Guidance on the Use of Antipsychotics

Version 4

April 2018

This guidance supersedes the following documents:

Guidance on the Use of Antipsychotics October 2009, March 2013 and October 2015

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 or consider depot / long acting injection of same drug*

Change to alternative antipsychotic

If ineffective or side effects unacceptable

If two antipsychotics have been ineffective and adherence good

If side effects unacceptable

If ineffective due to poor adherence

If side effects unacceptable

Patient naive 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.

If severe neurological side effects

Clozapine indicated – consider and discuss with patient

For non-adherent patients who are unsupervised

Consider depot medication or other long-acting antipsychotic injection

If adherence does not improve

If ineffective or if side effects unacceptable

For non-adherent patients who are supervised

Consider orodispersible or liquid preparation

If adherence improves, consider standard formulation

If two antipsychotics are ineffective

If adherence does not improve

If ineffective or if side effects unacceptable

If ineffective or side effects unacceptable

If ineffective or side effects unacceptable

If side effects unacceptable

If two antipsychotics have been ineffective

If ineffective due to poor adherence

Change to alternative antipsychotic

If ineffective or side effects unacceptable

If effective and side effects acceptable, MAINTAIN

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

If effective and side effects acceptable, MAINTAIN

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.

* - Discuss depot / long acting injection options with patient – it is increasingly becoming a preferred treatment option
Recommended Procedure.

1. Collaborative discussion around treatment options
2. Introduce drug, following BNF / manufacturers recommendations for initial dosage and titration.
3. Titrate to minimum effective dose. (Add sedative for short term behavioural control if needed).
4. Evaluate for at least two weeks.
5. If no response, increase dose according to response and tolerability, and assess over a further four to eight week period.
7. 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 collaboratively 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.)

Women of childbearing potential

Clinicians must ensure that women of childbearing potential with a severe mental health problem are given information at their annual review about how their mental health problem and its treatment might affect them or their baby if they become pregnant. Additionally, pregnant women with a previous severe mental
health problem or any current mental health problem must be given information at their booking appointment about how their mental health problem and its treatment might affect them or their baby.

**Treatment Resistance**

It is important to make the distinction between treatment resistance and treatment intolerance. Treatment resistance is described as being resistant to adequate therapeutic trials of at least two antipsychotics. In such circumstances service users must be offered a trial of clozapine at the earliest opportunity. This treatment offer should be documented clearly in the patient records. 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.

**Adjunctive use of valproate in women of childbearing potential**

Valproate is often used adjunctively with anti-psychotics as a mood stabiliser or to reduce the risk of seizures. However, the following now needs to be considered.

**Valproate medicines (Epilim▼, Depakote▼): are now contraindicated in women and girls of childbearing potential unless conditions of Pregnancy Prevention Programme are met.**

The link below is to the April 2018 edition of the MHRA Drug Safety Alert, which provides further details of the new EU-wide regulatory guidance on the use of valproate medicines in pregnancy and in women of childbearing potential. It is vitally important that all healthcare professionals are aware of this new guidance and tailor their practice and the advice they give to patients accordingly.


Further to this, the link below is to the May 2018 edition of the MHRA Drug Safety Alert, which provides links to online materials to help practitioners ensure that women and girls taking valproate medicines meet the requirements of the new Pregnancy Prevention Programme. In addition, it provides links to e-copies of the Patient Card, Patient Guide, Guide for Healthcare Professionals, and the Risk Acknowledgement Form.

**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) \(^{(27)}\)

<table>
<thead>
<tr>
<th>Test</th>
<th>Baseline</th>
<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
<th>On-going</th>
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<tbody>
<tr>
<td>Weight, BMI, Abdominal Girth</td>
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<td>Annually</td>
</tr>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Annually</td>
</tr>
<tr>
<td>Liver Function</td>
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<td></td>
<td></td>
<td></td>
<td>✓</td>
<td>Annually</td>
</tr>
</tbody>
</table>

**ECG**

Recommended pre-treatment and at dose increase for FGAs, high dose antipsychotic treatment and combination treatment with more than one antipsychotic or another drug at risk of causing QT prolongation.

<table>
<thead>
<tr>
<th>Test</th>
<th>Baseline</th>
<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
<th>On-going</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea &amp; Electrolytes</td>
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<tr>
<td>Thyroid Function</td>
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<tr>
<td>Prolactin</td>
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<td></td>
<td></td>
<td></td>
<td>✓</td>
<td>Annually</td>
</tr>
</tbody>
</table>

Check baseline serum prolactin if a drug has a history of causing hyperprolactinaemia. If symptoms of hyperprolactinaemia occur (menstrual disturbance, galactorrhoea, gynaecomastia, sexual dysfunction) recheck levels. Do not forget to consider other possible causes of hyperprolactinaemia.

<table>
<thead>
<tr>
<th>Test</th>
<th>Baseline</th>
<th>1 month</th>
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<th>6 months</th>
<th>12 months</th>
<th>On-going</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP and Pulse</td>
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<td></td>
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<td>Annually</td>
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</table>

**Clozapine**

<table>
<thead>
<tr>
<th>Test</th>
<th>Baseline</th>
<th>1 month</th>
<th>3 months</th>
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<th>12 months</th>
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<tbody>
<tr>
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<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Liver Function</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td>Annually</td>
</tr>
</tbody>
</table>

**ECG**

Clozapine may cause cardiomyopathies and myocarditis. Check ECG when maintenance dose is reached and after any dose changes. Check annually if high doses (>600mg).

<table>
<thead>
<tr>
<th>Test</th>
<th>Baseline</th>
<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
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<td></td>
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<td></td>
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<tr>
<td>Full Blood Count</td>
<td></td>
<td></td>
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</tbody>
</table>

As per clozapine protocol. Weekly for 18 weeks, then two weekly for up to 1 year then 4 weekly. Additional monitoring may be required if appropriate.

<table>
<thead>
<tr>
<th>Test</th>
<th>Baseline</th>
<th>1 month</th>
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<th>6 months</th>
<th>12 months</th>
<th>On-going</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolactin</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hyperprolactinaemia is rare with clozapine – check serum prolactin if symptoms occur (menstrual disturbance, galactorrhoea, gynaecomastia, sexual dysfunction). Consider other possible causes.

<table>
<thead>
<tr>
<th>Test</th>
<th>Baseline</th>
<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
<th>On-going</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP and Pulse</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Additional information on tests listed in the tables

- ECG = Electrocardiogram with automatic reporting and calculation of corrected QT Interval (<450mSec)
• QTc below 440ms (men) or below 470ms (women) is normal
• QTc above 440ms (men) or above 470ms (women) but below 500ms (both sexes - prescribe with care)
• QTc 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 HBA1C 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.

