Medicines Management Tool for Antipsychotics
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**Background**

Individual antipsychotic drugs differ by the range and extent of their side effect profile, principally in the following areas.

- Weight gain
- Hyperprolactinaemia
- Sedation
- EPSE
- Hyperlipidaemia
- Postural hypotension
- Other cardiovascular effects
- Hyperglycaemia

This Medicines Management tool is intended to be used assist clinicians and practitioners with the making of prescribing decisions, to target prescribing to produce a care plan that fits the individuals’ holistic needs.

The tool is a summary of current evidence for the selection of antipsychotics. Suggested monitoring parameters are included, as well as strategies for the prevention and management of side effects. There are a range of baseline and yearly monitoring parameters which vary dependent on which medications are being taken.

*Any tests and monitoring are the responsibility of the prescriber.*

The presence of adverse effects of medication should be considered on each occasion that an individual is reviewed.
## Weight Gain

<table>
<thead>
<tr>
<th>Risk/extent of weight gain</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Aripiprazole, pimozide</td>
</tr>
<tr>
<td>Mild</td>
<td>Amisulpride, fluphenazine, haloperidol, flupentixol, paliperidone¹, quetiapine, risperidone (low dose), sulpiride</td>
</tr>
<tr>
<td>Moderate</td>
<td>Risperidone (above low dose),</td>
</tr>
<tr>
<td>High</td>
<td>Chlorpromazine, clozapine, olanzapine zotepine</td>
</tr>
<tr>
<td>Unknown</td>
<td>Pipotiazine, trifluoperazine, zuclopenthixol</td>
</tr>
</tbody>
</table>

### Background

People with schizophrenia are at increased risk of weight gain and this can be partly attributed to some of the newer antipsychotic drugs having a greater propensity to cause weight gain.

Predisposing factors include:

- Younger age
- BMI<23
- Increased appetite while on treatment
- Good response to treatment

### Monitoring of Weight

- Baseline waist circumference, weight and measurement of BMI
- An on line calculator is also available
  - [http://www.nhs.uk/Tools/Pages/HealthyWeightcalculator.aspx](http://www.nhs.uk/Tools/Pages/HealthyWeightcalculator.aspx)
  - [http://tinyurl.com/majngz](http://tinyurl.com/majngz)

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¹ Paliperidone is not approved for general use by HFT and is only available by application to the DTC on a named patient basis
• Ranges of body mass index : weight(Kg)/height²(m²)

  • <17 - moderate to severe chronic protein-energy malnutrition (severe if <15)
  • 17-20 - chronic protein energy malnutrition but some normal subjects
  • 20-25 - desirable (some authorities 19-25)
  • 25-30 - mildly overweight (grade I obesity)
  • 30-40 - grade II obesity
  • >40 - grade III obesity

• Cardiovascular risk is increased if waist circumference exceeds following values
  • Men- 94cm (37 inches)  • Asian Men- 90cm (35 inches)
  • Women- 80cm (31.5 inches)  • Asian women- 80cm (31.5 inches)

• Cardiovascular risks are increased if BMI is over 25 (ideal BMI = 20 to 24.9)
• Measure waist circumference, weigh and calculate BMI monthly for the first 6 months
• Monitor waist circumference, weight and BMI every 3 months after first 6 months
• GPs and other primary healthcare professionals should monitor at least once a year
• Consider need for more frequent monitoring if increased weight is identified

**Strategies for Minimisation of Weight Gain**

• Choose low association agent whenever possible
• Prior to commencement discuss expected benefits and drawbacks of medication
• Discuss information regarding the potential for weight gain
• Encourage low fat, high fibre diet rich in fruit, vegetables and complex carbohydrates
• Educate on link between sugary drinks and weight gain
• Encourage exercise that builds on the individuals usual activities
Management of Weight Gain

Assess for possible causes of increased weight

Medication Review
- Consider contribution of antipsychotic
- Consider role of other medication

