- Cardiovascular side effects (including prolonging the QT interval)

- Hormonal side effects (including increasing plasma prolactin)
- Other side effects (including unpleasant subjective experiences).*

*If prescribing chlorpromazine, the person should be warned of its potential to cause skin photosensitivity and a sunscreen advised if necessary.[2,3]

Rapid weight gain, associated with antipsychotic medication and poor physical health (smoking, lack of exercise), leading to type 2 diabetes and metabolic syndrome are major sources of morbidity and premature mortality in young people with psychosis and schizophrenia.[3]

There are concerns that children and young people are more sensitive than adults to the potential adverse effects of antipsychotics, including weight gain, metabolic effects and movement disorders.[3]

High dose antipsychotics

There is no robust evidence that high doses of antipsychotic drug treatment are any more effective than standard doses for the treatment of schizophrenia. The majority of adverse effects associated with antipsychotic treatment are dose-related and there is clear evidence for a greater side-effect burden with high-dose antipsychotic drug use. Antipsychotic polypharmacy and 'when required' antipsychotic drug treatment are strongly associated with high-dose prescribing. The Royal College of Psychiatrists have issued a consensus statement with advice on doses of antipsychotic drugs above the BNF upper limits.[12]

The following should be considered when prescribing high doses:[12]

- Alternative approaches including adjuvant therapy and newer or second-generation antipsychotic drugs such as clozapine.
- Risk factors, including obesity and particular caution is indicated in older patients, especially those over 70.
- The potential for drug interactions.
- The results of an ECG to exclude untoward abnormalities such as prolonged QT interval. An ECG should be repeated periodically, and the dose reduced if a prolonged QT interval or other adverse cardiac abnormality develops.
- Increasing the dose slowly and not more often than once weekly.
- Carrying out regular pulse, blood pressure, and temperature checks and ensuring that the patient maintains adequate fluid intake.
- Considering high-dose therapy to be for a limited period and review regularly. High dose therapy should be abandoned if there is no improvement after three months and the dosage returned to a standard dosage.

Treatment failure and clozapine

Currently, about 30% of people with schizophrenia have symptoms that do not respond adequately to treatment with an antipsychotic. Although precise figures are unavailable, especially for children and young people, smaller percentages of people do not respond when a second, alternative, antipsychotic and an adequate course of psychological treatment have been tried.[3]

For these people, clozapine, which has a different dopamine receptor subtype blocking profile from other antipsychotics, has become an important treatment option in adults. Clozapine should be offered to adults with schizophrenia if their illness has not responded adequately to treatment despite the sequential use of adequate doses of at least two different antipsychotic drugs. At least one of the drugs should be a non-clozapine second-generation antipsychotic.[2]

In children and young people, however, evidence for the effectiveness of clozapine for 'treatment-

resistant schizophrenia' is lacking (only one study). Clozapine should be offered to children and young people with schizophrenia whose illness has not responded adequately to pharmacological treatment despite the sequential use of adequate doses of at least two different antipsychotic drugs each used for six to eight weeks, in line with the advice from NICE.[3]

For all patients with schizophrenia whose illness has not responded adequately to clozapine at an optimised dose, healthcare professionals should consider relevant NICE guidance before adding a second antipsychotic to augment treatment with clozapine. An adequate trial of such an augmentation may need to be up to eight to ten weeks, choosing a drug that does not compound the common side effects of clozapine.[2,3]

Clozapine has a wide range of side effects, some of which may be life threatening if not monitored correctly. The patient must be registered with a clozapine patient monitoring service.[10]

Long term treatment

Most evidence of adverse effects comes from short term studies of antipsychotics (maximum eight to 12 weeks). In contrast, very little is known about the longer-term adverse effects of antipsychotic drugs. Evidence is needed both on longer term adverse effects as well as on effective early intervention strategies that reduce these risk factors and improve physical health outcomes.[3]

There is growing concern about the long-term health risks, increased mortality and cortical grey matter loss linked to cumulative neuroleptic exposure in people with psychosis. The majority of young adults discontinue their medication in an unplanned way because of these risks.[2]

In a proportion of cases, the medication can be successfully withdrawn after a long period of use. In a proportion of cases, the dose can be reduced, although total withdrawal is not possible, and in some cases it is difficult to even reduce the dose of medication after a long period of use.[13]

