Guidance on the Use of Antipsychotics

Version 3
(October 2015)

This guidance supersedes the following document:
Guidance on the Use of Antipsychotics October 2009 and March 2013

If you require this document in an alternative format, i.e. easy read, large text, audio or Braille please contact the pharmacy team on 01243 623349.
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Suggested Antipsychotic Treatment Plan

Already on first generation (typical) or second generation (atypical) antipsychotic

If effective and side effects acceptable, MAINTAIN

If side effects unacceptable

Change to alternative antipsychotic

Ineffective or side effects unacceptable

If two antipsychotics are ineffective but adherence good

If ineffective due to poor adherence

For non-adherent patients who are unsupervised

Consider depot medication or other long-acting antipsychotic injection

If adherence does not improve

Consider orodispersible or liquid preparation

If adherence improves, consider standard formulation

If two antipsychotics are ineffective

If ineffective or if side effects unacceptable

Change to an alternative depot medication or other long-acting antipsychotic injection

If side effects unacceptable

If effective and side effects acceptable, MAINTAIN

Patient naïve to antipsychotics – in discussion with patient/carer give an appropriate second generation antipsychotic or sulpiride (see section 3). Optimise dose. Closely assess over 4 to 6 weeks.

Ineffective or side effects unacceptable

If severe neurological side effects

Clozapine indicated – consider and discuss with patient

If ineffective due to poor adherence

For non-adherent patients who are supervised

If adherence does not improve

Non-adherent patients who are supervised

If ineffective due to poor adherence

If two antipsychotics are ineffective but adherence good

If adherence improves, consider standard formulation

If adherence improves, consider standard formulation

If ineffective or side effects unacceptable

This suggested treatment plan cannot cover every eventuality, e.g. non-adherent patients who refuse injection or patients with treatment resistant schizophrenia who cannot tolerate or do not respond to clozapine. Further advice on other treatment options can be obtained from your local clinical pharmacist.
Recommended Procedure.

1. Introduce drug, following BNF / manufacturers recommendations for initial dosage and titration.

2. Titrate to minimum effective dose. (Add sedative for short term behavioural control if needed).

3. Evaluate for at least two weeks.

4. If no response, increase dose according to response and tolerability, and assess over a further four to eight week period.

5. Continue evaluation of response and tolerability.

6. Withdraw drug and consider alternative if insufficient response is seen after maintaining maximum tolerated dose for at least four weeks.

AUDITS

The Trust will undertake to audit the following prescribing on a regular basis.

1. Prescribing high dose and combined antipsychotics.

2. Screening of metabolic side effects of antipsychotic drugs

3. Use of antipsychotic medication in Children and Young Peoples Services (CHYPS)

4. Assessment of the side effects of depot antipsychotic medication

5. Prescribing antipsychotics for people with dementia
1. GENERAL PRINCIPLES IN THE TREATMENT OF PSYCHOSIS

Terminology

FGA – First Generation Antipsychotic also known as Typical Antipsychotic
SGA – Second Generation Antipsychotic also known as Atypical Antipsychotic

Which medicine to use?

With the exception of clozapine, the efficacy of all antipsychotics is very similar and the choice should primarily be governed by the side effect profile of the antipsychotic and its relative importance to the patient e.g. olanzapine has a significant risk of metabolic effects which may outweigh first line choice. When prescribing a new medication follow the recommendations below. The ‘Choice and Medication’ website has a number of Handy Charts that may help the prescriber and patient decide which antipsychotic is the most suitable, and can be found on the Trust’s Intranet using the following link:- http://www.choiceandmedication.org/sussex/

Where possible, it is important that the patient is involved in the decision making process as to the choice of antipsychotic to be used.

Whenever a patient is transferred between settings and a review of medication is needed after transfer, the date of the review and what needs reviewing must be clearly communicated to the receiving GP, community team or ward. This information must also be shared with the patient and if appropriate the carer.

Points to consider:

- What is the aim of the medication for the patient and their ultimate goals?
- Has the patient been given appropriate information to help them make an informed choice?
- Have the relevant benefits and side effects of all medication being considered been explained to the patient?
- Where necessary has the management of side effects been discussed?
- Does the patient have an Advance Decision (including for any acute phase of their illness)?

If, after these issues have been considered, there is still a choice of treatment to be made, then the relative cost and the black triangle status# of the treatment should be used to help govern the choice.

(# Black Triangle Status refers to an intensively monitored medicine as defined by the Medicines and Healthcare Regulatory Agency- MHRA.)
Treatment Resistance

It is important to make the distinction between treatment resistance and treatment intolerance. Treatment resistance is described as being resistant to adequate trials of at least two antipsychotics. In such circumstances service users must be offered a trial of clozapine at the earliest opportunity. Treatment intolerance could be described as experiencing adverse effects to such a degree that continuation with treatment is unwarranted. However, this does not mean that the service user is resistant to treatment and in such circumstances an alternative antipsychotic, other than clozapine, should be offered.
**Monitoring**

All patients receiving long term treatment with antipsychotic medication should be monitored routinely and regularly.\(^{(2)}\) The same criteria should be used as described in the monitoring section of this guideline on an annual basis.

In addition to the physical monitoring as per table below all patients should be offered the opportunity to complete a GASS at regular intervals to measure the impact of side effects.

**Antipsychotics – FGAs and SGAs (except clozapine)**

<table>
<thead>
<tr>
<th>Test</th>
<th>Baseline</th>
<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
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**Clozapine**

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<thead>
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<th>Test</th>
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<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
<th>On-going</th>
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<tr>
<td>Weight, BMI, Abdominal Girth</td>
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<td>✔</td>
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<tr>
<td>Blood glucose (random/fasting)</td>
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<td>✔</td>
<td>✔</td>
<td>✔</td>
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<td>✔</td>
<td>✔</td>
<td>✔</td>
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<tr>
<td>Prolactin</td>
<td>Hyperprolactinaemia is rare with clozapine – check serum prolactin if symptoms occur (menstrual disturbance, galactorrhoea, gynaecomastia, sexual dysfunction). Consider other possible causes.</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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</tr>
<tr>
<td>BP and Pulse</td>
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Additional information on tests listed in the tables

- **ECG** = Electrocardiogram with automatic reporting and calculation of corrected QT Interval (<450mSec)
  - QT$_c$ below 440ms(men) or below 470ms (women) is normal
  - QT$_c$ above 440ms (men) or above 470ms (women) but below 500ms (both sexes - prescribe with care)
  - QT$_c$ above 500ms - Stop suspected causative drug(s) and switch to drug of lower effect (if required). Repeat ECG after change. **Refer to cardiologist immediately.**

- **BMI** = Body Mass Index = weight in Kg divided by (height in metres x height in metres). BMI >30 = clinically obese. Alternatively waist circumference can be helpful.

- **Full Lipid Screen** - As per normal practice.
  - If the Total Cholesterol (TC) > 5mmol/l and/or the High Density Lipoprotein Level (HDL) is <1 mmol/L, then this result should be highlighted when reported to the GP for diagnostic testing, or seek further advice.

- **BP and Pulse** - Standing and sitting systolic and diastolic blood pressure. Pulse in heartbeats per minute.

- **Blood Glucose** –
  - If random blood glucose is >7.1mmol/l, check fasting blood glucose. If random glucose is >11.1mmol/l then the diagnosis of diabetes is highly likely but needs checking with fasting level and confirmation by the GP.
  - If the fasting glucose is > 6mmol/l, then this should be highlighted when reporting to the GP for diagnostic testing. All results should be reported to the GP and abnormal ones highlighted so that they can be followed by the GP and colleagues in primary care team.
  - Consider HBA$_1$C level as alternative to fasting glucose.

**Regular Monitoring**

Considerable thought should be given to the ongoing monitoring arrangements for patients on long-term therapy. A clear medication care plan advising on what monitoring arrangements are necessary and how often they will be conducted should be completed in consultation with the patient and included in the CPA.

**Additional Monitoring Requirements for Depots and Long-Acting Injections**

As any patient on antipsychotics, patients should be offered the opportunity to complete a GASS to measure the impact of the side effects of their depot
  - Routinely every 6 months preferably before the dose review
  - Approximately 6 weeks after a dosage alteration
Prior to each injection a discussion with the patient and an assessment of the previous injection site should be undertaken to ascertain if there are signs of swelling, pain, inflammation, infection or tissue viability damage.¹⁰⁻

See also

Positive Cardiometabolic Health Resource (Appendix 6)
http://www.rcpsych.ac.uk/quality/nationalclinicalaudits/schizophrenia/nationalschizophreniaaudit/nasresources.aspx

Aripiprazole long acting injection, Guidelines for Prescribing and Administration

Guidelines for the use of Clopixol Acuphase

Guidelines for the Administration of Long Acting Antipsychotic Injections in Adults

Olanzapine Long-Acting Injection Guidelines

Paliperidone Long-Acting Injection Guidelines for Prescribing and Administration
2. SELECTING AN ANTIPSYCHOTIC

With the exception of clozapine, the efficacy of all antipsychotics is very similar and often the choice is governed by the side effect profile of the antipsychotic and its relative importance to the service user.

Cost implications

Antipsychotic costs for 28 days treatment (from eDrug Tariff accessed 30.9.15) (1)
Based on commonly used doses

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE</th>
<th>MONTHLY COST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amisulpride</td>
<td>600mg/day</td>
<td>£21.08 (1 x 200mg + 1 x 400mg)</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>15mg/day</td>
<td>£75.47</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>15mg/day</td>
<td>£15.97 (1 x 5mg + 1 x 10mg)</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>74mg/day</td>
<td>£90.72</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>20mg/day</td>
<td>£3.00 (2 x 10mg)</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>600mg/day</td>
<td>£4.11</td>
</tr>
<tr>
<td>Quetiapine XL</td>
<td>600mg/day</td>
<td>£158.67</td>
</tr>
<tr>
<td>Risperidone</td>
<td>6mg/day</td>
<td>£4.08 (1 x 6mg)</td>
</tr>
<tr>
<td>Sulpiride</td>
<td>1200mg/day</td>
<td>£52.64 (3 x 400mg)</td>
</tr>
</tbody>
</table>

All prices are based on standard solid dose formulation, (orodispersible and liquid preparations usually cost considerably more).

Clozapine is the only antipsychotic with an evidence base for use in treatment resistant schizophrenia, hence cost implications are irrelevant. However, clozapine therapy is no longer expensive compared to other SGAs.

Prescribing generically wherever possible will ensure that costs are kept to a minimum. Branded formulation names such as “Quicklets” and “Velotabs” should also be avoided as use of these will mean that non-generic risperidone and olanzapine variants will be dispensed and charged at up to 10 times the cost of the generic equivalent.

Use of Depots (and Long Acting Injections)

Poor compliance with oral antipsychotics is common in patients with schizophrenia, mania and other psychoses which often results in a relapse of the illness. The use of depot medication can be considered for use in these situations as it promotes adherence to medication, allows for earlier detection of non-adherence with the potential for earlier intervention and possible decreased risk of severe relapse. It should not be forgotten that some patients elect to have depot medication as it is convenient and there is no onus on them to remember to take medication.

Aripiprazole Long Acting Injection is recommended in:
- Patients who have responded well to oral aripiprazole.
- Patients who have tolerated oral aripiprazole.
Risperidone Long Acting Injection (LAI) is recommended in:
- Patients who have responded well to oral SGAs but have compliance problems.
- Patients who have responded well to FGA depots but who find the side effects unacceptable

Paliperidone Long Acting Injection is recommended:
- As per Risperidone LAI
- In patients who have responded well to Risperidone LAI but 2 weekly injections cause problems.

Olanzapine Long Acting Injection is recommended in:
- Patients who have responded well to oral olanzapine
- Patients who have been assessed as having adherence problems with oral olanzapine.

Depot antipsychotics (and Long Acting Injections) are not recommended in children and adolescents due to the lack of safety and efficacy data. Children and adolescents have a higher risk of developing extrapyramidal side effects, including tardive dyskinesia. There are reports of Neuroleptic Malignant Syndrome following the administration of depot antipsychotics in children and adolescents.

See also
Guidelines for the Administration of Long Acting Antipsychotic Injections in Adults
3. PRESCRIBING GUIDELINES FOR FIRST EPISODE PSYCHOSIS (NON AFFECTIVE)

Whenever a patient is transferred between settings and a review of medication is needed after transfer, the date of the review and what needs reviewing must be clearly communicated to the receiving GP, community team or ward. This information must also be shared with the patient and if appropriate the carer.

First line

NICE recommends oral antipsychotics are prescribed first line for newly diagnosed schizophrenia.\(^{(2,103)}\) The first line drug prescribed is dependent on patient and carer choice following adequate explanation.

Based on up to date evidence, first line recommended antipsychotic options are:

- Amisulpride (greater comparative cost may outweigh first line choice).
- Aripiprazole
- Olanzapine (significant risk of metabolic adverse effects may outweigh first line choice).
- Quetiapine
- Risperidone
- Sulpiride (greater comparative cost may outweigh first line choice).

All drugs listed in this guideline are in alphabetical order.