Recent smoking cessation

Follow Trust Guidelines for the Prescribing of Medication in Pregnancy

Physical Considerations
- Thyroid function
- FBC
- LFTs
- Albumin
- Electrolytes

Stabilise physical parameters

Abnormality detected

Weight gain unresolved

Normal

Medication Review
- Consider referral to Primary Care for weight management
- Dietary advice
- Lifestyle changes
- Group
- Cognitive techniques
- Increased monitoring

Dietary advice not sufficient or decision not to switch

Consider switch to antipsychotic with lower association with weight gain

Switch

- Follow Guidelines for Antipsychotic Medication Switches
- Assess mental state regularly e.g. BPRS
- Increased monitoring
- Consider referral to Primary Care for weight management
- Dietary advice
- Lifestyle changes
- Cognitive techniques

Recent smoking cessation

Pregnancy

Follow Trust Guidelines for the Prescribing of Medication in Pregnancy
Hyperprolactinaemia

<table>
<thead>
<tr>
<th>Incidence/severity of hyperprolactinaemia</th>
<th>Aripiprazole, clozapine</th>
<th>Olanzapine, quetiapine</th>
<th>Amisulpride, flupentixol paliperidone², risperidone, sulpiride, zuclopenthixol</th>
<th>Chlorpromazine, fluphenazine, haloperidol, pimozide, pipotiazine, trifluoperazine, zotepine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Background
While there is no consistent correlation between antipsychotic dose, prolactin concentration and the occurrence of symptoms, elevated prolactin levels can be manifested by the following symptoms:
- Sexual dysfunction- such as reduced libido, impotence and anorgasmia
- Amenorrhea
- Galactorrhoea- breast milk production in the male or female
- Osteoporosis
- Infertility
- Gynaecomastia

Relatively little is known about the potential long-term harmful effects of sustained hyperprolactinaemia, and secondary gonadotrophin suppression. These effects are particularly important in younger individuals who may need antipsychotic medication for many years.

Monitoring for the Effects of Raised Prolactin
- Consider baseline prolactin - especially when using agents known to elevate prolactin
- Check against current reference values
- Complete sexual history and details of menstrual difficulties when appropriate
- Use a recognised, evidence based tool for screening of sexual side effects-SESCAM
- Reassess when symptoms suggestive of hyperprolactinaemia present

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Date Approved by HFT Jan 2011
Review date: Jan 2013
Strategies for Minimisation of Hyperprolactinaemia

• Choose low association agent whenever possible
• Prior to commencement discuss expected benefits and drawbacks of medication
• Discuss information regarding the potential for side effects associated with hyperprolactinaemia
Management of Hyperprolactinaemia

- Assess possible causes of symptoms associated with hyperprolactinaemia

  > Prolactin level check-compare to baseline where one is available

    - Antipsychotic dose reduction
    - OR
    - Switch to lower association agent

      - Monitor mental state – BPRS
      - Inform female individuals of potential return of menstruation and offer support and contraceptive advice
      - Review symptoms of hyperprolactinaemia at regular intervals

        > Resolution of symptoms of hyperprolactinaemia

          - Yes- and corrected
          - Physical cause identified

          > Investigate possible physical causes of hyperprolactinaemia E.g. prolactin secreting tumour

          > Recheck prolactin

          > Symptoms of hyperprolactinaemia persist

          > No
Sedation

<table>
<thead>
<tr>
<th>Incidence/severity of sedation</th>
<th>Amisulpride, aripiprazole, sertindole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low</td>
<td>Flupentixol, haloperidol, paliperidone³, pimozide, pipotiazine, quetiapine, risperidone, trifluoperazine, sulpiride.</td>
</tr>
<tr>
<td>Low</td>
<td>Fluphenazine, olanzapine, zotepine, zuclopenthixol,</td>
</tr>
<tr>
<td>Medium</td>
<td>Chlorpromazine.</td>
</tr>
<tr>
<td>High</td>
<td>Clozapine</td>
</tr>
</tbody>
</table>

Background
Sedation can be separated into non-specific sedation, which is characterised by drowsiness and somnolence and specific sedation, which is characterised by psychomotor inhibition and psychic indifference. While the sedative properties of medication can be perceived useful for individuals who are very agitated or aggressive, they can adversely affect well being and functional capability.