Withdrawal of antipsychotic drugs

Any withdrawal of antipsychotic medication should be undertaken gradually and the person monitored regularly for signs and symptoms of relapse. This monitoring should continue for at least two years after withdrawal.[2,3]

Treatment with coexisting substance misuse

There is no evidence for any differential benefit for one antipsychotic over another for people with psychosis and coexisting substance misuse.[14] The choice of formulation (e.g. depot/long-acting injectable antipsychotic) should not be used as a specific treatment for psychosis and coexisting substance misuse but should be prescribed in line with the recommendations outlined in the NICE guidance on schizophrenia and bipolar disorder.[2,6,14]

When prescribing medication for adults and young people with psychosis and coexisting substance misuse the following applies:[14]

- The level and type of substance misuse, especially of alcohol, should be taken into account as this may alter the metabolism of prescribed medication, decrease its effectiveness and/or increase the risk of side effects
- The person should be warned about potential interactions between substances of misuse and prescribed medication
- The problems and potential dangers of using non-prescribed substances and alcohol to counteract the effects or side effects of prescribed medication should be discussed.

There is insufficient evidence to guide healthcare professionals about the use of clozapine in people with psychosis and coexisting substance misuse. Expert opinion often advocates clozapine as having a particular role in this population, but the evidence to support such statements is lacking.[14]

Choice of antipsychotic drug

Antipsychotics are often referred to as first and second generation.[10]

First generation antipsychotic drugs

The first-generation antipsychotic drugs act predominantly by blocking dopamine D2 receptors in the brain.[10] First-generation antipsychotic drugs are not selective for any of the four dopamine pathways in the brain and so can cause a range of side-effects, particularly extrapyramidal symptoms and elevated prolactin.[10]

The **phenothiazine derivatives** can be divided into three main groups:[15]

- Group I: e.g. chlorpromazine hydrochloride, levomepromazine, and promazine hydrochloride, have pronounced sedative effects and moderate extrapyramidal and autonomic effects.
- Group II: e.g. pericyazine, have moderate sedative effects, fewer extrapyramidal but more autonomic effects.
- Group III: e.g. prochlorperazine and trifluoperazine, have fewer sedative effects, pronounced extrapyramidal but less autonomic effects.

Other groups include the butyrophenones (benperidol and haloperidol), diphenylbutylpiperidines (pimozide) and thioxanthenes (flupentixol and zuclopenthixol) have actions similar to the Group III piperazines, while the substituted benzamides (sulpiride) may be less sedative and associated with a lower incidence of tardive dyskinesia.[15]

Second-generation antipsychotic drugs

The second-generation antipsychotic drugs (sometimes referred to as atypical antipsychotic drugs) act on a range of receptors in comparison to first-generation antipsychotic drugs and have more distinct clinical profiles, particularly with regard to side-effects.[10]

They include:[10]

- Amisulpride
- Aripiprazole
- Asenapine
- Cariprazine
- Clozapine
- Lurasidone hydrochloride
- Olanzapine
- Paliperidone
- Quetiapine
- Risperidone.

There is little meaningful difference in efficacy between each of the antipsychotic drugs (other than clozapine) and response and tolerability to each antipsychotic drug varies.[10]

There is no first-line antipsychotic drug which is suitable for all patients.[10] Choice should primarily be governed by the side effect profile of the antipsychotic and its relative importance to the person.[13]

Specific considerations

Negative symptoms: Antipsychotic drugs are more effective at alleviating positive symptoms than negative symptoms.[10]

Extrapyramidal side effects: Second-generation antipsychotic drugs should also be prescribed if extrapyramidal side-effects are a particular concern.[10] Of these, aripiprazole, clozapine, olanzapine and quetiapine are least likely to cause extrapyramidal side-effects.[10]

QT interval: QT-interval prolongation is a particular concern with pimozide. Overall risk is probably dose-related but there is also a higher probability of QT-interval prolongation in patients using any intravenous antipsychotic drug, or any antipsychotic drug or combination of antipsychotic drugs with doses exceeding the recommended maximum. Antipsychotic drugs with a low tendency to prolong QT interval include aripiprazole, asenapine, clozapine, flupentixol, fluphenazine decanoate, loxapine, olanzapine, paliperidone, prochlorperazine, risperidone, and sulpiride.[10]

Diabetes: First-generation antipsychotic drugs are less likely to cause diabetes than second-generation antipsychotic drugs, and of the first-generation antipsychotic drugs, fluphenazine and haloperidol are the lowest risk. Amisulpride and aripiprazole have the lowest risk of diabetes of the second-generation antipsychotic drugs.[10]