First Generation Antipsychotics (FGA) and Second Generation Antipsychotics (SGA) have equal efficacy in first episode psychosis.\(^{(3,4,5,6)}\) SGAs are preferable first line due to lower propensity for extrapyramidal side effects within BNF dose range.\(^{(6,101)}\) Sulpiride is the only FGA included, following recent evidence.\(^{(3,7)}\)

To aid patient / carer / clinician choice, drugs with notable potential for major adverse effects are:

1. **Initial sedation**: amisulpride, FGAs, olanzapine, quetiapine, risperidone, sulpiride.
2. **Metabolic adverse effects**: SGAs but notably clozapine and olanzapine. Aripiprazole and possibly lurasidone has lowest potential for these effects.\(^{(6,7,83)}\)
3. **Movement disorders**: FGAs and the upper dose range of aripiprazole, amisulpride, olanzapine, risperidone and sulpiride, notably in younger populations.\(^{(6,101)}\)
4. **Hyperprolactinaemia**: amisulpride, FGAs, risperidone, sulpiride and lesser so olanzapine. Aripiprazole has lowest potential for these effects and may be associated with hypoprolactinaemia. Long-term effects of raised prolactin include sexual and reproductive impairment and reduced bone density, (young females more vulnerable)\(^{(9,102)}\)

First exposure and young age are risk factors for an increased likelihood of adverse effects and that those adverse effects are more pronounced if they occur, e.g. greater weight gain seen in teens exposed to antipsychotic medications when compared with adults. As such it is advisable to use low initial doses of antipsychotic medication with careful monitoring using tools such as the Glasgow Antipsychotic Side effect Scale (GASS).
Baseline investigations and metabolic monitoring to be conducted as per Trust and NICE guidelines.\(^{(2,103)}\)

Certain medications that are licensed for twice daily dosing may be used once daily, namely; amisulpride, quetiapine immediate release (IR) and sulpiride. Clozapine may also be used once daily to add compliance once a client has been successfully titrated up on a twice daily dose. Moving over to a once daily regimen should be done cautiously to minimise potential side effects. All of the first line options appear to be effective when administered once daily. (Note that once daily use of amisulpride, sulpiride and quetiapine (IR) is “off licence”).

Switch if:

1. Clear non-response at 2- 4 weeks with adequate antipsychotic dose. If partial response consider increasing dose (if tolerated) and longer trial \(^{(10)}\)
2. Intolerable or potentially harmful side effects.
3. Patient request / non-adherence related to nature of drug.
4. If olanzapine used first line in acute setting, review early for switch to antipsychotic with more favourable metabolic profile.

Second line

Whilst additional oral alternatives 2\(^{nd}\) line are low dose FGAs such as haloperidol,\(^{(2,3,103)}\) a trial of a second “first line” agent should be preferred before considering low dose FGAs.

Long acting injectable medication (risperidone / paliperidone/ low dose FGA / aripiprazole) should be considered, particularly if there is evidence of poor adherence.\(^{(11,12)}\) In line with oral guidance paliperidone or aripiprazole LAI should be considered first line LAI options in early episode schizophrenia, due to the impact of EPSE’s. Refer to Trust guidelines for these preparations.

Lurasidone is approved for second-line use in patients identified as having significant metabolic risk factors, eg. diabetes, obesity. In such circumstances aripiprazole must be tried before lurasidone.

Third line

If intolerant or non-adherent, choose other first or second line antipsychotic.

Do not delay offering clozapine if a second antipsychotic is ineffective. This should not be held in reserve at this stage.

Lurasidone is approved for third-line use after two previous antipsychotics have been tried, one of which must be aripiprazole, and at least one was effective but not tolerated. Lurasidone must not be used in place of clozapine third-line if two previous antipsychotics have been tolerated and are both ineffective as this is indicative of treatment resistance.

Polypharmacy is not indicated in these stages of treatment.
**Additional information for treatment of people under 18 with antipsychotic medication**

Licensed ages of antipsychotics for psychosis:

- Amisulpride: 18 years
- Aripiprazole: 15 years
- Clozapine: 16 years (for treatment resistant schizophrenia)
- Haloperidol: 12 years
- Olanzapine: 18 years
- Quetiapine: 18 years
- Risperidone: 18 years  
  Due to lack of conducted studies in younger group, but is recommended by NICE\(^{(13,103)}\) in young people aged 14-17 years. Risperidone is licensed from 5 years in children with conduct disorder.
- Sulpiride: 14 years

All LAI / depot antipsychotics: 18 years

Younger people are more vulnerable to adverse effects from antipsychotic medication so careful consideration should be given to drug choice and monitoring.

Clozapine remains an important drug in younger groups with treatment resistant schizophrenia.

Ideally, medication should be prescribed within the terms of the marketing authorisation. However, it is recognised that this in not always practical in a paediatric population. When prescribing outside of product licence this should be discussed and a joint decision made with the client and the discussion must be documented.

A Sussex Partnership Trust leaflet and medication consent forms are available to aid this discussion:


The *BNF for Children (BNFc)* gives further guidance on licensed and unlicensed prescribing.

Treatment options and their pro’s & con’s should be discussed with clients (and any carers the individual is happy to have involved) in order to co-create a treatment plan. [www.choiceandmedication.org/sussex](http://www.choiceandmedication.org/sussex) offer useful resources to support these discussions & decisions.
4. **HIGH DOSE ANTIPSYCHOTIC MEDICATION**\(^{(14,15)}\)

High dose antipsychotic therapy (HDAT) is defined by the Royal College of Psychiatrists (RCPsych) as a total daily dose of a single antipsychotic which exceeds the upper limit stated in the British National Formulary (BNF), or a total daily dose of two or more antipsychotics which exceeds the BNF maximum as calculated by percentages using the antipsychotic dose ready reckoner (see appendix 4).

**Example calculation:**
Zuclopenthixol depot 300mg weekly (50%) and olanzapine 15mg daily (75%)
= 50% + 75% = 125% (>100% therefore 'high dose')

Current evidence does not justify the routine use of HDAT. If high doses are to be used in an individual case this should be performed as an organised time limited therapeutic trial, with clear reasons and treatment plan documented in the patients notes.

Use of PRN or ‘when required’ antipsychotic medication should also be included when calculating maximum recommended daily doses. The use of PRN medication should be reviewed regularly as stated in The Medicines Code. Practitioners administering doses of antipsychotics above BNF maximum doses must check the notes for the rationale behind this decision and confirm that the dose is documented in the notes.

**Before prescribing**

- The decision to prescribe HDAT should involve an individual risk-benefit assessment by a Consultant Psychiatrist, the patient (where possible) and the multidisciplinary team.

- A high dose antipsychotic monitoring form should be completed and attached to the drug prescription and administration chart (if an inpatient) and filed in the case notes at the time of initial prescription (See Appendix 1). Target outcomes of the HDAT should also be documented.

- A baseline ECG should be performed to exclude cardiac contraindications such as QTc prolongation. In the event of a prolonged QTc interval (QTc > 440ms for men, QTc > 470ms for women) the prescribing should be halted and further advice sought (a cardiology assessment is recommended). If an ECG is not performed, the reason should be documented in the notes. The ECG should be repeated after a few days, and then every one to three months in the early stages of high dose treatment and then periodically as clinically indicated.

- Possible contra-indications and the potential for drug interactions to HDAT should be considered before prescribing. Drug interactions may include drugs that may prolong QTc intervals and drugs that may increase antipsychotic plasma levels.

- The use of a medicine at doses that exceed its marketing authorisation is termed off-license or off-label. This would apply to the use of HDAT and must be considered and discussed with the patient. Any discussion and decision reached should be documented in the notes including the risks and benefits, the aims and when and how the outcome will be assessed.
Monitoring / Risk Factors

- Use of HDAT is associated with an increased potential for adverse effects. This may include an association with tachycardia, postural hypotension, sedation, seizures, extrapyramidal side effects (EPSE), hyperprolactinaemia, tachycardia and sudden death. Arrhythmia is more likely to occur in the presence of electrolyte abnormalities, treatment with diuretics, alcohol dependence and liver disease.

- Use of HDAT is associated with a greater risk of adverse effects.

- Risk factors associated with HDAT are increased in old age, hepatic and renal impairment, obesity, heavy users of alcohol or tobacco and in those with a history of cardiac events.

- Serum urea and electrolytes and liver function must be checked at baseline, after one month, then three-monthly thereafter. Temperature, blood pressure and pulse must be monitored at baseline and for one week after dose increases, then periodically.

Side effects can be monitored using a scale such as the Glasgow Antipsychotic Side-effect Scale (GASS) or the Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS). GASS is the preferred scale and use is endorsed by the Trust (see Appendix 2).

Any dose increase of antipsychotic should be performed gradually at a minimum of weekly intervals. This will help to identify a clinical response at the lowest effective dose and may reduce the risk of neuroleptic malignant syndrome.

Progress should be monitored at least once every three months, preferably with the aid of a rating scale such as the Positive and Negative Symptoms of Schizophrenia Scale (PANSS) or the Brief Psychiatric Rating Scale (BPRS). If no significant progress is observed then the use of HDAT should cease and the future treatment plan should be reviewed. Continued use of HDAT where there is no improvement in clinical response must be fully and clearly justified in the case notes. In this instance consultants should consider seeking a second opinion from another senior colleague.

In a small proportion of cases HDAT may be justified provided the safety implications are considered and monitoring requirements are observed. These include; RT, partial response or red blood result with clozapine, when switching from one antipsychotic to another (short-term cross-tapering) and as a temporary measure with depot medication during an acute exacerbation of illness.

However, there is insufficient evidence for the use of HDAT for relapse prevention in schizophrenia, persistent aggression and treatment resistant schizophrenia. Before HDAT is used it must be ensured that the diagnosis is correct, previous treatments (including doses and durations) have been adequate, concordance with treatment is confirmed and that appropriate alternative antipsychotics and adjunctive drug therapies have been considered.
Consideration should also be given to the increased treatment costs associated with HDAT and the possibility of GPs being unwilling to assume prescribing responsibility after the patient is discharged if HDAT is being used.

**Consent**

Consent must be obtained from patient before the use of HDAT. This should be documented in the notes and included on form T3 where relevant. (Although a T2 is a ‘patient consent to treatment form’ it should specify that the doses are above BNF limits and by how much.)

Inpatients being administered high doses and those who are at risk of receiving high doses (where the prescription of regular and PRN antipsychotic doses could potentially lead to HDAT) should be identified by means of a sticker attached by pharmacy staff to the drug prescription and administration chart (where regularly prescribed medication is above BNF limits and/or regular use of PRN medication which puts them above BNF limits).

If a patient is discharged from an inpatient unit on HDAT then the patients GP and other relevant community mental health personnel must be informed of the HDAT status and the required monitoring/review arrangements by the discharging doctor.

Audits of high dose antipsychotic prescribing will be performed as a matter of routine practice.

See also:


The Rapid Tranquillization Policy Version 6 July 2014
5. **DRUG INTERACTIONS\(^{(15)}\)**

Drug Interactions may be pharmacodynamic or pharmacokinetic.

Pharmacodynamic – Interactions between drugs which have similar or antagonistic pharmacological effects or side effects. It may be due to competition at receptor sites, or occur between drugs acting on the same physiological system. They are usually predictable and occur to a greater or lesser extent in most patients who receive the interacting drugs.

Pharmacokinetic – Occurs when one drug alters the absorption distribution, metabolism or excretion of another. This results in an increase or reduction in the amount of drug available to produce its pharmacological effects. These interactions are not easy to predict and many only affect a small proportion of patients taking the combination of drugs.

Co-morbidity such as physical illness can result in multiple drug regimes. This increases the risk of drug interactions. Some of the important drug interactions are given in the table below but the British National Formulary (BNF) should be consulted for more detailed information.

Some of the interactions listed are commonly prescribed combinations of drugs and their inclusion in this table should not be read as a recommendation against their usage but more an indicator of where greater levels of monitoring may be required.