It is recommended that all patients prescribed antipsychotics be medically reviewed on an annual basis.

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

As part of collaborative treatment of patients depot / long acting injection dose should be reviewed at least annually as part of the medical review.

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.

See also

Positive Cardiometabolic Health Resource (Appendix 3)
http://www.rcpsych.ac.uk/quality/nationalclinicalaudits/schizophrenia/nationalschizophreniaaudit/nasresources.aspx

Aripiprazole long acting injection, Guidelines for Prescribing and Administration
http://www.sussexpartnership.nhs.uk/node/1456/attachment

Guidelines for the use of Clopixol Acuphase
http://www.sussexpartnership.nhs.uk/node/1465/attachment

Guidelines for the Administration of Long Acting Antipsychotic Injections in Adults
http://www.sussexpartnership.nhs.uk/node/1493/attachment

Olanzapine Long-Acting Injection Guidelines
http://www.sussexpartnership.nhs.uk/node/1507/attachment

Paliperidone Long-Acting Injection Guidelines for Prescribing and Administration
http://www.sussexpartnership.nhs.uk/node/1515/attachment
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 30 days treatment (from eDrug Tariff accessed 20.6.18)\(^{(1)}\)

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>£22.11 (1 x 200mg + 1 x 400mg) £8.39 (3 x 200mg)</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>15mg/day</td>
<td>£2.95 (1 x 15mg)</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>10mg/day</td>
<td>£23.89 (1 x 10mg)</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>74mg/day</td>
<td>£97.20 (1 x 74mg)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>20mg/day</td>
<td>£39.46 (1 x 20mg)</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>600mg/day</td>
<td>£72.57 (2 x 300mg)</td>
</tr>
<tr>
<td>Quetiapine XL</td>
<td>600mg/day</td>
<td>£170.00 (2 x 300mg)</td>
</tr>
<tr>
<td>Risperidone</td>
<td>6mg/day</td>
<td>£2.99 (1 x 6mg)</td>
</tr>
<tr>
<td>Sulpiride</td>
<td>1200mg/day</td>
<td>£56.40 (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. Therefore, depot medication should be offered early on as a treatment option.

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) can be used 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.
- Note – rarely initiated in new patients due to need for fortnightly administration. Monthly paliperidone LAI generally preferred.

Paliperidone Long Acting Injection is recommended:
- Patients who have responded well to oral risperidone who choose to have the LAI and / or those who have compliance problems
- Patients who have responded well to FGA depots but who find the side effects unacceptable
- In patients who have responded well to risperidone LAI historically.

Olanzapine Long Acting Injection may be considered in:
- Patients who have responded well to oral olanzapine
- Patients who have been assessed as having adherence problems with oral olanzapine.
- Where services are available to monitor patients for at least 3 hours post-administration as per the Summary of Product Characteristics.

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
http://www.sussexpartnership.nhs.uk/node/1493/attachment
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. 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. SGAs are preferable first line due to lower propensity for extrapyramidal side effects within BNF dose range. Sulpiride is the only FGA included.

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 have lowest potential for these effects
3. **Movement disorders**: FGAs and the upper dose range of aripiprazole, amisulpride, olanzapine, risperidone and sulpiride, notably in younger populations.
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)

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.\(^{(2,72)}\)

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,\(^{(2,3,72)}\) 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 offered early as a treatment option, 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 in the Trust for second-line use in patients identified as having significant metabolic risk factors, e.g. 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
Lurasidone: 18 years
Olanzapine: 18 years
Quetiapine: 18 years
Risperidone: 18 years
   Due to lack of conducted studies in younger group, but is recommended by NICE\textsuperscript{13,72} 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 is 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.

\url{http://www.sussexpartnership.nhs.uk/node/1849/attachment}
\url{http://www.sussexpartnership.nhs.uk/node/1848/attachment}

The BNF for Children (BNF\textsubscript{C}) 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. \url{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 Summary of Product Characteristics (SPC) or British National Formulary (BNF) with respect to the age of the patient and the indication being treated, and a total daily dose of two or more antipsychotics which exceeds the SPC or BNF maximum using the percentage method. (see appendix 2).

**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.

Ward/unit pharmacists can advise on HDAT prescribing and it’s monitoring. Also, to raise awareness and assist in its identification and review, they will apply a HDAT warning sticker to the front of inpatient drug charts if HDAT prescribing has taken place.

**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 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) for SGAs, or the Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS) for FGAs. GASS is the preferred scale and use is endorsed by the Trust.

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 section 58 and forms T2 or T3 where relevant in detained patients. (Although a T2 is a ‘patient consent to treatment form’ it should specify that the doses are above BNF limits and by how much.) For informal patients a Form B should be completed clearly specifying the doses and the HDAT status which should be signed by the patient.

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:*

**PMVA – Prevention and Management of Violence & Aggression Policy April 2017**

**The Rapid Tranquillization Policy**
[http://www.sussexpartnership.nhs.uk/node/1523/attachment](http://www.sussexpartnership.nhs.uk/node/1523/attachment)

**HDAT monitoring form**
[https://www.sussexpartnership.nhs.uk/node/1577/attachment](https://www.sussexpartnership.nhs.uk/node/1577/attachment)

**Physical Healthcare Policy**
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. Plasma concentration of lurasidone increased by verapamil.</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 and lurasidone possibly increased by macrolides (e.g. erythromycin, clarithromycin) – avoid concomitant use</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. St John’s Wort possibly reduces plasma concentration levels of aripiprazole and lurasidone.</td>
</tr>
<tr>
<td>Antipsychotics + antiepileptics</td>
<td>Antipsychotics lower seizure threshold. Carbamazepine reduces the plasma concentration of aripiprazole, clozapine, haloperidol, olanzapine, quetiapine, risperidone and possibly lurasidone.</td>
</tr>
</tbody>
</table>
Phenytoin reduces the plasma concentration of clozapine, haloperidol and quetiapine and possibly lurasidone. The risk of neutropenia is increased if olanzapine is given with sodium valproate.

| Antipsychotics and antivirals | 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. |
| Antipsychotics and atomoxetine | Increased risk of ventricular arrhythmias when antipsychotics that prolong the QT interval are given with atomoxetine |
| Antipsychotics and beta-blockers | Increased risk of ventricular arrhythmias particularly when sotalol is given with zuclopenthixol, haloperidol, amisulpride, phenothiazines and risperidone |
| Antipsychotics + lithium | 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. Increased risk of EPSE's when lithium given with quetiapine or sulpiride. |
| Antipsychotics and opioids | Increased risk of hypotension and sedation. Increased risk of convulsions with tramadol. Increased risk of ventricular arrhythmias when amisulpride is given with methadone. |
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 4)

For up to date information on drugs that prolong QTc see Credible Meds website [https://www.crediblemeds.org/](https://www.crediblemeds.org/)

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.