Weight gain: All antipsychotic drugs may cause weight gain, but the risk and extent varies. Clozapine and olanzapine commonly cause weight gain. Amisulpride, asenapine, aripiprazole, cariprazine, haloperidol, lurasidone hydrochloride, sulpiride, and trifluoperazine are least likely to cause weight gain.[10]

Sexual dysfunction: The antipsychotic drugs with the lowest risk of sexual dysfunction are aripiprazole and quetiapine.[10]

Hyperprolactinaemia: Most antipsychotic drugs, both first and second-generation, increase prolactin concentration to some extent because dopamine inhibits prolactin release. Aripiprazole reduces prolactin concentration in a dose-dependent manner because it is a dopamine-receptor partial agonist. Risperidone, amisulpride, sulpiride, and first-generation antipsychotic drugs are most likely to cause symptomatic hyperprolactinaemia. Hyperprolactinaemia is very rare with aripiprazole, asenapine, cariprazine, clozapine, and quetiapine treatment.[10]

Young people: For young people, when choosing between olanzapine and other 'second generation' antipsychotic medications, discuss with the young person and their parents or carers the increased likelihood of greater weight gain with olanzapine. Inform them that this effect is likely to happen soon after starting treatment.[3]

Aripiprazole is recommended as an option for the treatment of schizophrenia in people aged 15 to 17 years who are intolerant of risperidone, or for whom risperidone is contraindicated, or whose schizophrenia has not been adequately controlled with risperidone.[16]

People aged 15 to 17 years currently receiving aripiprazole for the treatment of schizophrenia who do not meet this criteria should have the option to continue treatment until it is considered appropriate to stop. This decision should be made jointly by the clinician and the person with schizophrenia, and if appropriate, their parents or carers.[16]

Costs of antipsychotics[10,17]

Across England and Wales £107 million is spend on antipsychotic drugs. [NHSBSA November 2020 to January 2021]. The current costs for the different antipsychotic treatment options are listed alphabetically below.

For those items in red in the tables below, review their use to see if a more cost-effective formulation would be more appropriate for the individual.

The most cost-effective orodispersible preparations of olanzapine are 5mg, 10mg, 15mg and 20mg orodispersible sugar free tablets. The sugar-containing versions and the lyophilisates, which are not available generically yet, should not be prescribed unless there is a clearly documented clinical reason to do so.

Amisulpride formulations	Cost
Amisulpride 50mg tablets	£4.34 for 60 tablets
Amisulpride 100 mg tablets	£6.97 for 60 tablets
Amisulpride 100mg/ml oral solution sugar free	£88.50 for 60 ml
Amisulpride 200mg tablets	£10.10 for 60 tablets
Amisulpride 400mg tablets	£42.08 for 60 tablets

Aripiprazole formulations	Cost
Aripiprazole 1mg/ml oral solution	£99.70 for 150 ml
Aripiprazole 5mg tablets	£1.38 for 28 tablets
Aripiprazole 10mg orodispersible tablets sugar free	£52.02 for 28 tablets
Aripiprazole 10mg tablets	£1.57 for 28 tablets
Aripiprazole 15mg orodispersible tablets sugar free	£46.86 for 28 tablets
Aripiprazole 15mg tablets	£1.74 for 28 tablets
Aripiprazole 30mg tablets	£13.53 for 28 tablets
Aripiprazole 400mg powder and solvent for suspension for injection pre-filled syringe	£220.41 for 1 syringe
Aripiprazole 400mg powder and solvent for suspension for injection vial	£220.41 for 1 vial

Benperidol formulation	Cost
Benperidol 250microgram tablets	£200.32 for 112 tablets

Chlorpromazine hydrochloride formulations	Cost
Chlorpromazine 25mg tablets	£16.47 for 28 tablets
Chlorpromazine 25mg/5ml oral solution	£2.35 for 150 ml
Chlorpromazine 25mg/5ml oral solution sugar free	£2.66 for 150 ml
Chlorpromazine 50mg tablets	£16.51 for 28 tablets
Chlorpromazine 100mg tablets	£16.51 for 28 tablets
Chlorpromazine 100mg/5ml oral solution	£5.50 for 150 ml