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Common Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotics + angiotensin-converting enzyme (ACE) inhibitors, Angiotensin-II receptor antagonists or calcium channel blockers</td>
<td>Risk of postural hypotension</td>
</tr>
<tr>
<td>Antipsychotics + antiarrhythmic drugs</td>
<td>Increased risk of ventricular arrhythmia with antiarrhythmic drugs that prolong the QT interval such as amiodarone.</td>
</tr>
<tr>
<td>Antipsychotics + antibacterials</td>
<td>Erythromycin possibly increases plasma concentration of clozapine so careful selection is required due to an increased risk of neutropenia and seizures. Ciprofloxacin increases plasma concentration of clozapine and possibly olanzapine. Plasma concentration of quetiapine possibly increased by macrolides (e.g. erythromycin).</td>
</tr>
<tr>
<td>Antipsychotics + antidepressants</td>
<td>Increased risk of arrhythmia with tricyclic antidepressants. Selective serotonin re-uptake inhibitors (SSRIs) and venlafaxine increase the plasma concentration of clozapine. Fluoxetine and venlafaxine increase the plasma concentration of haloperidol. Severe EPSEs have been reported with fluoxetine and haloperidol.</td>
</tr>
<tr>
<td>Antipsychotics + antiepileptics</td>
<td>Antipsychotics lower seizure threshold. Carbamazepine reduces the plasma concentration of aripiprazole, clozapine, haloperidol, olanzapine, quetiapine and risperidone. Phenytoin reduces the plasma concentration of clozapine, haloperidol and quetiapine. The risk of neutropenia is increased if olanzapine is given with sodium valproate.</td>
</tr>
<tr>
<td>Antipsychotics and antivirals</td>
<td>Plasma concentration of clozapine possibly increased by ritonavir (avoid concomitant use) and possibly by amprenavir. Plasma concentration of olanzapine reduced by ritonavir (may need to increase dose). Plasma concentration of aripiprazole possibly reduced by efavirenz and nevirapine, metabolism of aripiprazole possibly inhibited by amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir (reduce dose of aripiprazole) Plasma concentrations of antipsychotics possibly increased by ritonavir.</td>
</tr>
<tr>
<td>Antipsychotics and atomoxetine</td>
<td>Increased risk of ventricular arrhythmias when antipsychotics that prolong the QT interval are given with atomoxetine</td>
</tr>
<tr>
<td>Antipsychotics and beta-blockers</td>
<td>Increased risk of ventricular arrhythmias particularly when sotalol is given with zuclopenthixol, haloperidol, amisulpride, phenothiazines and risperidone</td>
</tr>
<tr>
<td>Antipsychotics + lithium</td>
<td>Increasing lithium levels has a direct neurotoxic effect, including increased risk of neuroleptic malignant syndrome (NMS), particularly with clozapine, haloperidol and phenothiazines. Lithium increases both neutrophil and WCC and has been used to maintain clozapine treatment in patients who have developed neutropenia.</td>
</tr>
</tbody>
</table>
6. CARDIAC RISK INCLUDING QT PROLONGATION

All antipsychotics have a degree of cardiac risk including

- Arrhythmias
- Syncope
- QT Prolongation
- Torsade de pointes (potentially life threatening heart arrhythmia)(17)
- Sudden cardiac death

Factors that increase the risk of QT prolongation include

- Increased antipsychotic dose(18) or using more than one antipsychotic in combination (QT interval appears dose dependent).
- Older age(17)
- Female gender(20)
- Cardiovascular disease, ischaemic heart disease, (20), structural heart disease e.g. valvular heart disease, myocarditis or cardiomyopathy
- Hypertension(17)
- Electrolyte disturbances including hypokalaemia or hypomagnesemia
- SSRIs increase antipsychotic drug levels which can result in QT prolongation e.g. fluoxetine(19)

Some non-psychotropic drugs commonly associated with QT prolongation include

- Erythromycin
- Ampicillin
- Chloroquine
- Clarithromycin
- Co-trimoxazole
- Tamoxifen

(A more extensive, but still not exhaustive, list can be found in Appendix 6)

<table>
<thead>
<tr>
<th>NO KNOWN EFFECT</th>
<th>LOW EFFECT</th>
<th>MODERATE EFFECT</th>
<th>HIGH EFFECT</th>
<th>UNKNOWN EFFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>Clozapine</td>
<td>Amisulpride</td>
<td>Haloperidol</td>
<td>Pipotiazine</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>Fluoxetine</td>
<td>Chlorpromazine</td>
<td>Pimozide</td>
<td>Trifluoperazine</td>
</tr>
<tr>
<td></td>
<td>Fluphenazine</td>
<td>Lurasidone(38)</td>
<td>Sertindole</td>
<td>Zuclopenthixol</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Melperone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perphenazine</td>
<td>Pericyazine(21)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>Promazine(22)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulpiride</td>
<td>Quetiapine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Zotepine</td>
</tr>
</tbody>
</table>

Quantifying Risk - Effect on QTc Interval

(QTc – QT corrected for heart rate)

- No Known Effect - No reported QTc prolongation at therapeutic doses or in overdose
- Low Effect - Severe QTc prolongation following overdose or small average increases (<10ms) at clinical doses.
- Moderate Effect - Prolonged QTc by >10ms on average at normal clinical doses or when ECG monitoring is officially recommended in some circumstances.
- High Effect - Extensive average QTc prolongation (usually >20ms at normal clinical doses) or where ECG monitoring is mandated by the manufacturer’s data sheet.
**Recommendations**
- Prescribe drugs with the lowest effect on QT interval
- Use minimum effective dose
- Avoid polypharmacy
- Avoid prescribing more than one drug that prolongs QT interval
- Avoid hepatic enzyme inhibitors
- Review ECG, if you have any concerns.

**Actions to be taken**
- \( QT_c \) <440ms (men) or <470ms (women)
  - No action required unless abnormal T wave morphology – consider referral to cardiologist if in doubt.
- \( QT_c \) >440ms (men) or >470ms (women) but <500ms (both sexes)
  - Consider switch to drug of lower effect, lower dose of drug. Repeat ECG after change and consider referral to cardiologist.
- \( QT_c \) >500ms (both sexes)
  - Stop suspected causative drug(s) and switch to drug of lower effect (if required). Repeat ECG after change. **Refer to cardiologist immediately.**
- Abnormal T – wave morphology
  - Review treatment. Consider switch to drug of lower effect. **Refer to cardiologist immediately.**
- Correct electrolyte disturbances (potassium and magnesium) if present

**ECG Monitoring recommendations** *(Maudsley Prescribing Guidelines 11thEdn)*

<table>
<thead>
<tr>
<th>Low effect</th>
<th>No other risk factors</th>
<th>Physiological/Pathological risk factors*</th>
<th>When co-administering with other QTprolonging drugs**</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Baseline ECG, then after dose change, consider referral to cardiologist</td>
</tr>
<tr>
<td>Moderate effect</td>
<td>None</td>
<td>Correct risk factors if possible, if not baseline ECG, then after dose change, consider referral to cardiologist</td>
<td>Avoid or refer to cardiologist</td>
</tr>
<tr>
<td>High effect</td>
<td>Baseline ECG, then after dose change, consider referral to cardiologist</td>
<td>Correct risk factors if possible, if not - avoid</td>
<td>Avoid</td>
</tr>
<tr>
<td>Unknown effect</td>
<td>None</td>
<td>Correct risk factors if possible, if not baseline ECG, then after dose change, consider referral to cardiologist</td>
<td>Avoid or refer to cardiologist</td>
</tr>
</tbody>
</table>

* In addition to those mandated by patient’s condition.
**Additional requirements to those already mandated by the use of these drugs alone.
Haloperidol – Specific Advice.

The ‘Summary of Product Characteristics’ for Haloperidol (last updated February 2014) states

Very rare reports of QT prolongation and/or ventricular arrhythmias, in addition to rare reports of sudden death, have been reported with haloperidol. They may occur more frequently with high doses and in predisposed patients.

The risk-benefit of haloperidol treatment should be fully assessed before treatment is commenced and patients with risk factors for ventricular arrhythmias such as cardiac disease, family history of sudden death and/or QT prolongation; uncorrected electrolyte disturbances, subarachnoid haemorrhage, starvation or alcohol abuse, should be monitored carefully (ECGs and potassium levels), particularly during the initial phase of treatment, to obtain steady plasma levels. The risk of QT prolongation and/or ventricular arrhythmias may be increased with higher doses or with parenteral use, particularly intravenous administration. ECG monitoring should be performed for QT interval prolongation and for serious cardiac dysrhythmias if haloperidol is administered intravenously.

Haloperidol should be used with caution in patients known to be slow metabolisers of CYP2D6, and during use of cytochrome P450 inhibitors. Concomitant use of antipsychotics should be avoided.

Baseline ECG is recommended prior to treatment in all patients, especially in the elderly and patients with a positive personal or family history of cardiac disease or abnormal findings on cardiac clinical examination. During therapy, the need for ECG monitoring (e.g. at dose escalation) should be assessed on an individual basis. Whilst on therapy, the dose should be reduced if QT is prolonged, and haloperidol should be discontinued if the QTc exceeds 500 ms.

Periodic electrolyte monitoring is recommended, especially for patients taking diuretics, or during intercurrent illness.
7. REGULATION OF PROLACTIN SECRETION

Prolactin is a hormone secreted in the anterior pituitary gland.

- Hypothalmic dopamine is a prolactin-inhibiting neurotransmitter\(^{(59)}\).
- Through portal pituitary circulation it binds to D\(_2\) receptors on the membrane of pituitary lactotroph cells. A reduction in dopamine results in a rapid increase in prolactin secretion.
- Stimulation of D\(_2\) receptors inhibits synthesis and release of prolactin in the tuberoinfundibular pathway of the brain\(^{(24)}\).

The normal range of prolactin is\(^{(43)}\):

<table>
<thead>
<tr>
<th>Sex</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male:</td>
<td>0 - 424 mIU/L (0-20 ng/ml)</td>
</tr>
<tr>
<td>Female:</td>
<td>0 - 530 mIU/L (0-25 ng/ml) (not-pregnant or breast-feeding)</td>
</tr>
</tbody>
</table>

Antipsychotic Effect on Prolactin\(^{(25,27,43,83,84,85)}\)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on Prolactin Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amisulpride/Sulpiride</td>
<td>++ / +++</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>-</td>
</tr>
<tr>
<td>Clozapine</td>
<td>-</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>- / +</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>- / +</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>++ / +++</td>
</tr>
<tr>
<td>Risperidone</td>
<td>++ / +++</td>
</tr>
</tbody>
</table>

Typical antipsychotics:

- Thioxanthenes (Flupentixol, Zuclopenthixol)
  - Increase of prolactin 2-3 fold during the 1\(^{st}\) month with reduction and normalisation after 6 months
- Phenothiazines (Chlorpromazine, Fluphenazine, Pipotiazine Trifluoperazine)
  - 2-3 fold increase occurs within hours of treatment initiation with further 2 fold elevation in the following weeks
- Butyrophenones (Haloperidol)
  - Similar to phenothiazines
Consequences of Hyperprolactinaemia

Hyperprolactinaemia is often superficially asymptomatic and may well not affect the quality of life. Prolactin levels can rise after exercise, meals, sexual activity, during REM sleep and in the early morning. But persistent elevation of prolactin levels is associated with a number of adverse consequences.

Acute effects of Hyperprolactinaemia(84)

<table>
<thead>
<tr>
<th>Male</th>
<th>Both sexes</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diminished ejaculate volume</td>
<td>Loss of libido or sexual dysfunction</td>
<td>Oligorrhoea or Amenorrhea</td>
</tr>
<tr>
<td>Oligospermia</td>
<td>Galactorrhoea</td>
<td>Atrophic changes in vaginal mucosa</td>
</tr>
<tr>
<td>Gynaecomastia</td>
<td>Infertility</td>
<td>Reduced vaginal lubrication</td>
</tr>
</tbody>
</table>

Long Term Complications of Hyperprolactinaemia(25)

Sexual Developments in Adolescents
Due to reduced levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), children and adolescents on prolactin elevating antipsychotics may have problems such as delayed sexual maturation or reduced bone growth.

Osteoporosis (60,66,67,68,69,70)

The patients greatest at risk of bone mineral density loss (BMD) are young women pre-puberty. Studies have reported that 25%–65% of patients with schizophrenia suffer from bone loss after taking antipsychotic drugs. Normalisation of serum prolactin prevents further bone loss, however BMD never returns to normal.

It is encouraged that patients are provided with information on the importance of a well-balanced diet with appropriate intake of calcium and vitamin D, weight-bearing exercise, smoking cessation, limiting caffeine and alcohol intake, and ensuring adequate exposure to sunlight.

In addition to monitoring BMD, bisphosphonates may be used as a preventive measure in patients at high risk for osteoporosis. Vitamin D therapy is also recommended in patients suffering from a decrease of bone mineral density.

Breast Cancer

There is conflicting data on whether hyperprolactinaemia is a contributory factor in breast cancer. Some studies suggest that raised prolactin may have an aetiological role in breast cancer, whilst others have reported no increased risk. Furthermore, hyperprolactinaemia, is often associated with hypogonadism, which may protect...
against breast and prostate cancer. It seems likely that most people receiving antipsychotics will not develop cancer as a result of the drug and any potential risk should be balanced against the therapeutic benefits of the drugs.

**Monitoring & Baseline Prolactin Levels**

A baseline prolactin level should be taken prior to initiation of antipsychotics known to cause hyperprolactinaemia, as in some instances even a single dose can elevate prolactin.\(^3\)

Measuring a baseline prolactin level, and finding it is normal, can often prevent an MRI of the pituitary at a later stage if hyperprolactinaemia were to occur. Levels of mild hyperprolactinaemia (up to about 1000mU/L) should have at least one repeated blood test before referral, assuming it is not drug related. In cases of only modest hyperprolactinaemia when the prolactin level remains persistently elevated and no cause is identified, pituitary imaging is indicated.\(^3\)

For levels > 1000mIU/L, taken prior to the initiation of any antipsychotic, the patient should be referred to an endocrinology department.

For levels >3000mIU/L (at any stage), the patient should be referred to endocrinology as such raised levels may indicate a prolactinoma.

**Interventions for Hyperprolactinaemia**

The diagnosis of hyperprolactinaemia should not be made on a single blood test as it should be remembered that stress can raise prolactin levels. In some individuals even the act of venupuncture can result in high levels.

Levels of mild hyperprolactinaemia (up to about 1000mU/L) should have at least one repeated blood test before referral assuming it is not drug related.

It has been noted that stress can cause levels of up to 2000mU/L while dopamine antagonists can cause levels in excess of 5000mU/L.