When reviewing QT prolongation the lower risk antipsychotics include: lurasidone, aripiprazole and paliperidone while higher risk antipsychotics include amisulpride and sertindole\(^{(90,91)}\)

**ECG Monitoring recommendations** (Maudsley Prescribing Guidelines 12\(^{th}\)Edn)

All patients should have ECG monitoring

- On admission
- If previous abnormality or known additional risk factor, at annual physical health check.
Actions to be taken

- **QTc <440ms (men) or <470ms (women)**
  No action required unless abnormal T wave morphology – consider referral to cardiologist if in doubt.

- **QTc >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.

- **QTc >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

**See also** [https://www.sussexpartnership.nhs.uk/node/3744/attachment](https://www.sussexpartnership.nhs.uk/node/3744/attachment)

**Haloperidol – Specific Advice.**

The ‘Summary of Product Characteristics’ for Haloperidol (last updated June 2017) states

*QTc prolongation and/or ventricular arrhythmias, in addition to sudden death, have been reported with haloperidol. The risk of these events appears to increase with high doses, high plasma concentrations, in predisposed patients or with parenteral use, particularly intravenous administration. Caution is advised in patients with bradycardia, cardiac disease, family history of QTc prolongation or history of heavy alcohol exposure. Caution is also required in patients with potentially high plasma concentrations (Poor metabolisers of CYP2D6).*  

*Electrolyte disturbances such as hypokalaemia and hypomagnesaemia increase the risk for ventricular arrhythmias and must be corrected before treatment with haloperidol is started. Therefore, baseline and periodic electrolyte monitoring is recommended. Tachycardia and hypotension (including orthostatic hypotension) have also been reported Caution is recommended when haloperidol is administered to patients manifesting hypotension or orthostatic hypotension.*

A baseline ECG is recommended before treatment. During therapy, the need for ECG monitoring for QTc interval prolongation and for ventricular arrhythmias must be assessed in all patients. Whilst on therapy, it is recommended to reduce the dose if QTc is prolonged, but haloperidol must be discontinued if the QTc exceeds 500 ms. **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.
Methadone - Specific Advice.
The ‘Summary of Product Characteristics’ for Physeptone (last updated March 2017) states:

Cases of QT interval prolongation and torsade de pointes have been reported during treatment with methadone, particularly at high doses (>100 mg/d).

Methadone should be administered with caution to patients at risk for development of prolonged QT interval, e.g. in case of:

- history of cardiac conduction abnormalities,
- advanced heart disease or ischaemic heart disease,
- Liver disease,
- family history of sudden death,
- Electrolyte abnormalities, i.e. hypokalaemia, hypomagnesaemia
- concomitant treatment with drugs that have a potential for QT prolongation,
- concomitant treatment with drugs which may cause electrolyte abnormalities,
- concomitant treatment with cytochrome P450 CYP 3A4 inhibitors

In patients with recognised risk factors for QT prolongation, or in case of concomitant treatment with drugs that have a potential for QT-prolongation, ECG monitoring is recommended prior to methadone treatment, with a further ECG test at dose stabilisation.

ECG monitoring is recommended, in patients without recognised risk factors for QT prolongation, before dose titration above 100 mg/d and at seven days after titration.

Caution should be exercised in patients who are concurrently taking CNS depressants.

Methadone, as with other opiates, has the potential to increase intracranial pressure especially where it is already raised.
7. REGULATION OF PROLACTIN SECRETION

Prolactin is a hormone secreted in the anterior pituitary gland.

- Hypothalamic 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\(^{(24)}\).

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

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

For further information on the treatment of hyperprolactinaemia see separate Trust guidelines –

*Guidance on the Treatment of Antipsychotic Induced Hyperprolactinaemia*

[https://www.sussexpartnership.nhs.uk/node/1487/attachment](https://www.sussexpartnership.nhs.uk/node/1487/attachment)
8. USE OF ANTIPSYCHOTICS DURING PREGNANCY (26,27,28)

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 (08448920909; http://www.uktis.org/)

General points:

<table>
<thead>
<tr>
<th>Name</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol, chlorpromazine, trifluoperazine</td>
<td>There is most experience with these FGAs. Considered to be a minimal risk of teratogenicity. Use of low dose is recommended by NICE. Chlorpromazine can cause sedation and constipation, which may be a problem.</td>
</tr>
<tr>
<td>Olanzapine, quetiapine and risperidone</td>
<td>These are the preferred SGAs. SGAs are unlikely to be major teratogens. Although it is recommended that supplementation with 5mg folic acid be considered as they are associated with low folate levels. They all have limited safety data. The potential for long-term postnatal developmental defects is not known. Metabolic disturbance may increase the risk of gestational diabetes may be a problem. Olanzapine – consider the risk factors for gestational diabetes and weight gain. Effect on foetal size should be monitored. Quetiapine - 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. Risperidone- Consider the risk factors for dose dependent hyperprolactinaemia and EPSE. Aripiprazole – limited data</td>
</tr>
</tbody>
</table>
• Although there are risks to the foetus/neonate associated with the use of medicines during pregnancy, there are also risks to the foetus/neonate if the mother’s mental illness were to relapse as a consequence of no treatment.\(^{(25)}\)

• 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.

• 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 SGAs 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.

• 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.

• Monitor for gestational diabetes in pregnant women taking antipsychotic medication in line with the guideline on diabetes in pregnancy (NICE guideline 2015 and BAP guidance) and offer an oral glucose tolerance test.
9. **USE OF ANTIPSYCHOTICS WHEN BREAST FEEDING** (26,27,28)

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 National Teratology Information Service (NTIS) uses case reports of drug exposure during pregnancy in order to expand their evidence base.

<table>
<thead>
<tr>
<th>Drugs Recommended (26)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine and quetiapine</td>
<td>Low amounts excreted in breast milk.</td>
</tr>
<tr>
<td>Haloperidol, perphenazine, trifluoperazine and chlorpromazine</td>
<td>Low amounts excreted in breast milk.</td>
</tr>
<tr>
<td>Risperidone and aripiprazole</td>
<td>Moderate amounts excreted in breast milk.</td>
</tr>
<tr>
<td>Amisulpride</td>
<td>High amounts excreted in breast milk.</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.