Clozapine formulations	Cost
Clozapine 25mg tablets	£16.64 for 84 tablets
Clozapine 50mg tablets	£39.60 for 100 tablets
Clozapine 50mg/ml oral suspension sugar free	£39.60 for 100 ml
Clozapine 100mg tablets	£66.53 for 84 tablets
Clozapine 200mg tablets	£158.40 for 100 tablets
Clozapine 200mg tablets orodispersible tablets sugar free	£44.35 for 28 tablets

Flupentixol formulations	Cost
Flupentixol 500microgram tablets	£2.88 for 60 tablets
Flupentixol 1mg tablets	£4.86 for 60 tablets
Flupentixol 3mg tablets	£13.92 for 100 tablets

Flupentixol formulations	Cost
Flupentixol 20mg/1ml solution for injection ampoules	£15.17 for 10 ampoules
Flupentixol 40mg/2ml solution for injection ampoules	£25.39 for 10 ampoules
Flupentixol 50mg/0.5ml solution for injection ampoules	£34.12 for 10 ampoules
Flupentixol 100mg/1ml solution for injection ampoules	£62.51 for 10 ampoules
Flupentixol 200mg/1ml solution for injection ampoules	£97.59 for 5 ampoules

Haloperidol formulations	Cost
Haloperidol 500microgram tablets	£113.13 for 28 tablets
Haloperidol 1.5mg tablets	£4.21 for 28 tablets
Haloperidol 5mg tablets	£5.13 for 28 tablets
Haloperidol 5mg/1ml solution for injection ampoules	£47.47 for 10 ampoules
Haloperidol 5mg/5ml oral solution sugar free	£6.48 for 100 ml
Haloperidol 10mg tablets	£17.04 for 28 tablets
Haloperidol 10mg/5ml oral solution sugar free	£7.10 for 100 ml
Haloperidol decanoate 50mg/1ml solution for injection ampoules	£19.06 for 5 ampoules
Haloperidol decanoate 100mg/1ml solution for injection ampoules	£25.26 for 5 ampoules
Haloperidol 200micrograms/ml oral solution sugar free	£89.90 for 100 ml

Levomepromazine formulations	Cost
Levomepromazine 25mg tablets	£20.26 for 84 tablets
Levomepromazine 25mg/1ml solution for injection ampoules	£20.13 for 10 ampoules

Olanzapine formulations	Cost
Olanzapine embonate 210mg powder and solvent for suspension for injection vial	£142.76 for 1 vial
Olanzapine embonate 300mg powder and solvent for suspension for injection vial	£222.64 for 1 vial
Olanzapine embonate 405mg powder and solvent for suspension for injection vial	£285.52 for 1 vial
Olanzapine 2.5mg tablets	£1.82 for 28 tablets
Olanzapine 5mg oral lyophilisates sugar free	£48.07 for 28 tablets
Olanzapine 5mg orodispersible tablets	£29.87 for 28 tablets
Olanzapine 5mg orodispersible tablets sugar free	£14.54 for 28 tablets*
Olanzapine 5mg tablets	£1.85 for 28 tablets
Olanzapine 7.5mg tablets	£2.13 for 28 tablets
Olanzapine 10mg oral lyophilisates sugar free	£87.40 for 28 tablets
Olanzapine 10mg orodispersible tablets	£49.80 for 28 tablets
Olanzapine 10mg orodispersible tablets sugar free	£24.97 for 28 tablets*
Olanzapine 10mg tablets	£2.70 for 28 tablets
Olanzapine 15mg oral lyophilisates sugar free	£131.10 for 28 tablets
Olanzapine 15mg orodispersible tablets	£48.79 for 28 tablets

Olanzapine formulations	Cost
Olanzapine 15mg orodispersible tablets sugar free	£28.64 for 28 tablets*
Olanzapine 15mg tablets	£3.25 for 28 tablets
Olanzapine 20mg oral lyophilisates sugar free	£174.79 for 28 tablets
Olanzapine 20mg orodispersible tablets	£79.78 for 28 tablets
Olanzapine 20mg orodispersible tablets sugar free	£18.93 for 28 tablets*
Olanzapine 20mg tablets	£4.28 for 28 tablets

**Most cost-effective if orodispersible is required.*

Pericyazine formulations	Cost
Pericyazine 2.5mg tablets	£27.90 for 84 tablets
Pericyazine 10mg tablets	£72.00 for 84 tablets
Pericyazine 10mg/5ml oral solution	£82.80 for 100 ml