- A patient receiving antipsychotic treatment for several years may continue to have significantly higher baseline prolactin levels than untreated healthy controls.\(^{(23)}\)
- Women are likely to seek medical attention as a result of menstrual disturbances, galactorrhoea or infertility, but not if they are asymptomatic.
- An endocrine cause of elevated serum prolactin should be excluded – do not miss pituitary adenoma (MRI). Check thyroid function.
- Macroprolactin (biologically inactive form of prolactin) should be considered and tested for if prolactin levels are high but there are no associated signs or symptoms.
- Check sex hormones if there are concerns about long term cardiovascular and bone health.
- It is good practice to have a baseline prolactin level pre-initiation of antipsychotic medication – this may save unnecessary investigation.
Management Steps\(^{(43,72,73)}\)

- If the prolactin is raised but the patient is asymptomatic, continue antipsychotic and monitor for symptoms. Inform the patient and be aware of long term complications.
- If the prolactin is raised and the patient is symptomatic consider:
  - A dose reduction or withdrawal of the antipsychotic.
  - Substitution of the current antipsychotic with one with a lower potential to elevate prolactin (See table 1). However, consider full profile of replacement drug to ensure benefits of the change exceed any new associated risk.
  - If the above are not feasible, consider low dose aripiprazole as an add-in to treat the hyperprolactinaemia. **Before add-on therapy is considered, aripiprazole monotherapy should be evaluated and tried where possible.**
  - If neither the above are appropriate, consider the cautious administration of dopamine agonists (they have the potential to worsen psychosis – see below for more information)

When oral antipsychotic therapy is discontinued baseline level of prolactin may take up to 3 weeks to return to normal range,\(^{(13)}\) whilst in the case of depot medication normalization may take as long as 6 months.\(^{(13)}\)

**Treatment with Dopamine agonists**

The dopamine agonists available and licensed for use are bromocriptine, cabergoline (both ergot derived) and quinagolide (non ergot-derived). The advice of a specialist should be sought whenever treatment with a dopamine agonist is considered.

**Side effects and Cautions\(^{(15)}\)**:

- Side effects: Nausea, constipation and headache are common. For a full list of side effects, please consult the manufacturer’s leaflet.
- Cautions: **All dopamine agonists have the potential to worsen psychosis.**
  - Cabergoline and bromocriptine should be used with caution in patients with a history of peptic ulcer.
  - Cabergoline and bromocriptine have been associated with fibrotic reactions.

**Fertility and Pregnancy:**

- Successful treatment of hyperprolactinaemia in women of child-bearing age will restore periods and increase fertility.
- Informing patients of this is necessary, as contraception may be required.
- If a client is to become pregnant, their treatment with a dopamine agonist will need to be reviewed by their endocrinologist.

8. **USE OF ANTIPSYCHOTICS DURING PREGNANCY** (26,27,28)

<table>
<thead>
<tr>
<th>Name</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol, Chlorpromazine,</td>
<td>There is most experience with these FGAs. Use of low dose is recommended by NICE</td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td><strong>Chlorpromazine</strong> can cause sedation and constipation, which may be a problem.</td>
</tr>
<tr>
<td>Olanzapine, Quetiapine and</td>
<td>These are the preferred SGAs They all have limited safety data. The potential for long-term postnatal developmental defects is not known.</td>
</tr>
<tr>
<td>Risperidone</td>
<td><strong>Olanzapine</strong> – consider the risk factors for gestational diabetes and weight gain. Effect on foetal size should be monitored</td>
</tr>
<tr>
<td></td>
<td><strong>Quetiapine</strong> - If a clinical decision is made to prescribe, there is more experience with the immediate release preparation (rather than XL) and this should be used in preference. The incidence of hyperglycaemia in patients exposed to quetiapine appears to be lower than that for olanzapine or risperidone.</td>
</tr>
<tr>
<td></td>
<td><strong>Risperidone</strong> - Consider the risk factors for dose dependent hyperprolactinaemia and EPSE.</td>
</tr>
</tbody>
</table>

Notes:

- If a pregnant woman is stable on an antipsychotic and likely to relapse without medication, advise her to continue the antipsychotic.

- Contraception and the risks of pregnancy (including relapse, risks associated with stopping or changing medication, and risk to the foetus) should be discussed with all women of childbearing potential who have a mental disorder and/or who are taking antipsychotic medication.

- Patients taking antipsychotics who are planning a pregnancy should be advised that hyperprolactinaemia reduces the chance of conception. If levels are raised an alternative drug should be considered.

- Do not introduce medication during pregnancy unless clearly necessary and only after careful consideration of the risk/benefit.

- When choosing an antipsychotic, take into account that there are limited data on the safety of these drugs in pregnancy and the postnatal period.

- Patients receiving antipsychotic treatment are at a risk of relapse and may need to be maintained on treatment during and after pregnancy. The risk of relapse is not eliminated even if medication is continued throughout pregnancy and postpartum.

- As a general prescribing principle during pregnancy, the lowest effective dose should be used. Polypharmacy should be avoided whenever possible.
• All antipsychotics are associated with neonatal withdrawal syndrome. Therefore, if clinically appropriate, consideration should be given to reducing the dose near term. The risk of relapse must be considered.

• In the management of mania associated with bipolar disorder, a low dose FGA or SGA is recommended as the treatment of choice by NICE.

• Infants born to women with schizophrenia exposed to FGAs may be at an increased risk of neural tube defects. Folic acid supplementation is recommended (as with any pregnancy). Specific dosage recommendations should be considered on an individual basis.

• Clozapine is associated with a theoretical risk of agranulocytosis in the foetus. Consider the risk factors for gestational diabetes and neonatal seizures. Do not routinely prescribe.

• Depot antipsychotics are associated with EPSE in the neonate, which may persist for several months. Do not routinely prescribe.

• Anticholinergic drugs for treatment of EPSE may be associated with a small increase in the risk of congenital malformations and also neonatal withdrawal effects. Do not routinely prescribe. Consideration should be given to dose adjustment and timing changes of the antipsychotic or a switch to an alternative drug.

• Advise pregnant women taking antipsychotic medication about diet and monitor for excessive weight gain, in line with the guideline on weight management before, during and after pregnancy (NICE guideline PH27).

• Monitor for gestational diabetes in pregnant women taking antipsychotic medication in line with the guideline on diabetes in pregnancy (NICE guideline CG63) and offer an oral glucose tolerance test.

Specialist Advice

Always obtain up to date advice and treat each case individually. Experience with newer drugs is growing and a change in treatment may not be necessary or advisable. Contact The National Teratology Information Service for specialist advice (0191 232 1525).
## 9. USE OF ANTIPSYCHOTICS WHEN BREAST FEEDING \(^{(26,27,28)}\)

<table>
<thead>
<tr>
<th>Drugs Recommended (^{(26)})</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine</td>
<td>Low amounts excreted in breast milk. Limited data available.</td>
</tr>
<tr>
<td>Sulpiride</td>
<td>Low amounts excreted in breast milk.</td>
</tr>
</tbody>
</table>

### Also commonly prescribed

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>Amounts excreted in breast milk are variable.</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Amounts excreted in breast milk are variable.</td>
</tr>
</tbody>
</table>

### Notes:

- Guidance from NICE \(^{(26)}\) encourages women with a mental health problem to breastfeed, unless they are taking carbamazepine, clozapine or lithium (valproate is not recommended to treat a mental health problem in women of childbearing potential). However, support each woman in the choice of feeding method that best suits her and her family.

- Up to date advice should be obtained and the lowest effective dose used. Specific enquiries regarding the use of antipsychotics during lactation can be addressed to the National Medicines Information Service via their website: [www.ukmicentral.nhs.uk](http://www.ukmicentral.nhs.uk)

- The benefits of breast-feeding to the mother and infant must be weighed against the risks due to exposure in the infant. Data on safety is largely derived from small studies or case reports. Information must be interpreted with caution. A treatment that allows breast-feeding should be explored rather than recommending not to breast-feed.

- The treatment regime established during pregnancy should be continued after delivery if clinically indicated. All antipsychotics are detected in the milk. Drug exposure to an infant whilst breast-feeding is less than when in utero. All breast-fed infants should be monitored for sedation and extrapyramidal adverse effects.

- Infant exposure can be reduced by timing feeds to avoid peak drug levels.

- When prescribing medication to breast-feeding women, consideration should be given to the health of the neonate. Premature infants are at greater risk from exposure due to immature excretory function and consequent risk of drug accumulation.

- Clozapine is associated with a risk of agranulocytosis and seizures in the infant. Do not routinely prescribe whilst breast-feeding.

- The advice of a clinical pharmacist can be sought to aid the patient and clinician in the decision making process.

- The National Teratology Information Service (NTIS) uses case reports of drug exposure during pregnancy in order to expand their evidence base and should be contacted for further advice regarding reporting individual cases.
10. THE USE OF ANTIPSYCHOTIC MEDICATION IN PEOPLE WITH LEARNING DISABILITIES

Whenever a patient is transferred between settings and a review of medication is needed after transfer, the date of the review and what needs reviewing must be clearly communicated to the receiving GP, community team or ward. This information must also be shared with the patient and if appropriate the carer.

10.1 Introduction

Although the use of antipsychotic medication in people with learning disabilities (LD) is a relatively common occurrence, there are specific issues relating to this patient group concerning assessment, titration and long-term treatment (16). Diagnosis can be difficult in people with limited language skills although this may be easier in those with a mild degree of LD if sufficient allowance is made for their reduced vocabulary. Many individuals with LD may have a concomitant behaviour disorder which may confound diagnosis, particularly where there is major impairment of social interaction (16).

People with LD are more likely to develop side effects with antipsychotics due to their underlying brain damage. The most common side effects are neurological, particularly extrapyramidal side effects such as Parkinsonism, dystonia, akathisia and tardive dyskinesia. People with LD are also likely to experience other side effects such as QT interval prolongation, hepatic impairment and blood dyscrasia, due to their multisystem impairment. There is good evidence in adults with normal intelligence that antipsychotics may cause sedation, psychomotor impairment and decreased ability to concentrate. These effects may be compounded in adults with LD because of the underlying organic condition (16).

A study designed to review the efficacy of antipsychotics in this patient group found no trial-based evidence for the effectiveness or ineffectiveness of any antipsychotic medication, noting that trials often exclude people with LD (30). The study authors concluded that until better evidence is forthcoming, clinicians will have to continue to base practice on clinical experience and evidence from the non-learning disabled population.

Every effort should be made to involve service users and carers in shared decision making around medication use, using appropriate resources, which may need to be tailor made to meet an individual’s need and should include information as to the evidence base for treatment, along with side effect and monitoring information.

It is critical to use accessible information to support choice and consent in this client group, as traditional resources may not be helpful and in some cases may cause confusion & treatment failure. This may be preventable by involving family and carers in treatment choices and utilising their expertise to find bespoke solutions for that individual.

Please see Sussex Partnership medicines information section for further information about accessible information.

The main areas of use for antipsychotics in people with LD are psychosis, self-injurious behaviour and autistic spectrum disorders.
10.2 Psychosis

It is preferable to use SGAs first line with starting doses lower than those used in the general population. A minimum of one week between each increment in dose is recommended. If initial treatment is ineffective or poorly tolerated, another SGA should be considered. If the second drug is also found to be ineffective, this may indicate drug resistance and clozapine should be tried. Informed consent would be needed for the use of clozapine and if that is impossible, a multidisciplinary meeting, with the intention of a 'best interests' decision, arranged. If clozapine is also found to be ineffective, augmentation strategies should be considered, for example mood stabilization if required.

10.3 Self-injurious behaviour (SIB)

Often SIB is behavioural and therefore requires a behavioural approach. The cause of SIB should be investigated and antipsychotics only used if associated with mental illness. Consideration should be given to physical illness as the cause of SIB and appropriate investigations conducted into possible causes for a change in behaviour. Drug treatment should only be considered if and when adequate trials of psychological treatments or physical health interventions have failed. It is believed that super sensitivity of dopamine neurons in the nigrostriatal pathways may predispose to SIB. Dopamine D2 blockers may be more effective than D2 blockers, for example the thioxanthenes flupentixol and zuclopenthixol. SGAs are poorly evaluated but there is most experience with risperidone. If there is poor or no response to risperidone or intolerable side effects, olanzapine may be tried. Other non antipsychotic drug treatments for SIB include; opiate antagonist naltrexone for pain insensitivity, SSRI for OCD associated SIB, and anxiolytics / mood stabilizers for SIB associated with high arousal or distress. However, it should be borne in mind that the evidence base for the use of these medications is at best rather slim and not robust enough to draw a firm conclusion of benefit. Using these medications for SIB would constitute an off license use. As such clear plans for monitoring target symptoms pre and post introduction of any medication should be used to assess both beneficial and adverse effects.

10.4 Autistic Spectrum Disorder (ASD)

Please note this section only applies to patients above 18 years. For the treatment of patients less than 18 years please refer to Section 11.3 (Prescribing in Children and Young Peoples Services).

Several classes of medication, included antipsychotics are not recommended for the treatment of core symptoms of autism in adults. These should be dealt with using psychosocial interventions. The Nice Clinical Guidelines for the treatment of Autism states “Antipsychotic medication should be prescribed by a specialist and quality of life outcomes monitored carefully. Review the effects of the medication after 3-4 weeks and discontinue if there is no indication of a clinically important response at 6 weeks.”

Small doses of risperidone, may be tried for aggression and anxiety. Small doses of risperidone, olanzapine or haloperidol may help with stereotypical behaviours and rituals. Particular attention needs to be paid to the possible development of movement disorders when using antipsychotics because individuals with ASD have a tendency to develop movement disorders and tics as part of their autistic disorder. As such it is advisable to assess for the presence of movement disorders prior to the introduction of any psychototropic medication, this can then be used as a baseline measurement, to understand whether the medication is a causative factor. Any assessment of potential side effects should always include the dose and frequency of any medication taken and
outline where no medication is currently being taken or has recently been commenced or discontinued.\(^{(16)}\)

It should be noted that the evidence basis for the use of antipsychotics in ASD is small and mainly related to the use of risperidone.\(^{(49)}\) Therefore, care should be taken to ensure treatment is appropriate and efficacious, with monitoring for side effects and any behavioural changes clearly documented.