- 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 (apart from clozapine). 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 extrapyrmidal 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.
• Take care with any sedating medication especially in the postnatal period since excessive sedation can hinder baby care and breastfeeding. Although sedation can often resolve over a short period after starting a medication, alternative options may need to be considered.

• 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.
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\(^{(16)}\). It should also be borne in mind that individuals with LD may have atypical presentations related to their level of intellectual functioning, for example positive symptoms of psychosis may be very simple in nature, such as hearing noises, whilst delusions may be a lot less complex than those of the non-LD population.\(^{(16)}\) There are also considerable difficulties in terms of differential diagnosis due to a number of overlapping symptoms between conditions such as affective disorders & schizophrenia, autism and schizophrenia, and epilepsy and schizophrenia.\(^{(16)}\)

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, carers and specialists in communication e.g. speech and language therapists in treatment choices and utilising their expertise to find bespoke solutions for that individual.
Please see the Choice and Medication website [https://choiceandmedication.org/sussex](https://choiceandmedication.org/sussex) for access to a wide selection of Very Easy-Read Leaflets (VERAs) and Quick Information Leaflets (QuILLs) for psychiatric medications which may be useful depending on the service users’ level of functioning.

The main areas of use for antipsychotics in people with LD are psychosis, bi-polar affective disorder, self-injurious behaviour, autism spectrum conditions, and challenging behaviour.

### 10.2 Psychosis

It is preferable to use antipsychotics first line with starting doses lower than those used in the general population. Subsequent dose increases should be in relatively small increments and allow adequate time for response \(^{(16)}\). A minimum of one week between each increment in dose is recommended. The maximum tolerated dose should be continued for at least 3 to 4 weeks to assess efficacy. \(^{(16)}\)

If this initial treatment is found to be ineffective or poorly tolerated, another antipsychotic should be trialled. If this second drug is also found to be ineffective, this may indicate treatment resistant psychosis and that clozapine should be considered.

Informed consent would be needed for the use of clozapine and if that is impossible, a multidisciplinary best interest meeting involving family, carers, or an advocate, with the intention of a agreeing a ‘best interests’ decision, should be arranged.

If clozapine is also found to be ineffective, augmentation strategies should be considered, for example mood stabilization if required. \(^{(16)}\)

Antipsychotic polypharmacy and high dose antipsychotic treatment should only be considered after evidence-based strategies have failed and as part of a carefully monitored therapeutic trial \(^{(16)}\). See section 10.8 for further details.

### 10.3 Bipolar Affective Disorder

Treatment of bipolar affective disorder in individuals with LD should generally follow the same evidence-based guidelines as in the non-LD population, but bearing in mind their increased sensitivity to medication adverse effects & thus starting with lower doses and more gradual dose titrations. Full details can be seen in the Trust’s guidance on the use of mood stabilizers for the treatment of bipolar affective disorder and NICE CG185: Bipolar Disorder: assessment and management.

In line with these recommendations, an antipsychotic such as olanzapine, quetiapine, risperidone, or aripiprazole are first line choices for management and treatment of hypomania and mania in bipolar affective disorder in individuals with LD. \(^{(16)}\)

In patients who are presenting with bipolar depression, an antipsychotic such as olanzapine, or quetiapine are first line choices for management and treatment of bipolar depression.

Choice of antipsychotic to initiate in bipolar affective disorder should always take into account the individual, carer, family, or advocate preferences, previous response to antipsychotics, adverse effects, and interactions with other medications when choosing which medication to initiate. \(^{(16)}\)
10.4 Self-injurious behaviour (SIB)

Often SIB often serves a specific function for the individual and therefore requires a behavioural approach throughout.

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.\(^{(16)}\)

It is hypothesised that super sensitivity of dopamine neurons in the nigrostriatal pathways may predispose to repetitive and stereotypic SIB.

Dopamine D\(_1\) blockers may be more effective than D\(_2\) blockers, for example the thioxanthines flupentixol and zuclopenthixol\(^{(27)}\).

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\(^{(16)}\).

Other non-antipsychotic drug treatments for SIB include; opiate antagonist naltrexone for extreme self-inflicted tissue damage related to insensitivity to pain, SSRIs for agitation when SIB is interrupted associated with OCD and anxiolytics/mood stabilizers for SIB associated with high arousal or distress.\(^{(16)}\)

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 a significant 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.

10.5 Autistic Spectrum Conditions (ASC)

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, including antipsychotics are not recommended for the treatment of core symptoms of autism in adults.\(^{(62)}\) These should be dealt with using psychosocial interventions. The Nice Clinical Guidelines for the treatment of Autism only suggests antipsychotics in relation to the management of challenging behaviour in autism and not for the core features of autism.\(^{(62)}\) It recommends that they should only be used where psychological interventions have failed or had little response in managing the challenging behaviour, or whereby psychological interventions could not be delivered due to the severity of the challenging behaviour.

The following statement is included\(^{(62)}\) “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.”\(^{(62)}\)
Of the antipsychotics available the following have some very low level evidence of benefit when used in behavioural problems associated with autism:

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Dosing</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risperidone</strong></td>
<td>1mg to 2mg daily</td>
<td>Some evidence of benefit for irritability, repetition, and social withdrawal in autism. Given the adverse effects observed, and lack of clear benefit with regard to core autism symptoms it has been suggested that risperidone is reserved for moderate to severe behavioural problems associated with autism.(^{(16)})</td>
</tr>
<tr>
<td><strong>Aripiprazole</strong></td>
<td>2mg daily increasing to 5mg and subsequent increases of dose up to 15mg if necessary</td>
<td>Licensed in U.S. by the FDA for the management of irritability associated with ASC in children, but only in combination with psychological, educational, and social interventions. No robust evidence of benefit in adults with autism, but use in clinical practice has been extrapolated from use in children. (^{(16)})</td>
</tr>
<tr>
<td><strong>Olanzapine</strong></td>
<td></td>
<td>Very limited evidence available. Low level evidence has shown some benefits in alleviating behavioural symptoms associated with autism including irritability, hyperactivity, non-compliance, lethargy, and withdrawal. However there are large concerns in regards to weight gain and metabolic syndrome. (^{(16)})</td>
</tr>
<tr>
<td><strong>Haloperidol</strong></td>
<td>1mg to 2mg daily</td>
<td>Licensed for short-term adjunctive management of psychomotor agitation, excitement, and violent and dangerous impulsive behaviours. Haloperidol has been found to be effective in reducing behavioural symptoms such as hyperactivity, aggression, stereotypies, affective lability, and tantrums, but <strong>not</strong> for treating the core symptoms of autism. Use of haloperidol is severely limited by the high incidence of tardive dyskinesia. (^{(16)})</td>
</tr>
<tr>
<td><strong>Quetiapine</strong></td>
<td></td>
<td>Low level evidence using low doses has shown limited short-term effects on aggression in autism. (^{(16)})</td>
</tr>
</tbody>
</table>