Pimozide formulation	Cost
Pimozide 4mg tablets	£40.31 for 100 tablets

Prochlorperazine formulations	Cost
Prochlorperazine 5mg/5ml oral solution	£3.34 for 100 ml
Prochlorperazine 12.5mg/1ml solution for injection am-poules	£5.23 for 10 ampoules

Promazine formulations	Cost
Promazine 25mg tablets	£45.33 for 100 tablets
Promazine 25mg/5ml oral solution	£40.78 for 150 ml
Promazine 50 mg tablets	£76.17 for 100 tablets
Promazine 50mg/5ml oral solution	£51.10 for 150 ml

Quetiapine formulations	Cost
Quetiapine 25mg tablets	£2.08 for 60 tablets
Quetiapine 50mg modified-release tablets	£67.66 for 60 tablets
Quetiapine 100mg tablets	£4.33 for 60 tablets
Quetiapine 150mg modified-release tablets	£113.10 for 60 tablets
Quetiapine 150mg tablets	£4.41 for 60 tablets
Quetiapine 200mg modified-release tablets	£113.10 for 60 tablets
Quetiapine 200mg tablets	£5.22 for 60 tablets
Quetiapine 20mg/ml oral suspension sugar free	£132.00 for 150 ml
Quetiapine 300mg modified-release tablets	£170.00 for 60 tablets
Quetiapine 300mg tablets	£6.11 for 60 tablets
Quetiapine 400mg modified-release tablets	£226.20 for 60 tablets
Quetiapine 600mg modified-release tablets	£70.73 for 30 tablets

Risperidone formulations	Cost
Risperidone 250microgram tablets	£12.00 for 20 tablets
Risperidone 500microgram orodispersible tablets sugar free	£18.28 for 28 tablets
Risperidone 500microgram tablets	£1.38 for 20 tablets
Risperidone 1mg orodispersible tablets sugar free	£22.50 for 28 tablets
Risperidone 1mg tablets	£1.61 for 20 tablets
Risperidone 1mg/ml oral solution sugar free	£4.16 for 100 ml
Risperidone 2mg orodispersible tablets sugar free	£38.14 for 28 tablets
Risperidone 2mg tablets	£3.84 for 60 tablets
Risperidone 3mg orodispersible tablets sugar free	£43.50 for 28 tablets
Risperidone 3mg tablets	£4.86 for 60 tablets
Risperidone 4mg orodispersible tablets sugar free	£50.29 for 28 tablets
Risperidone 4mg tablets	£5.12 for 60 tablets
Risperidone 6mg tablets	£49.21 for 28 tablets
Risperidone 25mg powder and solvent for suspension for injection vial	£79.69 for 1 vial
Risperidone 37.5mg powder and solvent for suspension for injection vial	£111.32 for 1 vial
Risperidone 50mg powder and solvent for suspension for injection vial	£142.76 for 1 vial

Sulpiride formulations	Cost
Sulpiride 200mg tablets	£9.38 for 30 tablets
Sulpiride 200mg/5ml oral solution sugar free	£50.89 for 150 ml
Sulpiride 400mg tablets	£22.50 for 30 tablets

Trifluoperazine formulations	Cost
Trifluoperazine 1mg tablets	£59.12 for 112 tablets
Trifluoperazine 1mg/5ml oral solution sugar free	£136.88 for 200 ml
Trifluoperazine 5mg tablets	£134.89 for 112 tablets
Trifluoperazine 5mg/5ml oral solution sugar free	£30.00 for 150 ml

Zuclopenthixol formulations	Cost
Zuclopenthixol 2mg tablets	£3.14 for 100 tablets
Zuclopenthixol 10mg tablets	£8.06 for 100 tablets
Zuclopenthixol 25mg tablets	£16.13 for 100 tablets
Zuclopenthixol acetate 50mg/1ml solution for injection ampoules	£24.21 for 5 ampoules
Zuclopenthixol decanoate 200mg/1ml solution for injection ampoules	£31.51 for 10 ampoules
Zuclopenthixol decanoate 500mg/1ml solution for injection ampoules	£37.18 for 5 ampoules

Switching from olanzapine orodispersible tablets or oral sugar free lyophilisates to olanzapine orodispersible sugar free tablets **could save £2 million nationally over 12 months (NHSBSA November 2020 to January 2021) This is equivalent to £3,132 per year per 100,000 patients.**

A proportion of these patients without a clinical need for an orodispersible formulation could also be switched to olanzapine tablets with an even greater cost saving. This is also applicable for aripiprazole, risperidone and other antipsychotics prescribed as more expensive formulations without a clinical need.