### 10.5 Challenging Behaviour

An understanding of the factors associated with challenging behaviour is essential for a successful intervention. Again a physical health review may prevent the need for psychotropic intervention in some cases.

NICE NG11 states that medication should be considered for coexisting mental or physical health problems identified as a factor in the development and maintenance of behaviour that challenges shown by children, young people and adults with a learning disability.

Drug treatment for challenging behaviour should only be considered as a last resort and used in combination with psychological or other interventions as outlined by NG11. The choice of treatment will depend on the degree of sympathetic arousal, the extent of hyperactivity and the presence of epilepsy or an abnormal EEG. Historically, antipsychotics have been used to manage challenging behaviour. However, the evidence to support this practice outside of the context of mental illness is sparse. Cochrane suggests that “without randomised controlled trial-based evidence, clinicians will have to continue to base practice on clinical experience and humane judgement.”\(^{(49)}\)

As with all medication, collaboration with patient and carers should be sought wherever possible, to inform treatment choice.

The following should be documented once the target behaviour has been identified & the method for monitoring effectiveness of treatment agreed:

- A rationale for medication (explained to the person with a learning disability and everyone involved in their care, including their family members and carers)
- How long the medication should be taken for
- A strategy for reviewing the prescription and stopping the medication.

NICE guidance NG11, which offers more detailed information, may be accessed via the following link:


### 10.6 Drug Interactions

Co-morbidity is common in people with LD such as physical illness or epilepsy resulting in multiple drug regimes. This increases their risk of drug interactions. Some of the important drug interactions are given in section 5 of the BNF or the pharmacy team should be consulted for more detailed information.
10.7 Prescribing and monitoring

Ideally only one antipsychotic should be prescribed at any given time and it is generally unacceptable for more than two antipsychotics to be prescribed concurrently. If two or more antipsychotics are considered necessary, a second opinion is advisable. For all people with LD prescribed an antipsychotic, it is important to document the rationale for treatment (including some measure of baseline target behaviours), potential risk/benefit and consent in the patient’s notes. The impact of medication, side effects experienced and a consideration of drug interactions should also be recorded.

Physical health monitoring in line with NICE guidance should be standard in all patients with a Learning Disability as those without. It is important to consider that individuals with a Learning Disability often have poorer health outcomes than the general populations & are more prone to side effects of psychotropic medication.

As such, a proactive approach to physical health monitoring & care is critical to ensuring quality of life & minimising risks associated with treatment.
11. THE USE OF ANTIPSYCHOTICS IN CHILDREN AND YOUNG PEOPLE.

11.1 Introduction

Antipsychotics are used for a variety of presentations in children and adolescents, however very few antipsychotics are licensed for use in childhood disorders, and the evidence base for their use in children and adolescents is poor.

Whenever a patient is transferred between settings and a review of medication is needed after transfer, the date of the review and what needs reviewing must be clearly communicated to the receiving GP, community team or ward. This information must also be shared with the patient and if appropriate the carer.

Antipsychotics are also less well tolerated in children and adolescents than in adults. This population appear to have a higher risk of experiencing/developing adverse effects including extrapyramidal symptoms (EPSEs), prolactin elevation, sedation, weight gain and metabolic side-effects.\(^{31,32}\)

This makes the choice of antipsychotic particularly challenging. The following general recommendations can be made for all patients prescribed antipsychotics, irrespective of diagnosis.\(^{27}\)

- Antipsychotics should only be used where their use has been fully explained (verbally and written), and consent sought from the patient’s parent(s) or carer(s) where appropriate. Appropriate forms are available on the Trust website.

- Choice of antipsychotic should be based on limited efficacy data available and side-effect profile.

- Patient and/or parent(s) or carer(s) should be directly involved in the choice of medication, with the expected benefits and risks fully discussed and recorded.

- Before initiation of any antipsychotic therapy, baseline investigations as indicated in section 11.6.4 should be completed.

- Use of antipsychotics should target symptoms, not the diagnosis.

- Low starting doses should be used, then increase gradually to response.

- An adequate trial of medication before changing. (8-12 weeks is a reasonable time for benefits of treatment to be witnessed in children and adolescents).

- Only one medication should be changed at a time.

- Outcome, tolerability and dose should be regularly reviewed.

11.2 Management of Psychosis & Schizophrenia:

Onset of schizophrenia often occurs in adolescence. Childhood onset is much less common, psychotic illness rarely occurs in prepubertal children. The response of children and adolescents with psychosis to antipsychotics is relatively low. Childhood and adolescent-onset schizophrenia is generally more severe and treatment-refractory than adult-onset, and has a poorer prognosis.\(^{33}\)
There is a limited amount of data in child- and adolescent-onset psychosis. Most data is derived from adult studies, open labelled studies and case reports. However children and adolescents may not respond in the same way as adults.

11.2.1 Dosing recommendations:

Risperidone:
Not licensed for use in children and adolescents (other than for conduct disorder). Widely used for the management of psychosis, although raised prolactin and weight gain are problematic. (35)
Suggested dosing for the management of psychosis in children and adolescents aged 12-18 years. (34)

- Day 1: 2mg daily (in 1-2 divided doses).
- Day 2: increased to 4mg daily (in 1-2 divided doses).
- Usual dose range 4-6mg daily (in 1-2 divided doses).
- Doses >6mg/day only if benefit outweighs risk. Max 16mg/day. (Care: Higher dosing significantly increases the risk of EPSE)

Olanzapine:
Not licensed for any indication in children and adolescents.
Sedation, weight gain & derangement of blood lipids are problematic with the use of olanzapine in children and young people (86)
Suggested dosing for management of psychosis in children and adolescents aged 12-18 years. (34)

- Initially 5-10mg/day
- Adjusted to usual range of 5-20mg/day.
- Doses >10mg only after reassessment.
- Max 20mg/day.
Note: When one or more risk factors for slower metabolism are present e.g. female or non-smoker consider lower initial dose and slower dose titration

Quetiapine:
Not licensed for use in children and adolescents.
The recent evidence update to NICE CG155 (103) suggests that there is evidence (87) that quetiapine after 6 weeks appears to improve schizophrenia symptoms in young people aged 13–17 years, with a safety profile similar to that in adult populations. However such use of quetiapine over 26 weeks can be limited by a number of adverse effects, including potentially clinically significant lipid disturbance, weight gain, and raised blood pressure (88)
Suggested dosing for the management of psychosis in children and adolescents aged 12-18 years (34).

- Initially 25mg BD adjusted in steps of 25-50mg according to response/tolerability.
- Usual dose range of 400-600mg
- Max 750mg/day.

Aripiprazole:
Licensed for the use in adults and adolescents aged 15 years and over for the treatment of schizophrenia (36). Indicated for the treatment (up to 12 weeks) of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older (36).
Suggested dosing regime for the management of psychosis & mania/hypomania associated with bipolar disorder in children and adolescents aged 12-18 years.\(^{(36)}\)

- Initially 1 - 2 mg once daily; increase to 5 mg after 2 days and to 10 mg (target dose) after 2 further days.\(^{(36)}\)
- If further dose increase clinically indicated, increase in 5mg steps
- Maximum BNF daily dosage is 30 mg; in psychosis efficacy is shown to be no greater at 30 mg/day compared to 10 mg/day \(^{(36)}\). The trust recommends a maximum of 15mg daily.

**Amisulpride:**
Not licensed for use in children and adolescents \(^{(34)}\): Recommended dosing regime\(^{(34)}\)

- Acute psychotic episode: 200-400mg BD. Max 1.2g daily.
- Predominantly negative symptoms: 50-300mg daily. Max 300mg daily.

**Clozapine:**
Licensed for the management of treatment resistant schizophrenia in patients aged 16 years and over.\(^{(38)}\)
Clozapine treatment in children and adolescents has been demonstrated to improve psychosis, bipolar disorder, treatment refractory schizophrenia, tardive dyskinesia, and aggression\(^{(27,32,33,39)}\)\(^{\text{40}}\). Clozapine has been shown to be more effective than haloperidol\(^{(40)}\) and olanzapine\(^{(41)}\) in the treatment of psychosis in children and adolescents.

Use of clozapine may be appropriate in treatment resistant patients (as with adult population). Refer to Appendix 3 for initiation guidelines.

This population may however be more prone to seizures and neutropenia than the adult population.\(^{(40)}\) Cardiovascular adverse effects are also documented as being more prevalent in children and adolescents. Orthostatic hypotension (12%) and tachycardia (28%) were commonly reported in one study.\(^{(40)}\)

**11.3 Aggression associated with Autism:**

**11.3.1 SGAs:**

Risperidone is currently the only licensed SGA for the management of conduct disorder. Licensed for children aged 5 years and over for short term use (up to 6 weeks).\(^{(42)}\) There is some evidence that effects persist for several months.\(^{(27,37)}\) Long-term (unlicensed) use (up to three years) appears safe and effective, and may be effective in relapse prevention and reducing disruptive behaviour.\(^{(43)}\) Risperidone has been shown to reduce hyperactivity, stereotyping, aggression and repetitive behaviour, and may possibly be effective in treating depression and irritability.\(^{(27,43)}\)
<table>
<thead>
<tr>
<th>The Manufacturers’ dosage recommendations according to child weight</th>
<th>Initial starting dose</th>
<th>Optimal Dose</th>
<th>Max. Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 kg</td>
<td>0.25mg OD</td>
<td>0.5mg OD</td>
<td>0.75mg OD</td>
</tr>
<tr>
<td>50 kg</td>
<td>0.5mg OD</td>
<td>1mg OD</td>
<td>1.5mg OD</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BNFc dosage recommendations according to age/weight</th>
<th>Initial starting dose</th>
<th>Optimal Dose</th>
<th>Max. Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Over 5 years age (15-20kg)</td>
<td>250mcg</td>
<td>Increased to 500mcg after 4 days, then by 250mcg daily at 2-week intervals</td>
<td>1mg OD</td>
</tr>
<tr>
<td>Up to 12 years (&gt;20kg)</td>
<td>500mcg</td>
<td>Increased to 1mg after 4 days, then by 500mcg daily at 2-week intervals</td>
<td>Under 45kg = 2.5mg Over 45kg = 3mg</td>
</tr>
</tbody>
</table>

If risperidone is ineffective or not tolerated, aripiprazole is a suitable alternative. Aripiprazole, whilst not licensed in the UK is licensed in the US for treatment of irritability associated with autism in children and adolescents of 6-17 years old with two short term and one long term studies showing efficacy. Somnolence and weight gain were noted.

Suggested Dosing: 
- Initially 0.5 - 1mg daily
- Increase gradually in line with symptom control, aim for 5-10mg daily
- Maximum dose of 15mg daily

Evidence for the use of other SGAs is limited. However, olanzapine and clozapine may also be effective. Weight gain and sedation may be more problematic than with risperidone and aripiprazole.

Quetiapine appears not to be effective in the treatment of aggression in autistic patients.

11.3.2 FGAs:

Use of FGAs is generally avoided, due to concerns over extrapyramidal side-effects, including tardive dyskinesia, elevated prolactin and QTc prolongation. Haloperidol is licensed for the treatment of childhood behavioural disorders, associated with hyperactivity and aggression, and small placebo-controlled studies have shown it to be effective in reducing withdrawal, over activity, mood dysregulation, and irritability.

Children aged 3-13 years:
- Initially 0.25mg daily in 2-3 divided doses
- Usual target dose of 0.5 - 3mg daily in divided doses
Children aged 13-18 years:\(^{(34)}\)
- Initially 0.25mg daily in 2-3 divided doses
- Usual target dose of 2 – 6mg daily in 2-3 divided doses
- Maximum 6mg daily

Pimozide has also been shown to be effective in reducing aggression.\(^{(27)}\) However it is rarely used in practice due to the potential for QTc prolongation. ECG monitoring is essential. It is licensed for schizophrenia and other psychoses in patients aged over 12 years.

### 11.4 Tourette's Disorder and Tics:

Haloperidol is licensed for the treatment of Tourette’s disorder.\(^{(44)}\)

Risperidone has been shown to be superior to placebo\(^{(38)}\) and as effective as clonidine.\(^{(39)}\)

Aripiprazole has limited open label study data showing efficacy in reducing the severity of tics in Tourette's disorder\(^{(51)}\)

Pimozide (unlicensed) may be as effective as, or superior to haloperidol. QTc prolongation limits use, and ECG monitoring is essential.\(^{(27)}\)

### 11.5 Bipolar Disorder:

Estimates for the prevalence of bipolar affective disorder (BAD) in children and adolescent population vary, reported as 2% in one meta-analysis.\(^{(52)}\) However Bipolar disorder in children under 12 years is considered to be very rare\(^{(92)}\).

Both current NICE guidance\(^{(92)}\) and the British Association for Psychopharmacology (BAP)\(^{(53)}\) evidence based guidance on the use of medication in BAD in children & adolescents, suggest that adult treatment guidelines should be followed due to the limited evidence base available in the under 18 age group.

Currently only aripiprazole has a UK license for the short term treatment (12 weeks) of mania in 13 years and over. Hence to treat mania or hypomania in young people see NICE’s technology appraisal guidance on aripiprazole for treating moderate to severe manic episodes in adolescents with bipolar I disorder\(^{(93)}\) and also consider the recommendations for adults (see relevant sections of this guideline).