Particular attention needs to be paid to the possible development of movement disorders when using antipsychotics because individuals with ASC have a tendency to develop movement disorders and tics as part of their autistic condition. \(^{(16)}\)

As such it is advisable to assess for the presence of movement disorders prior to the introduction of any psychotropic medication, this can then be used as a baseline measurement, to understand whether the medication is a causative factor. Great consideration should be given to regularly using targeted adverse effect rating scales such as the Abnormal Involuntary Movement Scale (https://mmcp.health.maryland.gov/pap/docs/Abnormal%20Involuntary%20Movement%20Scale.pdf) and the Barnes Akathisia Rating Scale both prior to initiating antipsychotics and throughout treatment.\(^{(16)}\)

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.\(^{(49)}\) Most trials have shown no benefits in the core features of autism and some small improvements in associated behavioural...
symptoms and challenging behaviours.\(^{(16)}\) Therefore, care should be taken to ensure treatment is appropriate and efficacious, with monitoring for side effects and any behavioural changes clearly documented.

### 10.6 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 for example in emergencies or when other interventions haven’t made clinically significant improvements. However even in these circumstances they should only be 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 mental illness is sparse. Cochrane suggests that “\textit{without randomised controlled trial-based evidence, clinicians will have to continue to base practice on clinical experience and humane judgement.}”\(^{(49)}\)

When choosing which antipsychotic medication to offer for challenging behaviour, take into account the individual’s preference (or that of their family member, carer, or advocate if appropriate), side effects, response to previous antipsychotics and interactions with other medications.

When initiating an antipsychotic for the management of challenging behaviour the following guidance should be followed to maximise the safety of treatment:

- Identify the target behaviour
- Decide how to monitor effectiveness, including frequency and severity of behaviour, and impact on functioning.
- Start with a low dose and use the minimum effective dose needed.
- Only prescribe a single medication.
- Monitor for side effects as per NICE recommendations, including measures of movement disorders, weight, waist circumference, pulse & blood pressure, fasting glucose, HbA1c, blood lipids, and overall physical health.
- Review the effectiveness and any side effects of the medication after 3 to 4 weeks.
- Stop the medication if there is no indication of a response at 6 weeks, reassess the behaviour that challenges and consider further psychological or environmental interventions.
- Only prescribe PRN (when required) medication for as short a time as possible and ensure that its use is recorded and reviewed.

Review the medication if there are changes in the person’s environment (including staff or care setting changes) or their physical or mental health.
It is vital that the following information is documented in the individual’s electronic records:

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.

Where a positive response to antipsychotic medication is seen it is vital that the following process is followed:

- Record the extent of the response, how the behaviour has changed, and any adverse effects or adverse events.
- Conduct a full multidisciplinary review after 3 months and then at least every 6 months covering all prescribed medication (including effectiveness, side effects, and plans for stopping.
- Only continue to prescribe medication that has proven benefit.

When transferring the care of individuals to the community, GP led care, or between specialist services it is important that the transfer of care contains clear guidance in regards to continued prescribing including:

- Which behaviours to target
- Monitoring of benefits and adverse effects
- Only prescribing the lowest effective dose
- How long the medication should be taken for
- Plans for stopping the medication

Full details can be found in NICE guidance NG11 which can be access via the following link: [https://www.nice.org.uk/guidance/ng11/chapter/1-Recommendations](https://www.nice.org.uk/guidance/ng11/chapter/1-Recommendations)

### 10.7 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 the BNF or the pharmacy team should be consulted for more detailed information.

### 10.8 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 e.g. Aberrant Behaviour Checklist), potential risk/benefit and capacity and consent in the patient’s electronic records. 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.

When prescribing for people with learning disabilities consideration should be given to the risks of co-prescribing other psychotropic medication concurrently, as other classes of psychotropics can have an impact on behaviour.

As far as possible, prescribe one medication at a time and given an adequate time to see if an effect before considering withdrawing and prescribing an alternative.

There is a lack of studies of combinations of psychotropic medication to manage behaviour problems among adults with a learning disability. Therefore, it is not possible to recommend any combination of medication as enhancing the efficacy of medication prescribed on their own.

The risk of drug–drug interactions must be considered, as many individuals with a learning disability are likely to be on other drugs for their associated health comorbidities. Prescribers should make sure they are aware of all the drugs the patient is receiving when prescribing.

In a proportion of cases, the medication can be successfully withdrawn after a long period of use. In a proportion of cases, the dose can be reduced, although total withdrawal is not possible, and in some cases it is difficult to even reduce the dose of medication after a long period of use. Many factors affect the success of withdrawal of medication, including nonmedical factors such as the training and the attitude of care staff.

The following general recommendations are proposed.

- Try to stabilise the person’s behaviour on a minimum number of medicines prescribed at the lowest possible dose, or no medication.
- Withdraw one medication at a time.
- Withdraw medication slowly.
- If necessary, allow time (sometimes a few weeks) after withdrawing one medication and before starting to withdraw another.

10.8 Antipsychotic Polypharmacy & High-Dose Antipsychotic Treatment (HDAT)

See section 4 for in-depth explanations of high dose antipsychotic prescribing and monitoring.

In adults with LD, who may be more prone to suffering from concomitant physical health problems, including cardiac defects, the use of antipsychotic polypharmacy or high dose antipsychotics is not recommended. (16)

In rare circumstances when the use of antipsychotic polypharmacy or high dose antipsychotics is thought to be the only available option for managing an underlying mental health problem the following guidance should be followed to maximise safety of such an option: (16)
- Antipsychotic polypharmacy or high-dose antipsychotic treatment should only be considered after non-pharmacological and evidence-based pharmacological approaches have failed.
- Treatment with antipsychotic polypharmacy or high-dose antipsychotics should only be based upon an individual risk-benefit analysis.
- The decision to prescribe should be made at a multidisciplinary level involving the individual with LD and their carer or advocate.
- Issues in relation to capacity to consent should be fully and clearly addressed and documented.
- If a decision to prescribe is made, clear plans should be in place for a specified period of trial, the aims of treatment, and when and how outcomes will be assessed including regular review arrangements and physical health and mental health monitoring.
- Clear documentation is a vital part of this process.
- Before starting an individual with LD on such a regime, any potential contraindications and interactions should be considered.
- Necessary physical examinations and baseline investigations, including an ECG, should be carried out prior to starting on the proposed regime and repeated as appropriate in short intervals, preferably every few weeks.
- Doses of medication should only be increased if absolutely necessary, and increases should be made slowly and not more often than once weekly.