There is also a significant price difference between the modified-release quetiapine (as XL) and the immediate release (IR) formulation and there is scope to achieve substantial cost savings by changing from XL to IR.

The pharmacokinetics of the two formulations are similar. When Seroquel XL administered once daily was compared to the same total daily dose of immediate-release quetiapine fumarate (Seroquel immediate release) administered twice daily, the area under the plasma concentration-time curve (AUC) was equivalent, but the maximum plasma concentration (Cmax) was 13% lower at steady state.[18]

Switching from quetiapine modified release (Seroquel XL) to quetiapine IR **could save £895k nationally over 12 months (NHSBSA November 2020 to January 2021). This is equivalent to £1,401 per year per 100,000 patients.**

Switching options

- Consider switching all patients prescribed quetiapine modified release to an equivalent dose of the immediate release formulation unless there is a documented clinical reason for an MR preparation (e.g. patients who do not tolerate quetiapine IR but are able to tolerate MR or where compliance with a twice daily formulation may cause a problem). Suggested dose conversions when switching from quetiapine MR to IR are set out in table 1 (page 17).
- Patients prescribed a more costly orodispersible preparation (aripiprazole, olanzapine or risperidone), where this is not clinically indicated (e.g. unless for swallowing difficulties, patients who are PEG fed or for patients with compliance issues) should be reviewed to determine the appropriateness of switching to a more cost-effective formulation.
- Patients still requiring an orodispersible formulation of olanzapine, should be switched to the same dose of generic orodispersible sugar free tablets as these are the least costly.
- Patients requiring a liquid formulation of an antipsychotic should be reviewed to determine their appropriateness for switching to a more cost-effective formulation.
- All switches of formulations of antipsychotic drugs should be on specialist advice only with the appropriate shared care agreement updated accordingly, with the exception of switching olanzapine orodispersible to a less costly orodispersible formulation, and quetiapine MR to IR, if agreed locally.
- As always, switches should be tailored to the individual patient.

Table 1 - Suggested dose conversion when switching from quetiapine MR to IR

Current dose of quetiapine XL	Quetiapine IR dosing options		
	Patients who are tolerating quetiapine well and do not have compliance concerns	Patients who are (or at risk of) experiencing sedation or postural hypotension following the switch	Patients who are tolerating quetiapine well but have compliance concerns IR is ONLY licensed once daily in patients with major depressive episodes in bipolar disorder
50mg XL once daily	25mg twice daily	50mg at night	50mg at night
100mg XL once daily	50mg twice daily	25mg in the morning, 75mg at night	100mg at night
200mg XL once daily	100mg twice daily	50mg in the morning, 150mg at night	200mg at night
300mg XL once daily	150mg twice daily	100mg in the morning, 200mg at night	300mg at night
400mg XL once daily	200mg twice daily	150mg in the morning, 250mg at night	400mg at night
600mg XL once daily	300mg twice daily	200mg in the morning, 400mg at night	-
800mg XL once daily	400mg twice daily	-	-

The first dose of IR formulation should be given approximately 24 hours after the last dose of the XL formulation.

Summary

Antipsychotics should only be prescribed in primary care after the effects of treatment have been monitored for 12 months, or the person's condition has stabilised, whichever is longer. Until then, the secondary care team should maintain responsibility for monitoring the person's physical health and the effects of antipsychotic medication.

After this time, responsibility for the prescribing of antipsychotics may be transferred to primary care under appropriate care arrangements, if the primary care prescriber is willing to take this on.

Some antipsychotics are available in a variety of formulations, several of which are significantly more costly than others. Review of the prescribing of these preparations and switching to less costly alternatives, where clinically appropriate, will represent significant cost savings to the NHS.

All switches of formulations of antipsychotic drugs should be on specialist advice only with the appropriate shared care agreement updated accordingly, with the exception of switching olanzapine orodispersible to a more cost-effective orodispersible formulation, and quetiapine MR to IR if agreed locally.

As always, switches should be tailored to the individual patient.

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Additional PrescQIPP resources

Briefing	https://www.prescqipp.info/our-resources/bulletins/bulletin-286-antipsychotic-drugs/
Implementation tools	
Data pack	https://data.prescqipp.info/views/B268_Antipsychoticdrugs/FrontPage?:iid=1&:isGuestRedirectFromVizportal=y&:embed=y

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