When prescribing an antipsychotic refer to section 11.2.1 and the BNF for children\(^{(34)}\) to modify drug treatments, be aware of the increased potential for a range of side effects, and do not routinely continue antipsychotic treatment for longer than 12 weeks.

The choice of medication in the treatment for BPAD will often come down to the severity of the condition presented. The actual medication prescribed should be based on patient specific factors such as physical history, previous response (if applicable), medications prescribed as well as family and patient preferences so affecting compliance.

Almost all the studies completed in patients under the age of 18 years were conducted in the US.\(^{(50)}\)

#### 11.5.1 Severe Mania with psychotic features

In patients who present with severe behavioural disturbance or if psychotic symptoms are present, antipsychotics should be considered first due to the more rapid anti-manic
response compared to lithium \(^{(27,53)}\). If there is no response after a suitable trial treatment period then switching to another antipsychotic in such patients is appropriate.

### 11.5.2 Mild to Moderate Mania

Where there is less severe behavioural disturbance and lack of psychotic symptoms valproate or lithium should be considered as well as antipsychotics as first-line treatments \(^{(27,53)}\).

Do not offer valproate to girls or young women of childbearing potential.

Aripiprazole, olanzapine, quetiapine, and risperidone resulted in more improvement on the CGI–Bipolar scale (version adapted for manic and depressive symptoms) than placebo in child and adolescent patients who primarily had mania or mixed states \(^{(50)}\). There was no significant difference between SGAs and placebo for suicide-related behaviours. The strength of evidence for these outcomes was moderate. \(^{(50)}\)

### 11.5.3 FGAs:

Risk of EPSEs and tardive dyskinesia has limited the use of FGAs in children and adolescents with bipolar affective disorder.

### 11.5.4 SGAs:

**Clozapine:** (not licensed for bipolar disorder)

Clozapine was shown to be effective in treatment of bipolar affective disorder in children and adolescents. \(^{(74,33,50)}\) Leucopenia and seizures were not observed in one study; however, somnolence, enuresis, sialorrhoea, and increased appetite were among the side effects reported. Mean weight gain was 7kg over 6-month treatment period in patients aged 12-17 years \(^{(74,33,50)}\).

**Risperidone:** (not licensed in children or adolescents)

One trial supports the use of risperidone in the management of bipolar affective disorder \(^{(95)}\), which gave it a US license for treatment of mania & mixed states in children 10 years and over \(^{(33,50)}\). Response was achieved in 84% of patients. Reported side effects included weight gain, somnolence and sialorrhoea.

**Olanzapine:** (not licensed in children or adolescents)

Only limited data exists for the use of olanzapine in the management of bipolar affective disorder in under 18 year olds. One open-label study reported response rates of 61% \(^{(96)}\). Weight gain is a significant problem. \(^{(33,50)}\)

**Quetiapine:** (not licensed in children or adolescents)

A placebo controlled trial comparing quetiapine/valproate treatment with valproate/placebo found response rates were significantly greater in the quetiapine/valproate group (87%) than in the valproate/placebo group (53%) \(^{(97)}\). Adjunctive treatment with quetiapine appeared effective and well tolerated; somnolence was the main reported side-effect (80% of patients). \(^{(33,50)}\)

**Aripiprazole:** (Licensed for treatment of mania up to 12 weeks in duration in patients 13 years and over)

Aripiprazole was studied in a 30-week placebo-controlled trial involving 296 children and adolescents (10-17 years), who met DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes with or without psychotic features and had a Young Mania
Rating Scale (Y-MRS) score ≥20 at baseline (98) Aripiprazole was superior to placebo in change from baseline at week 4 and at week 12 on the Y-MRS total score (98).

11.6 Adverse effects:

11.6.1 Extrapyramidal side effects:

Extrapyramidal side effects as a result of antipsychotic treatment are more severe and frequent in children and adolescents in comparison to the adult population (27,31). One study reported 74% of patients exposed to haloperidol developed extrapyramidal side effects (46).

Although use of SGAs in children and adolescents are associated with lower rates of extrapyramidal side-effects and tardive dyskinesia compared with FGAs, these effects have still been reported (27).

A secondary analysis of the C U tLASS-1 trial as well as other retrospective analyses in adult patients, have suggested that SGAs may have as high an incidence in causing EPSE’s as FGA’s in such populations. (54) No such findings to date have been shown in children and young people.

Avoid FGAs where possible. Start at a low dose and increase gradually to an effective dose. Monitor all patients treated with antipsychotic agents, especially those at the upper limit of dosage range.

11.6.2 Prolactin elevation:

The long-term consequences of hyperprolactinaemia are not known. However, these could include: delayed sexual maturation, sexual dysfunction, menstrual abnormalities, infertility, galactorrhoea, gynaecomastia, osteoporosis and reduced bone mineral density (45).

Of the SGAs, risperidone and amisupiride are the most commonly associated with causing hyperprolactinaemia. However, long term studies in children and adolescents have shown only a transient and asymptomatic elevation in prolactin levels (45).

Modest and transient elevations in prolactin have also been reported in children and adolescents receiving treatment with clozapine, olanzapine and quetiapine (45).

11.6.3 Weight gain & metabolic effects:

There are indications that children are more sensitive than adults to the metabolic adverse effects of second generation antipsychotics and the risk of weight gain may be greater in younger populations (32,55). Children tend to gain proportionately more weight and do so more rapidly during treatment than adults (32,55). These increments are rarely seen in adults (55). Early weight gain has lifelong negative metabolic implications (32,45).

Weight gain has been reported in children and adolescents exposed to clozapine, olanzapine, risperidone, quetiapine and aripiprazole (32). The prevalence of weight gain associated with other antipsychotics is not clear. One study reported obesity in 64% of clozapine patients, 56% other SGAs, 30% FGAs and 28% in patients not receiving treatment with an antipsychotic (55).

In a randomized trial comparing olanzapine to quetiapine, in adolescent patients with a first psychotic episode, the increase in weight was 15.5 kg and 5.5 kg over 6 months respectively (56). Similarly one trial reports 78% of patients receiving treatment with
risperidone demonstrated significant weight gain, in comparison with 24% of patients receiving placebo\(^{(32)}\). Weight gain was most rapid in the initial two months of treatment. Other long-term studies have failed to repeat these results.

Blood glucose and lipid levels are also important considerations. One study in children and adolescents reported differing results for changes to lipid profiles and glucose between aripiprazole, olanzapine, quetiapine, and risperidone over the course of 12 weeks\(^{(32)}\). All the antipsychotics saw increases in weight, with olanzapine and quetiapine also showing significant increases of cholesterol and triglyceride levels, whilst risperidone saw significantly elevated levels of triglycerides. Aripiprazole did not show any changes from baseline for these parameters.

The long-term consequences of weight gain and changes in lipid profiles and glucose levels on the cardiovascular system are important considerations. Baseline and regular BMI, weight checks and blood monitoring of biochemical parameters are strongly recommended and endorsed by current NICE Bipolar\(^{(92)}\) & Psychosis\(^{(63)}\) guidance.

### 11.6.4 Monitoring:

The most recently published NICE guidance\(^{(63)}\) on the use of antipsychotics in children and young people (in psychosis and schizophrenia) has indicated that the following investigations should be undertaken and recorded at baseline and also as a subsequent part of routine monitoring.

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Before initiation of antipsychotic therapy</th>
<th>Weekly for first 6 weeks</th>
<th>At 12 weeks</th>
<th>Monitor every 6 months thereafter</th>
<th>Regularly during treatment and particularly during titration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (^1)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Height (^1)</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist and hip circumference (^2)</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP (^2) &amp; Pulse</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting blood glucose</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA(_1c)</td>
<td>Yes</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Blood lipid profile</td>
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</tr>
<tr>
<td>Prolactin</td>
<td>Yes</td>
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<tr>
<td>Movement disorders</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nutritional status</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side effects patient is most or least willing to tolerate</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG (^3)</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side effects</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adherence</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Plotted on a growth chart
2. Plotted on a centile chart
3. To be carried out if the drug SPC states; the child or young person is being admitted as an in patient; specific cardiovascular risk or disease have been identified e.g. high blood pressure, personal or family history of cardiovascular disease such as sudden cardiac death or prolonged QT\(_c\) interval
12. THE USE OF ANTIPSYCHOTICS IN THE ELDERLY

Elderly patients often receive multiple drugs for their multiple diseases. This greatly increases the risk of drug interactions as well as adverse reactions, and may affect compliance. The balance of benefit and harm of some medicines may be altered in the elderly. Therefore, elderly patients’ medicines should be reviewed regularly and medicines which are not of benefit should be stopped. (15)

Whenever a patient is transferred between settings and a review of medication is needed after transfer, the date of the review and what needs reviewing must be clearly communicated to the receiving GP, community team or ward. This information must also be shared with the patient and if appropriate the carer.

Age related changes in pharmacokinetics and pharmacodynamics results in an increased sensitivity to drugs and their side effects.

Prescribing Recommendations(27,43)

- Pre – treatment assessment repeated every 3 – 6months to detect common side effects e.g. postural hypotension, antimuscarinic effects, and Parkinsonism.
- Single daily doses are usually appropriate once stable.
- Doses should be reviewed regularly and a periodic reduction in dose (for some patients) may be indicated.
- Try not to treat the side effects of one drug with another. Find a better tolerated alternative.
- Avoid, where possible, drugs that block α<sub>1</sub> adrenoceptors, have antimuscarinic effects, are very sedative, have a long half life or are potent inhibitors of hepatic metabolising enzymes.

Table of general risk for antipsychotic use in the elderly(43)

<table>
<thead>
<tr>
<th>Lower Risk</th>
<th>Moderate Risk</th>
<th>Higher Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amisulpride</td>
<td>Butyrophenones</td>
<td>Clozapine</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Lurasidone&lt;sup&gt;(58)&lt;/sup&gt;</td>
<td>Phenothiazines</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>Olanzapine</td>
<td>Pimozide</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Quetiapine</td>
<td></td>
</tr>
<tr>
<td>Sulpiride</td>
<td>Thioxanthines</td>
<td></td>
</tr>
</tbody>
</table>

12.1 Use of antipsychotics in dementia

In 2004 the Committee on Safety of Medicines advised of a clear increase in the risk of stroke with the use of the antipsychotics risperidone or olanzapine in elderly people with dementia (approximately three-fold increased risk compared with placebo), and that the magnitude of risk outweighed any likely benefit of treating dementia-related behavioural problems with these drugs. This increased risk is also a cause for concern in any patient with a high baseline risk of stroke. A year later a Europe-wide review concluded that this risk could not be excluded for other antipsychotics (atypical or typical) (57) In a 2009 report for the Minister of State for Care Services Professor Banerjee examines the use of antipsychotic medication within the NHS for people with
dementia and concludes that these drugs appear to be used too often but that, at their likely level of use, potential benefits most probably outweigh their risks\(^{(61)}\)

**Risperidone – Specific Indication**

Only one antipsychotic, risperidone, is licensed for treatment of dementia-related behavioural disturbances in the UK: and then only specifically for short-term (up to six weeks’) treatment of persistent aggression in moderate to severe Alzheimer’s dementia unresponsive to non-pharmacological approaches (i.e. those that do not involve use of medicines) and where there is risk of harm to the patient or others. The risperidone licence for the short-term treatment of persistent aggression in Alzheimer’s dementia was granted in 2008 after a new analysis of three randomised controlled trials conducted on behavioural problems in the elderly showed a clear benefit for the short-term use of risperidone when aggression only was considered. \(^{(57)}\)

12.2 Alternatives to antipsychotics in BPSD

- Pain is a common cause of challenging behaviour and this should be treated first.

- Consider the impact of physical impairment by ensuring eyesight and hearing is optimized and that lighting, heating and room layouts are suitable.

- Non Drug Measures – A variety of non pharmacological methods have been developed \(^{(27)}\) including behavioural management techniques, music therapy, complementary therapies, and aromatherapy. Some positive results from controlled trials have shown reduction in agitation.

- Alternative drugs – The acetylcholineserase inhibitors donepezil, rivastigmine and galantamine may have some benefit in reducing behavioural disturbance in dementia\(^{(27)}\), although their use remains controversial.

See also:
- Responding to Behaviours that Challenge (BPSD) in older people and those with dementia [http://www.sussexpartnership.nhs.uk/search/site/BPSD](http://www.sussexpartnership.nhs.uk/search/site/BPSD)
13. **THE USE OF ANTIMUSCARINICS (ANTICHOLINERGICS)**

Antimuscarinic drugs are very effective at treating the antipsychotic induced parkinsonism side effects (rigidity, bradykinesia and tremor) as well as dystonic reactions including oculogyric crisis. However, akathisia is unlikely to be helped by antimuscarinics and tardive dyskinesia can be exacerbated by these drugs.

These drugs should not be prescribed regularly on the initial prescription of an antipsychotic, but on a PRN basis and kept under review as to need.

It should not be forgotten that antimuscarinic drugs have side effects of their own as well as exacerbating the antimuscarinic effects of the antipsychotics. In regular usage they can reduce the effectiveness of the antipsychotic and can cause an acute toxic confusional state, (with agitation and psychotic features), especially in the elderly.