Prior to initiating antipsychotic polypharmacy or high dose antipsychotic treatment it is vital that the following factors are considered: (16)
- Adherence to treatment
- Sufficient period of trial to assess response
- Alternative antipsychotics, including clozapine
- Appropriateness of other adjunctive medications (e.g. mood stabilisers, antidepressants)
- Psychological approaches
- Physical health risk factors (cardiac history, hepatic or renal impairment, substance use, old age, frailty, obesity.
- Medication interactions

Where antipsychotic polypharmacy or high dose antipsychotic treatment is prescribed physical health monitoring must be carried out, either by the individual's community team or the individuals GP under the supervision of the consultant psychiatrist. If monitoring is to be carried out by primary care services, then monitoring arrangements must be discussed and agreed in advance with the individuals GP. However responsibility for all aspects of treatment and management of antipsychotic polypharmacy or high dose antipsychotic treatment continues to lie with the consultant psychiatrist overseeing the case. (16)

If individuals with LD decline or refuse physical health monitoring, this must be clearly documented, and the risks and benefits of continuing treatment should be reviewed with the individual, their carer or advocate, and the multidisciplinary team at a minimum of every 3 months. (16)

The progress of the individual should be reviewed at least every 3 months, and antipsychotic polypharmacy stopped or the doses of medication reduced to within BNF limits if no significant progress is being observed and alternative approaches reconsidered. (16)
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. This makes the choice of antipsychotic particularly challenging.

The following general recommendations can be made for all patients prescribed antipsychotics, irrespective of diagnosis. 

- 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 product licence, 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.

- Patient and/or parent(s) or carer(s) should be given information on licensing, safety, efficacy and possible interference of any non-prescribed therapies. The effects of alcohol, tobacco and illicit drugs on therapy and symptom control should also be discussed.

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

- 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. The response of children and adolescents with psychosis to antipsychotics is relatively low. Childhood and
adolescent-onset schizophrenia maybe more severe and treatment-refractory than adult-onset, and has a poorer prognosis.\(^{33,73}\)

Early consideration should be given to the use of clozapine as the evidence is good for longer term prognosis when used.

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\(^{72}\) 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 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.

**Lurasidone:**
Not licensed for use in children and adolescents. (83)
One trial supports the use of lurasidone in acutely symptomatic adolescent patients, which gave it a US licence for the management of schizophrenia in adolescents 13 years and over. Response was achieved in 63% of patients and reported side effects included nausea, somnolence and akathisia with minimal effects on weight gain and metabolic parameters. (68,69)

In the Trust, lurasidone is approved for second-line use in patients identified as having significant metabolic risk factors, e.g. diabetes, obesity. In such circumstances aripiprazole must be tried before lurasidone. All patients to be prescribed lurasidone must be recorded on the Trust database via submission of a patient notification form, see separate Trust guidelines. (60)

**Amisulpride:**
Not licensed for use in children and adolescents: Recommended dosing regimen. (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) 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 1 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) Constipation is also reported (14-60%) and serious gastrointestinal hypomobility could be lethal. (66,67)
11.2.2 Long-acting antipsychotic injections (LAs)

There are no licensed long-acting injections currently for use in under 18s. The safety and clinical data in this age group is limited (see individual manufacturer data). However, the use of LAs is becoming more frequent in specific clinical cases, for more information on LAs please refer to separate Trust guidelines.

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). There is some evidence that effects persist for several months. Long-term (unlicensed) use (up to three years) appears safe and effective, and may be effective in relapse prevention and reducing disruptive behaviour. Risperidone has been shown to reduce hyperactivity, stereotyping, aggression and repetitive behaviour, and may possibly be effective in treating depression and irritability.

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.\(^{[27]}\) However, olanzapine and clozapine may also be effective.\(^{[37]}\) Weight gain and sedation may be more problematic than with risperidone and aripiprazole.

Lurasidone\(^{[58]}\) appear not to be effective in the treatment of aggression in autistic patients,\(^{[37]}\) while there is low level evidence using low doses that quetiapine has shown limited short-term effects on aggression in autism.

### 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.\(^{[27]}\)

Haloperidol is licensed for the treatment of childhood behavioural disorders, associated with hyperactivity and aggression,\(^{[44]}\) and small placebo-controlled studies have shown it to be effective in reducing withdrawal, over activity, mood dysregulation, and irritability.\(^{[43]}\)

**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.\(^{[51]}\)

Sulpiride has been shown to be effective and relatively well tolerated.\(^{[27]}\)

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

Clonidine has a more tolerable side effect profile than antipsychotics but regular blood pressure monitoring is required and there is a risk of rebound hypertension if the drug is stopped abruptly.\(^{[27,70]}\)
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. However Bipolar disorder in children under 12 years is considered to be very rare. Both current NICE guidance and the British Association for Psychopharmacology (BAP) 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 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 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.

See also Mood Stabiliser Guidelines for use in Bipolar Disorder https://www.sussexpartnership.nhs.uk/node/1441/attachment

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. 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.

Do not offer valproate to girls or young women of childbearing potential. Risks to the unborn child and the need for effective contraception planning have been emphasised by the latest MHRA alert update. Valproate should be initiated only as a last resort when other medication have not been tolerated or have been found to be ineffective and supervised by a specialist.

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.
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 \(^{80}\), 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% \(^{79}\). 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%) \(^{78}\). 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 \(^{29}\). Aripiprazole was superior to placebo in change from baseline at week 4 and at week 12 on the Y-MRS total score \(^{29}\).

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 CUtLASS-1 trial as well as other retrospective analyses in adult patients, have suggested that SGAs may have as high an incidence in causing EPS’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 amisulpride 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. (32,55,71). 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. Antipsychotic use in in children and adolescent has been found to increase the risk of Type 2 diabetes mellitus, 3-fold which is associated with higher rates of therapeutic failure and a 4-fold faster deterioration of diabetes, compared to adults (71). 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. Lurasidone is licensed in the US in children and adolescents as an alternative to Aripiprazole in patients at high risk of metabolic syndrome\(^{(69)}\).

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 \(^{(82)}\) & Psychosis \(^{(63)}\) guidance.