- Negative aspects of the illness such as apathy should be differentiated from sedation.
- Consider the potential for depression.
- Sedation is more prominent during the early stages of treatment.
- Some degree of tolerance may develop.
- Degree of sedation can be such that the individual becomes unaware of the level of sedation that they are experiencing and perceive it normal.

Monitoring for the Effects of Sedation

- Consider a detailed assessment of the individuals current sleep pattern and history, especially if using atypical associated with high levels of sedation.
- Utilise sleep charts to identify problems.
- Assessment by the bed partner can provide additional information about the individual’s behaviour whilst asleep, when appropriate.

Strategies for Minimisation of Sedation

- Inform individuals of the risks that medication may cause sedation and advise against driving or using machinery if affected.
- Advise that sedation is sometimes more common in the early stages of treatment.
- Emphasise the need to review, should they experience sedation.

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Management of Sedation

- Individual reports sedation
  - Allow 3 to 4 weeks on medication to allow for tolerance
    - Sedation resolved or does not impede on functional capability
      - Review antipsychotic dose and/or assess need for antidepressant
        - Symptoms
          - suggestive of negative features of schizophrenia
          - suggestive of depression
        - Assess risks of medication
          - Consider
            - Taking once daily doses at bedtime?
            - Asymmetrically splitting dose of twice daily doses, with majority of dose at bedtime
            - Change to low association agent

Date Approved by HFT Jan 2011
Review date: Jan 2013
Extrapyramidal Side Effects (EPSE)

<table>
<thead>
<tr>
<th>Incidence/severity of EPSE</th>
<th>Aripiprazole, clozapine, olanzapine, quetiapine, sertindole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>Amisulpride, paliperidone, risperidone (low dose), sulpiride, zotepine</td>
</tr>
<tr>
<td>Medium</td>
<td>Chlorpromazine, fluphenazine, flupentixol, pimozide, pipotiazine, risperidone (above low dose), trifluoperazine</td>
</tr>
<tr>
<td>High</td>
<td>Fluphenazine, haloperidol, zuclopenthixol</td>
</tr>
</tbody>
</table>

**Background**

EPSE can be divided into four types:
- **Dystonias-** usually acute and within a few days of treatment
- **Parkinsonian-** usually appear in first few months of treatment
- **Akathisia-** can occur in first few weeks of treatment
- **Tardive Dyskinesia-** late onset, may be irreversible

There is evidence that certain groups are more susceptible to EPSE, even with the atypical antipsychotics. These include:
- **First episode**
- **The elderly (especially females)**
- **Presence of affective symptoms**
- **Younger individuals-** acute dystonia
- **Males-** acute dystonia

The risk of EPSE with all the atypical agents is much lower than with the conventional antipsychotics, but there is still the potential for individuals to experience a difficult side effect that society has little or no understanding of. The occurrence of EPSE plays a significant role in non-concordance.

**Monitoring for EPSE**

Careful monitoring is essential, especially with mild to moderate EPSE. The individual should be assessed prior to treatment using a validated assessment tool such as:

**Side Effects Scale/Checklist for Antipsychotic Medication (SESCAM- Bennett 1995)**
- 2 part scale- observer and self rated
- First part focused on EPSE
- Second part focused on other known side effects
- Includes description of assessment procedure, severity ratings and glossary

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4 Paliperidone is not approved for general use by HFT and is only available by application to the DTC on a named patient basis
Modified Abnormal Involuntary Movement Scale (AIMS- Munetz & Benjamin 1988)

- 12 item scale
- Assesses presence and severity of Tardive Dyskinesia
- Dependent mainly on examination and observer ratings
- Includes instruction for examination procedure

Monitoring should be carried at baseline and then biannually if asymptomatic. Should symptoms emerge the increased frequency of monitoring is established by the effectiveness of remedial strategies.