If a patient suffers from EPSEs

- Consider reducing the dose of the antipsychotic and maintaining the lowest effective dose.
- Consider substituting an alternative antipsychotic with a lower risk of EPSE.
- Consider they may be self limiting and often resolve within a few weeks of prescribing or increasing the dose of antipsychotic. In this case antimuscarinics will only need to be prescribed for a short period.
- If they are as a result of depot medication they may only require antimuscarinics for a few days after each depot is given on initiation of the depot and once established even this may no longer be necessary.
- Antimuscarinic drugs should be prescribed sparingly and kept under constant review.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Available Forms</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procyclidine</td>
<td>Tablets, liquid, injection</td>
<td>May cause euphoria</td>
</tr>
<tr>
<td>Orphenadrine</td>
<td>Tablets, liquid</td>
<td></td>
</tr>
<tr>
<td>Trihexiphenidyl</td>
<td>Tablets, liquid</td>
<td>May be of some benefit for hypersalivation (99)</td>
</tr>
<tr>
<td>Benzotropine</td>
<td>Injection</td>
<td></td>
</tr>
</tbody>
</table>

N.B. The above antimuscarinics often have little effect on hypersalivation and the antimuscarinic, hyoscine hydrobromide (more commonly prescribed for travel sickness) is usually used for this side effect (although an ‘off-license’ indication).
# HIGH DOSE ANTIPSYCHOTIC MONITORING FORM

**Name:**

**Ward/Team/Clinic:**

**Consultant:**

**Patient number:**

**DOB:**

**Risk Factors (please circle) – Increased risk in the following areas**

- Age (over 70 years):
  - Y / N
- Hepatic Impairment:
  - Y / N
- Renal Impairment:
  - Y / N
- Weight:
  - .............
- BMI:
  - ............ Obesity:
  - Y / N
- Epilepsy:
  - Y / N
- Heavy Smoker:
  - Y / N
- Heavy Drinker:
  - Y / N
- Illicit Substances:
  - Y / N
- Cardiac History:
  - Y / N
  (if yes specify details)

**Reason(s) for High Dose Antipsychotic Therapy (HDAT) (Documented in Case Notes Y / N)**

**Target symptoms**

**Antipsychotic Medication (regular)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>%BNF Max</th>
</tr>
</thead>
</table>

**Interacting Medication: Y / N**

(inc. drugs with additive ECG effects)

If Yes please specify (– includes PRN)

**High Dose Antipsychotic Monitoring**

<table>
<thead>
<tr>
<th>Pre-Treatment</th>
<th>Month 3</th>
<th>Month 6</th>
<th>Month 9</th>
<th>Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG (QTc – state interval)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LFTs (√ if okay, state value if abnormal)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U&amp;Es (√ if okay, state value if abnormal)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP, Pulse Temperature</td>
<td>Please, record daily for one week on separate monitoring sheet - on initiation of HDAT, and after each increase in dose of antipsychotic.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Doctors Signature**

**Has patient/carers been informed of the high dose nature of therapy?**

- Y / N

**Is high dose therapy covered on the consent form?**

- Y / N / NA

**Consultant signature:**

……………………………

**Date:**

Attach to drug prescription and administration chart and file a copy in patient’s notes.
Glasgow Antipsychotic Side-effect Scale (GASS) – modified version

Name:                                                                          Age:                      Sex:  M  /  F

Please list current medication and total daily doses below:

This questionnaire is about how you have been recently. It is being used to determine if you are suffering from excessive side effects from your antipsychotic medication. Please place a tick in the column which best indicates the degree to which you have experienced the following side effects. 

Also tick the end or last box if you found that the side effect was distressing for you. © Waddell & Taylor, 2007

<table>
<thead>
<tr>
<th>Over the past week:</th>
<th>Never</th>
<th>Once</th>
<th>A few times</th>
<th>Everyday</th>
<th>Tick this box if distressing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I felt sleepy during the day</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. I felt drugged or like a zombie</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. I felt dizzy when I stood up and/or have fainted</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. I have felt my heart beating irregularly or unusually fast</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. My muscles have been tense or jerky</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. My hands or arms have been shaky</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. My legs have felt restless and/or I couldn’t sit still</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. I have been drooling</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. My movements or walking have been slower than usual</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. I have had uncontrollable movements of my face or body</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. My vision has been blurry</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. My mouth has been dry</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. I have had difficulty passing urine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14 (a). I have felt like I am going to be sick or have vomited</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14 (b) I have had problems opening my bowels (constipation)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15. I have wet the bed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16. I have been very thirsty and/or passing urine frequently</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17. The areas around my nipples have been sore and swollen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18. I have noticed fluid coming from my nipples</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19. I have had problems enjoying sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20. <strong>Men only:</strong> I have had problems getting an erection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Tick yes or no for the last three months**

| 21. **Women only:** I have noticed a change in my periods | No | Yes | Tick this box if distressing |
| 22. **Men and women:** I have been gaining weight        |    |    |                               |
Staff Information

1. Allow the patient to fill in the questionnaire themselves. All questions relate to the previous week.

2. Scoring

   For questions 1-20 award 1 point for the answer “once”, 2 points for the answer “a few times” and 3 points for the answer “everyday”. Please note zero points are awarded for an answer of “never”.

   For questions 21 and 22 award 3 points for a “yes” answer and 0 points for a “no”.

   Total for all questions=

3. For male and female patients a score of:
   0-21 absent/mild side effects
   22-42 moderate side effects
   43-63 severe side effects

4. Side effects covered include:
   1-2 sedation and CNS side effects
   3-4 cardiovascular side effects
   5-10 extra pyramidal side effects
   11-13 anticholinergic side effects
   14 gastro-intestinal side effects
   15 genitourinary side effects
   16 screening question for diabetes mellitus
   17-21 prolactinaemic side effects
   22 weight gain

   The column relating to the distress experienced with a particular side effect is not scored, but is intended to inform the clinician of the service user’s views and condition.
# GASS for Clozapine

Name: 

Date: 

Current Medications: 

Caffeine intake: ............ cups/day

Smoker: Y / N ............ cigarettes/day

Has there been a recent change in your smoking habit? Increase/Decrease by ............ cigarettes/day

This questionnaire is being used to determine if you are suffering from excessive side effects from your medication. Please put a tick in the column which best indicates how often or how severely you have experienced the following side effects.

<table>
<thead>
<tr>
<th>Over the past week:</th>
<th>Never</th>
<th>Once</th>
<th>A few times</th>
<th>Everyday</th>
<th>Tick if severe or distressing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I felt sleepy during the day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>I felt drugged or like a zombie</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>I felt dizzy when I stood up or have fainted</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>I have felt my heart beating irregularly or unusually fast</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>I have experienced jerking limbs or muscles</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>I have been drooling</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>My vision has been blurry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>My mouth has been dry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>I have felt sick (nauseous) or have vomited</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>I have felt gastric reflux or heartburn</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>I have had problems opening my bowels (constipation)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>I have wet the bed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>I have been passing urine more often</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>I have been thirsty</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>I have felt more hungry than usual or have gained weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>I have been having sexual problems</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

I have also experienced: (please write down any other side effects OR PHYSICAL PROBLEMS OR COMPLAINTS that you may have experienced over the past week)

17
18
19
20

Adapted from the Glasgow Antipsychotic Side-effect Scale© 2007 by St. John of God Hospital and South London and Maudsley Trust

Waddell, Taylor and Hynes 2012
DT, PG, AA, PH, RD comments
Staff Information

1. Allow the service user to fill in the side-effects scale themselves. All questions relate to the previous week.

2. **Scoring**

<table>
<thead>
<tr>
<th>Points</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>“Never”</td>
</tr>
<tr>
<td>1</td>
<td>“Once”</td>
</tr>
<tr>
<td>2</td>
<td>“A few times”</td>
</tr>
<tr>
<td>3</td>
<td>“Everyday”</td>
</tr>
</tbody>
</table>

3. **Results**

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-16</td>
<td>absent/mild side-effects</td>
</tr>
<tr>
<td>17-32</td>
<td>moderate side-effects</td>
</tr>
<tr>
<td>33-48</td>
<td>severe side-effects</td>
</tr>
</tbody>
</table>

4. **Side-effects covered include:**

<table>
<thead>
<tr>
<th>1-2</th>
<th>Drowsiness and sedation</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Postural hypotension</td>
</tr>
<tr>
<td>4</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>5</td>
<td>Myoclonus</td>
</tr>
<tr>
<td>6</td>
<td>Hypersalivation</td>
</tr>
<tr>
<td>7-8</td>
<td>Anticholinergic side-effects</td>
</tr>
<tr>
<td>9-10</td>
<td>Gastrointestinal side-effects</td>
</tr>
<tr>
<td>11</td>
<td>Constipation</td>
</tr>
<tr>
<td>12</td>
<td>Nocturnal enuresis</td>
</tr>
<tr>
<td>13-14</td>
<td>Screening for diabetes mellitus</td>
</tr>
<tr>
<td>15</td>
<td>Weight gain</td>
</tr>
<tr>
<td>16</td>
<td>Sexual dysfunction</td>
</tr>
</tbody>
</table>

5. The column relating to the severity/distress experienced with a particular side effect is not scored, but is intended to inform the clinician of the service user’s views and condition.

6. Questions 17 to 20 invite the service user to report any other side-effects or problems not already mentioned. These questions should not be scored but may instigate a discussion with the service user if clinically appropriate.

Adapted from the Glasgow Antipsychotic Side-effect Scale © 2007 by St. John of God Hospital and South London and Maudsley Trust

Waddell, Taylor and Hynes 2012
DT, FG, AA, PH, RD comments
INITIATING CLOZAPINE IN CHILDREN & ADOLESCENTS

Before commencing treatment:
- Ensure individual meets criteria of treatment resistant schizophrenia.
- Ensure individual/carers/relatives have been given information verbally and in writing about clozapine, and obtain consent where appropriate.
- Monitor baseline observations: BP / pulse / temperature / weight / FBC / lipids / glucose / LFT’s / U+E’s / TFT’s / ECG / EEG (if possible).
- Register with the clozapine monitoring service.
- Details required include: Diagnosis of Treatment Resistant Schizophrenia
- Full Blood Count with differential results
- Demographic details including ethnicity
- Review prescribed medications for possible interactions with clozapine.

Commencing treatment:
- Clozapine must commence in a titrating scale:
  - Children and adolescents have been shown to have an increased incidence of adverse effects of clozapine and it is recommended to increase the dose in 12.5mg increments.[46]
  - Other antipsychotics to be slowly tapered and stopped whilst clozapine initiated. If prescribed a depot, clozapine must not to be commenced until the next due date for depot.
- Monitor BP/pulse hourly for the first 6 hours on commencement of treatment, then twice daily, at same time of day during initiation. Dose to be adjusted according to BP/pulse measurements.
- Observe for possible adverse effects which may include:
  - Fever (in first 3 weeks)
  - Nausea/vomiting
  - Drowsiness and sedation
  - Hypotension
  - Hypersalivation
  - Weight Gain
  - Tachycardia
  - Seizures
  - Constipation
- Blood tests to be taken weekly for the first 18 weeks.

Maintaining treatment:
- After a minimum of 18 weeks of weekly blood sampling, monitoring may be changed to fortnightly for the next 34 weeks, (i.e. up to the end of the first year’s treatment). Thereafter monitoring must occur every 4 weeks whilst individual remains on clozapine.
- Once a stable dose is achieved repeat ECG.
- If clozapine is omitted for more than 48 hours it is essential to restart clozapine gradually. Dose is to recommence at 12.5mg once or twice a day on the first day then increase gradually back to previous dose.
- If individual presents with temperature or infection, monitor WBC as precautionary measure. If temperature exceeds 38.5°C clozapine must be stopped until the WBC is checked.

Clozapine Levels
- It has been shown that in children and adolescent’s clozapine may be more quickly metabolised. The norclozapine level may be greater than the clozapine level.[47]. Therefore, it is important and both levels should be read in conjunction e.g. if the ratio value is greatly below 1.33 (>0.66 norclozapine : clozapine) then as well as poor compliance being a potential cause the patient could be a fast metaboliser of clozapine or on concurrent hepatic enzyme inducing medication.
- An interesting study[100] witnessed 1408 samples from 454 patients, collected from patients in the UK and Eire aged <18 years, 1994–2010. The plasma clozapine concentration was <0.35 mg L−1 in 36%, and ≥0.60 mg L−1 in 31% of samples (6.4% samples ≥1.0 mg L−1). Although plasma clozapine was broadly related to prescribed dose, there was much variation: 10% of samples had plasma clozapine >0.60 mg L−1 at prescribed clozapine doses of 50–150 mg d−1 (66% <0.35 mg L−1), while 12% of samples had plasma clozapine <0.35 mg L−1 at doses >650 mg d−1 (62% >0.6 mg L−1). The covariates studied in the 16–17-year-olds had proportionately similar influences to those observed in adults. Together they explained 48% of the variance observed in plasma clozapine, with dose, smoking habit, MR and sex being major influences.

Antipsychotic Dosage Ready Reckoner – © The Royal College of Psychiatrists

Available to Trust staff via the following link:

dGFslwiaGVhbHRoliwicHJlc2NyaWJpmbmcgb2JzZXJ2YXRvcmkiLCJwcmVzY3JpYmluZ
yBvYnNlcnZhdG9yeSBmb3iLCJvYnNlcnZhdG9yeSBmb3iLCJvYnNlcnZhdG9yeSBmb3iLCJv
cy5GFlsliwiZm9yIHBvbGlhYWx0aCJd#
Positive Cardiometabolic Health Resource

An intervention framework for people experiencing psychosis and schizophrenia

This clinical resource supports the implementation of the physical health CQUIN for people with severe mental illness. It focuses on antipsychotic medication for adults, but many of the principles can be applied to other psychotropic medicines given to adults with long-term mental disorders, e.g. mood stabilisers.