### 11.6.4 Monitoring:

The most recently published NICE guidance \(^{(72)}\) 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></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>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Fasting blood glucose</td>
<td>Yes</td>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>HbA(_1c)</td>
<td>Yes</td>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Blood lipid profile</td>
<td>Yes</td>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Prolactin</td>
<td>Yes</td>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Movement disorders</td>
<td>Yes</td>
<td></td>
<td></td>
<td>Yes(^3)</td>
<td></td>
</tr>
<tr>
<td>Nutritional status</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td>Yes</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>Yes</td>
<td></td>
</tr>
<tr>
<td>Side effects</td>
<td>Yes</td>
<td></td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Adherence</td>
<td>Yes</td>
<td></td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

1. Plotted on a growth chart (including BMI record)
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 α₁ 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>Lurasidone</td>
<td>Amisulpride</td>
<td>Clozapine</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Aripiprazole</td>
<td>Haloperidol</td>
</tr>
<tr>
<td></td>
<td>Flupentixol</td>
<td>Phenothiazines</td>
</tr>
<tr>
<td></td>
<td>Olanzapine</td>
<td>Pimozide</td>
</tr>
<tr>
<td></td>
<td>Quetiapine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paliperidone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sulpiride</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Zuclopenthixol</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)


*Delirium - Diagnosis, prevention and management* [http://www.sussexpartnership.nhs.uk/node/1475/attachment](http://www.sussexpartnership.nhs.uk/node/1475/attachment)

*Dementia - Non-pharmacological Approaches to Challenging Behaviour* [http://www.sussexpartnership.nhs.uk/node/1476/attachment](http://www.sussexpartnership.nhs.uk/node/1476/attachment)
13. THE USE OF ANTIMUSCARINICS (ANTICHOLINERGICS)\textsuperscript{(48)}

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.

**Anticholinergic Burden (ACB)\textsuperscript{(27)}**

Anticholinergic drugs that cross the blood brain barrier cause sedation, cognitive impairment, delirium and falls. These effects may be worse in older patients with dementia. Combining several drugs with anticholinergic activity increases the anticholinergic burden for an individual. It has been shown that a high ACB was associated with a greater decline in MMSE score and a higher mortality.

Patients may be prescribed anticholinergic drugs for conditions other than EPSEs e.g. urinary incontinence, gastrointestinal disorders, and so may already have a high ACB before treatment for EPSEs and should be taken into account.

**Anticholinergic Burden Scale (SLAM):**
https://www.sussexpartnership.nhs.uk/node/3762/attachment

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>Trihexphenidyl</td>
<td>Tablets, liquid</td>
<td>May be of some benefit for hypersalivation \textsuperscript{(77)}</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).
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.
- 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. 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 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

The most up to date version is available to Trust staff via the following link:

https://www.rcpsych.ac.uk/POMHResources/Login1.aspx

Trust log-in details will be required and are available via the Trust intranet.
Positive Cardiometabolic Health Resource

An intervention framework for people experiencing psychosis and schizophrenia

This clinical resource supports the implementation of the physical health CQUIN, http://www.england.nhs.uk/wp-content/uploads/2014/02/sc-cquin-guid.pdf (page 36) which aims to improve collaborative and effective physical health monitoring of patients experiencing 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 supervising the provision of physical health interventions. The psychiatrist will usually lead on decisions to significantly change antipsychotic medication.

This resource was co-produced by NHS England, NHS Improving Quality, Public Health England and the National Audit of Schizophrenia Team.

The following organisations support the use of this resource:
- Royal College of Psychiatrists (RCPsych)
- Royal College of General Practitioners (RCGP)
- Royal College of Physicians
- Royal College of Nursing
- Royal College of Surgeons (RCS)
- UK Faculty of Public Health (FPH)
- UCL Partners – Academic Health Science Partnership
- Healthcare Quality Improvement Partnership (HQIP)
- National Collaborating Centre for Mental Health (NCCMH)
- Diabetes UK
- MASH Mental Illness

Don’t just SCREEN – INTERVENE for all patients in the “red zone”

Download Lester UK Adaptation: www.rcpsych.ac.uk/quality/NAS/resources
Positive Cardiometabolic Health Resource

An intervention framework for people experiencing psychosis and schizophrenia

**Smoking**
- Current smoker

**Lifestyle and Life Skills**
- Poor diet AND/OR Sedentary lifestyle

**Body Mass Index (BMI) Weight**
- BMI ≥ 25 kg/m² (=23 kg/m² if South Asian or Chinese) AND/OR Weight gain >5kg over 3 month period

**Blood Pressure**
- >140 mm Hg systolic AND/OR >90 mm Hg diastolic

**Glucose Regulation**
- HbA1c or Glucose threshold: HbA1c >42 mmol/mol (>6%) AND/OR FPG ≥ 5.5 mmol/l OR RGP ≥ 11.1 mmol/l

**Blood Lipids**
- Total chol/HDL ratio to detect high (>10%) risk of CVD based on QRISK2 Tool
  [http://qrisk.org/](http://qrisk.org/)
  Note: CVD risk scores can underestimate risk in those with psychosis

**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.

**INTERVENTIONS**

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

**Follow NICE hypertension guidelines**
- [http://publications.nice.org.uk/hypertension-cg127](http://publications.nice.org.uk/hypertension-cg127)
  - Consider anti-hypertensive therapy
  - Limit salt intake in diet

**At High Risk of Diabetes**
- HbA1c >48 mmol/mol (>6.5%)
- FPG ≥ 7.0 mmol/l
- RGP ≥ 11.1 mmol/l

**Endocrine review**

**Follow NICE diabetes guidelines**
- [http://www.nice.org.uk/CG87](http://www.nice.org.uk/CG87)

**Diabetes**
- HbA1c >48 mmol/mol (>6.5%)

**Follow NICE guidelines for lipid modification**
- AND
- Refer to specialist if total cholesterol >9, non-HDL chl >7.5 or TG >20 (mmol/l)

**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%)
- FPG <5.5 mmol/l

**HbA1c 47-58 mmol/mol**
- (6.5-7.5%)

**Primary Prevention:**
- Consider statin treatment if >10% risk based on QRISK2
- OR
- Secondary Prevention:
  - aim to reduce non-HDL chol by 40% and review in 3 months

FPG = Fasting Plasma Glucose | RGP = Random Plasma Glucose | BMI = Body Mass Index | Total Chol = Total Cholesterol | HDL = High Density Lipoprotein | TRIG = Triglycerides
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/or the situation should be reviewed at least every 3 months.

**At review**

**History:** Seek history of substantial weight gain (e.g. 5kg), especially 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 gestational diabetes. Note ethnicity.

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

**Investigations:** Fasting estimates of plasma glucose (FPG), Hba1c, and lipids (total cholesterol, non-HDL, triglycerides). If fasting samples are impractical then non-fasting samples are satisfactory for most measurements except for triglycerides.

**ECG:** Include if history of CVD, family history of CVD, where examination reveals irregular pulse (if ECG confirms atrial fibrillation, follow NICE recommendations [http://guidance.nice.org.uk/CG36], or if patient taking certain antipsychotics (e.g. SPC) or other drugs known to cause ECG abnormalities (e.g. erythromycin, intravenous anti- depressants, anti- anemics – 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 urine:
   - a) proteinuria (dip stick),
   - b) albumin creatinine ratio (laboratory analysis)

*Presence of chronic kidney disease additionally increases risk of CVD: follow 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 first 6 weeks</th>
<th>12 weeks</th>
<th>Annually</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal FAQs</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Lifestyle Review 3</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td></td>
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<tr>
<td>Wcc</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>BP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPG/Hba1c</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipid Profile</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*Smoking, diet, and physical activity. *Fasting lipid profile cannot be obtained.


**Specific lifestyle and pharmacological interventions**

Specific lifestyle interventions should be discussed in a collaborative, supportive and encouraging way, 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 caffeinated drinks and juices, and increase fibre intake.
- **Physical activity:** structured education lifestyle intervention. Advise physical activity such as a minimum of 150 minutes of "moderate-intensity" physical activity per week [http://bit.ly/0e70Es]. 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:*

- **Anti-hypertensive therapy:** Normally GP supervised. Follow NICE recommendations [http://publications.nice.org.uk/hypertension-cg127].
- **Lipid lowering therapy:** Normally GP supervised (if total cholesterol >3.5, non-HDL Chol >2.5 or TG>2.0 mmol/l, refer to metabolic specialist). Follow NICE recommendations [http://www.nice.org.uk/nicemedia/pdf/CG57NICEguideline.pdf].
- **Treatment of diabetes:** Normally GP supervised. Follow NICE recommendations [http://www.nice.org.uk/CG87].
- **Treatment of those at high risk of diabetes:** FPG 5.5-6.9 mmol/l; Hba1c 42-47 mmol/l (6.0-6.4%). Follow NICE guideline PH.38 Preventing type 2 diabetes: risk identification and interventions for individuals at high risk (recommendation 140) – [http://guidance.nice.org.uk/PH38].

- Where intensive lifestyle intervention has failed consider a metformin trial (normally by GP supervised).
- Please be advised that off-label use requires documented informed consent as described in the CMC guidelines [http://www.gmc-uk.org/guidance/ethical_guidance/14327.asp]. These CMC guidelines are recommended by the NPS and MND 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. 300mg once daily and build up, as tolerated, to 1500-2000mg daily.

**Review of antipsychotic and mood stabiliser 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. 5kg <3 months) following antipsychotic initiation.
- Rapid development (<3 months) of abnormal lipids, 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 dosages should follow RMA recommendations, rationalise any polypharmacy.
- Changing antipsychotic medication requires careful clinical judgment to weigh any benefits against the risk of relapse of the psychosis.
- An effective trial of medication is considered to be the patient taking the medication, at an optimum dosage, for a period of 4-8 weeks.
- If clinical judgment and patient preference supports continuing with the same treatment, then ensure appropriate further monitoring and clinical considerations are carried out regularly.

It is advised that all side effects to antipsychotic medication are repeatedly monitored, especially when commencing a new antipsychotic medication (GASS questionnaire [http://mentalhealthpartnerships.co.uk/resource/glasgow-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 anti-psychotic medication or at least the first 12 months or until the person’s condition has stabilised, whichever is longer.

Then 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 care 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 or using the link below.
https://www.crediblemeds.org/

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. Hypokalaemia or hyperkalaemia 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 Psychotropic Drug Directory 2016

<table>
<thead>
<tr>
<th>No effect at therapeutic concentrations</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>Amisulpride</td>
<td>Chlorpromazine</td>
<td>Lithium</td>
<td>Anticholinergic drugs (procyclidine, trihexyphenidyl, etc)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Bupropion</td>
<td>Clomipramine</td>
<td>Melperone</td>
<td></td>
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<tr>
<td>Carbamazepine</td>
<td>Citalopram</td>
<td>Clozapine</td>
<td>Methadone</td>
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<tr>
<td>Duloxetine</td>
<td>Escitalopram</td>
<td>Fluoxetine</td>
<td>Pimozide</td>
<td>Buspirone</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Flupentixol</td>
<td>Levomepromazine</td>
<td>Quetiapine</td>
<td>Loxapine</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>Fluphenazine</td>
<td>Risperidone</td>
<td>Sertindole</td>
<td>Pipotiazine</td>
</tr>
<tr>
<td>MAOIs incl moclobemide</td>
<td>Haloperidol</td>
<td>Sulpiride</td>
<td>TCAs (except clomipramine)</td>
<td>Trifluoperazine</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>Olanzapine</td>
<td>Ziprasidone</td>
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<tr>
<td>Mirtazapine</td>
<td>Perphenazine</td>
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<tr>
<td>Paliperidone</td>
<td>Promethazine</td>
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<tr>
<td>Reboxetine</td>
<td>Trazodone</td>
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<tr>
<td>SSRIs (except Citalopram/Escitalopram)</td>
<td>Venlafaxine</td>
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<tr>
<td>Valproate</td>
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<tr>
<td>Zuclopenthixol</td>
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</tbody>
</table>
Other drugs

**Antiarrhythmic drugs**
- Amiodarone
- Bretylium
- Disopyramide
- Dronedarone
- Flecainide
- 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
Links to forms referred to within this document

Antipsychotic Monitoring Form for use in CHYPs
https://www.sussexpartnership.nhs.uk/node/1574/attachment

High Dose Antipsychotic Monitoring Form
https://www.sussexpartnership.nhs.uk/node/1577/attachment

Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS)
https://www.sussexpartnership.nhs.uk/node/2701/attachment

Glasgow Antipsychotic Side Effect Scale
https://www.sussexpartnership.nhs.uk/node/1603/attachment

Glasgow Antipsychotic Side Effect Scale for clozapine
https://www.sussexpartnership.nhs.uk/node/2248/attachment

Easy read adapted Glasgow Antipsychotic Side Effect Scale for clients with Learning Difficulties
https://www.sussexpartnership.nhs.uk/node/2695/attachment

Barnes Akathisia Rating Scale

Abnormal Involuntary Movement Scale

Broset Violence Checklist
https://www.sussexpartnership.nhs.uk/node/3625/attachment

Cross Reference with current editions of:

Sussex Partnership NHS Foundation Trust

- Formulary and Prescribing Guidance
- Procedure and Guidance for the use of Clozapine
- Rapid Tranquillization Policy

Acknowledgements:

Royal College of Psychiatrists and Curtis J, Newall H, Samaras K. (Positive Cardiometabolic Health Resource)

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