For all patients in the “red zone” (see center page spread): The general practitioner, psychiatrist, and patient will work together to ensure appropriate monitoring and interventions are provided and communicated. The general practitioner will usually lead on the supervision of physical health interventions. The psychiatrist will usually lead on decisions to significantly change antipsychotic medication.


For more information, please visit: www.rcpsych.ac.uk/quality/NAS/resources
Positive Cardiometabolic Health Resource

**Smoking**
- Current smoker

**Lifestyle and Life Skills**
- Poor diet
- Sedentary lifestyle

**Body Mass Index (BMI) Weight**
- BMI >25 kg/m²
- Weight gain >5kg over 3 month period

**Blood Pressure**
- >140 mm Hg systolic
- >90 mm Hg diastolic

**Glucose Regulation**
- Fasting blood glucose (FPG), random blood glucose (RBG), HbA1c
- HbA1c or Glucose threshold:
  - FPG >5.5 mmol/L
  - OR
  - RBG >7.5 mmol/L

**Blood Lipids**
- Total cholesterol/HDL ratio
detect high (>10%) risk of CVD based on QRSK2 Tool
- http://qrsks.org/
- Note: CVD risk scores can underestimate risk in those with psychosis

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**INTERVENTIONS**

**Medication review and lifestyle advice to include diet and physical activity**

NB Family history of diabetes and/or premature heart disease heightens cardiometabolic risk.

Refer for investigation, diagnosis and treatment by appropriate clinician if necessary.

**Brief intervention**
- Combined NRT and/or varenicline
- Individual/group behavioral support or specialist support if high dependency
- Referral to Smoking Cessation service

**Follow NICE guidelines for hypertension**
- http://publications.nice.org.uk/hypertension-cg127
- Consider antihypertensive therapy
- Limit salt intake in diet

**At High Risk of Diabetes**
- HbA1c >42 mmol/mol (6.0% - 6.4%)
- FPG >5.5 - 6.9 mmol/L
- Follow NICE diabetes guidelines

**Diabetes**
- HbA1c >48 mmol/mol (6.5%)
- FPG >7.0 mmol/L
- RBG >11.1 mmol/L
- Endocrine review
- Follow NICE diabetes guidelines

**Follow NICE guidelines for lipid modification**
- AND
- Consider lipid modification for those with CVD or diabetes

**TARGET**

**Stop smoking**
- Improve quality of diet
- Contain calorie intake
- Daily exercise of 30 mins/day
- BMI 18.5-24.9 kg/m²
- 18.5-22.9 kg/m² if South Asian or Chinese
- <140/90 mm Hg
- <130/80 mm Hg for those with CVD or diabetes
- Prevent or delay onset of diabetes
- HbA1c <42 mmol/mol (6.5%)
- FPG <5.5 mmol/L
- HbA1c 47-58 mmol/mol (6.5-7.5%)

Primary Prevention: consider statin treatment if >10% risk based on QRSK2
OR Secondary Prevention: aim to reduce non-HDL chol by 40% and review in 3 months
History and examination following initiation or change of antipsychotic medication

**Frequency:** Normally supervised by the psychiatrist. As a minimum review those prescribed a new antipsychotic at baseline and at least once after 3 months.

Weight should be assessed weekly in the first six weeks of taking a new antipsychotic, as rapid early weight gain may predict severe weight gain in the longer term.

Subsequent reviews should take place annually unless an abnormality of physical health emerges. In these cases, appropriate action should be taken and the situation should be reviewed at least every 3 months.

**At review**

**History:** Seek history of substantial weight gain (e.g., >5 kg), specially where this has been rapid (e.g., within 3 months). Also review smoking, exercise and diet. Ask about family history (diabetes, obesity, CVD in first degree <55 yrs male relatives and <65 yrs female relatives) and gastrointestinal disease. Note ethnicity.

**Examination:** Weight, BMI, BP pulse.

**Investigations:** Fasting estimate of plasma glucose (FPG), HbA1c, and lipids (total cholesterol, non-HDL, HDL, triglycerides); if fasting samples are impractical than non-fasting samples are satisfactory for most measurements except for triglycerides.

**ECG:** Include if history of CVD, family history of CVD, or where examination reveals irregular pulse (if ECG confirms atrial fibrillation, follow NICE recommendations http://guidance.nice.org.uk/CG36). If patient is taking aminothiazole, carbamazepine, or other drugs known to cause ECG abnormalities (e.g., low potassium, non-cardiac anti-depressants, anti-arrhythmics—see British National Formulary for further information).

**Chronic Kidney Disease:** Screen those with co-existing diabetes, hypertension, CVD, family history of chronic kidney disease, structural renal disease (e.g., renal stones) routinely.

1. Monitor renal function: 
   a. urea & electrolytes
   b. estimated glomerular filtration rate (eGFR)
2. Test urines: 
   a. for proteinuria (diip stick)
   b. albumin creatinine ratio (laboratory analysis)

**Presence of chronic kidney disease additionally increases risk of CVD:** Follow appropriate NICE guidelines on chronic kidney disease.

**Monitoring: How often and what to do**

Applies to patients prescribed antipsychotics and mood stabilizers.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Weekly within 6 weeks</th>
<th>12 weeks</th>
<th>Annually</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Personal/Flix</strong></td>
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<tr>
<td><strong>Lifestyle Review</strong></td>
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<tr>
<td><strong>Weight</strong></td>
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<td></td>
<td></td>
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<tr>
<td><strong>Waist Circumference</strong></td>
<td></td>
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<td></td>
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<tr>
<td><strong>BP</strong></td>
<td></td>
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<td></td>
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<tr>
<td><strong>FPG/HbA1c</strong></td>
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<tr>
<td><strong>Lipid Profile</strong></td>
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</tbody>
</table>

*Smoking, diet, and physical activity. **Fasting lipid profile cannot be obtained. a non-fasting sample is satisfactory.*


**Specific lifestyle and pharmacological interventions**

Specific lifestyle interventions should be discussed in a collaborative, supportive way encouraging taking into account the person's preferences.

- **Nutritional counselling:** reduce take-away and "junk" food, reduce energy intake to prevent weight gain, avoid soft and caffeine containing drinks and juices, and increase fibre intake.
- **Physical activity:** structured education/lifestyle intervention. Advise physical activity such as a minimum of 150 min per week (https://bit.ly/3e7oE35). For example suggest 30 minutes of physical activity on 5 days a week.

**If the patient has not successfully reached their targets after 3 months, consider specific pharmacological interventions:**

**Antihypertensive therapy:** Normally GP supervised. Follow NICE recommendations http://publications.nice.org.uk/hypertension-cg127.

**Lipid lowering therapy:** Normally GP supervised. Follow NICE guidelines (FDL cholesterol <5, non-HDL cholesterol <2.5, or TG <1.90 mmol/l), refer (to metabolic specialist). Follow NICE recommendations http://www.nice.org.uk/nicemedia/pdf/CG57NICEguideline.pdf.


**Treatment of those at high risk of diabetes:** FPG 5.5-6.9 mmol/l, HbA1c 42-47 mmol/l, (6.0-7.5%)

Follow NICE guideline PH 2B Preventing type 2 diabetes: risk identification and interventions for individuals at high risk (recommendations 19). Follow NICE guidelines http://guidance.nice.org.uk/PH2B.

- Where intense lifestyle intervention has failed consider a metformin trial (normolipidaemia and low glomare filtration rate are acceptable)
- Please be advised that off-label use requires documented informed consent as described in the GMC guidelines, http://www.gmc-uk.org/guidance/ethical_guidance/14337.asp. These GMC guidelines are recommended by the MPS and MOJ and the use of metformin in this context has been agreed as a relevant example by the Defence Unions.
- Adhere to British National Formulary guidance on safe use (in particular ensure renal function is adequate).
- Start with a low dose e.g. 500mg once daily and build up, as tolerated, to 1500-2000mg daily.

**Review of antipsychotic and mood stabilizer medication:** Discussions about medication should involve the patient, the general practitioner and the psychiatrist. Should be a priority if there is:

- Rapid weight gain (e.g., >5 kg in <3 months) following antipsychotic initiation.
- Rapid development (<3 months) of abnormal smptoms, BP or glucose.

The psychiatrist should consider whether the antipsychotic drug regimen has played a causative role in these abnormalities and, if so, whether an alternative regimen could be expected to offer less adverse effects.

- As a first step prescribed dosage should follow NICE recommendations, rationalise any polypharmacy.
- Changing antipsychotic medication requires careful clinical judgment to weigh the benefits against the risk of relapse of the psychosis.
- An effective trial of medication is considered to be the patient taking the medication, at optimum dosage, for a period of 4-6 weeks.
- If clinical judgement and patient preferences support continuing with the same treatment, then ensure appropriate further monitoring and clinical considerations are carried out regularly.

It is advisable that all side effects to antipsychotic medication are regularly monitored, especially when commencing a new antipsychotic medication (SASS questionnaire http://www.mentalhealthfirstaid_MAX.shoppingcom/resource-and-glucose-and-antipsychotic-side-effect-scale), and that any side effects, as well as the rationale for continuing, changing or stopping medication is clearly recorded and communicated with the patient.

The Psychiatrist should maintain responsibility for monitoring the patient's physical health and the effects of antipsychotic medication 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.

Discuss any non-prescribed therapies the patient wishes to use including complementary therapies, with the patient, and if appropriate. Discuss the safety and efficacy of the therapies, and possible interference with the therapeutic effects of prescribed medication and psychological treatments.
Drugs known to prolong QT Interval \(^{(27,64,65)}\)

Please Note: this list is NOT exhaustive and further advice should be sought from a member of the pharmacy team.

Patients may be admitted on drugs prescribed from abroad. Advice can be obtained from pharmacy on the active ingredient in overseas products.

Disclaimer:
1. Concomitant administration of enzyme-inducing or enzyme-inhibiting drugs (e.g., anti-retrovirals, macrolide antibiotics), with drugs known to prolong the QT interval that are metabolised by these enzymes, may result in a potentiated QT interval prolongation.
2. Drugs with particular modes of action that involve electrolyte or fluid disturbances (e.g., diuretics) may affect blood potassium levels. Hypo-kalemia or hyper-kalaemia can induce cardiac arrhythmias, which may manifest as QT interval prolongation.
3. Certain drugs (e.g. cytotoxics) may cause cardiac toxicity. This may result in QT interval prolongation.

Table taken from the South London and Maudsley NHS Trust Guidelines 11th Edition

<table>
<thead>
<tr>
<th>No known effect</th>
<th>Low effect</th>
<th>Moderate effect</th>
<th>High effect</th>
<th>Unknown effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>Asenapine</td>
<td>Amisulpride</td>
<td>Any intravenous antipsychotic</td>
<td>Anticholinergic drugs (procyclidine, benzhexol, etc)</td>
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<tr>
<td>Benzodiazepines</td>
<td>Bupropion</td>
<td>Chlorpromazine</td>
<td>Haloperidol</td>
<td>Loxapine</td>
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<td>Carbamazepine</td>
<td>Clozapine</td>
<td>Citalopram</td>
<td>Pimozide</td>
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<td>Flupentixol</td>
<td>Escitalopram</td>
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<td>Lamotrigine</td>
<td>Fluphenazine</td>
<td>Iloperidone</td>
<td>Sertindole</td>
<td>Trifluoperazine</td>
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<tr>
<td>MAOIs</td>
<td>Lithium</td>
<td><strong>Lurasidone</strong></td>
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<td>Moclobemide</td>
<td>Melperone</td>
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<td>Olanzapine</td>
<td>Pericyazine</td>
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<tr>
<td>Reboxetine</td>
<td>Perphenazine</td>
<td>Promazine</td>
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<tr>
<td>SSRIs (except Citalopram/Escitalopram)</td>
<td>Prochlorperazine</td>
<td>Quetiapine</td>
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<tr>
<td>Valproate</td>
<td>Risperidone</td>
<td>TCAs</td>
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<td>Sulpiride</td>
<td>Ziprasidone</td>
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<td>Trazodone</td>
<td>Zotepine</td>
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<tr>
<td>Venlafaxine</td>
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</tbody>
</table>
### Other drugs

#### Antiarrhythmic drugs
- Amiodarone
- Bretylium
- Disopyramide
- Dronedarone
- Flecaïnide
- Procainamide
- Quinidine
- Sotalol

#### Antiemetics
- Domperidone
- Droperidol
- Granisetron
- Ondansetron

#### Antimicrobials
- Ampicillin
- Azithromycin
- Clarithromycin
- Co-Trimoxazole
- Erythromycin
- Fluconazole
- Ketoconazole
- Moxifloxacin
- Pentamidine isetionate (Pentacarinat ®)

#### Antimalarials
- Chloroquine
- Mefloquine (Lariam®)
- Quinine

#### Miscellaneous other drugs
- Alfuzosin
- Amantadine
- Astemizole
- Atomoxetine
- Boceprevir
- Bupropion
- Ciclosporin
- Cisapride
- Chloral
- Cocaine
- Diphenhydramine (others)
- Hydroxyzine (others)
- Galantamine – at high dose
- Lofexidine
- Methadone
- Nicardipine
- Sumatriptan
- Tamoxifen
- Telaprevir
- Terfenadine
- Protein kinase inhibitors e.g. sunitinib
- Some antiretrovirals
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• The Rapid Tranquillization Policy, Version 6,July 2014

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