Strategies for Minimisation of EPSE

- Use lowest effective dose possible
- Use antipsychotic monotherapy wherever possible
- Re-assess need for antipsychotic regularly
- Consider withdrawing other drugs that may induce/exacerbate movement disorders

Drug Treatment of EPSE

The evidence for the effectiveness of drug treatment is more robust for the treatment of dystonia and parkinsonian type symptoms. The treatment of akathisia and tardive dyskinesia is largely based on small case reports.

Dystonia

Oral, intramuscular (IM) or intravenous (IV) anticholinergic medication depending on severity of symptoms

- Individual may be unable to swallow
- Response to IV usually within 5 minutes
- Response to IM usually around 20 minutes
- Response to oral medication may take up to 2 hours

Parkinsonian type

Oral anticholinergic medication

- Majority of individuals do not require long term treatment
- Review continued need at least 3 monthly
- May induce dependence
- May induce psychosis
- Have a range of adverse side effects
- Potentially lethal in overdose

Akathisia

Anticholinergics are generally unhelpful

All treatments are unlicensed:

- Propranolol 30 to 80 mg daily
- Cyproheptadine 8 to 16 mg daily
- Clonazepam 500 micrograms to 3 mg daily

Tardive dyskinesia

Anticholinergics may exacerbate

- Tetrabenazine started at 12.5 mg daily and titrated to 25 to 75 mg daily (Max 200 mg daily) is the only licensed treatment
- Calcium-channel blockers may have some efficacy
- Clonazepam has possible efficacy
Management of EPSE

- Individual presents with symptoms suggesting EPSE
- Assess using validated instrument
  - SESCAM
  - AIMS

- Consider relative risk of prescribed medication
  - Antipsychotic
  - Other medication

  - Medication has associated risks
    - Consider switch to agent with lower association with EPSE
    - YES
    - NO

  - Monitor mental state

  - Strategies to minimise EPSE
    - lowest effective dose possible
    - monotherapy wherever possible
    - assess need for continued antipsychotic
    - withdraw other medication that may exacerbate EPSE

- Consider drug treatment of EPSE

- Resolution of symptoms or reduction to acceptable level
Hyperlipidaemia

There are no large scale trials that quantify the effects of atypical antipsychotics on lipid metabolism. Several studies suggest that changes in lipid profile are concordant with weight changes and that clozapine and olanzapine tend to be associated with adverse changes in serum concentrations of triglyceride and cholesterol. This is reflected in the SPC for olanzapine therapy, reporting elevated serum cholesterol levels as common and elevated triglyceride levels as very common. Additionally, changes from levels of total cholesterol (serum fasting levels) within desirable range at baseline to high levels post therapy were noted as common. The SPC for clozapine notes very rare hypercholesterolemia and for quetiapine the SPC notes evidence of adverse lipid profile in clinical studies.

There are reports of hyperlipidaemia with phenothiazine therapy and included in the SPC for zuclopenthixol.

Background

Antipsychotic induced weight gain is known to be associated with hyperlipidaemia. Under standard 4 of the National Service Framework for Coronary Heart Disease (CHD), the role of the GP and primary health care team to identify individuals who are at risk of CHD, but who are asymptomatic has been highlighted.

NICE CG 67 – Lipid Modification – Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease was re-issued in March 10. Blood cholesterol has a log-linear relationship to the risk of CHD and is a key modifiable factor. Blood cholesterol can be reduced by dietary change, physical activity and medication. Treatment should be aimed at reducing overall CHD risk. A combined approach that addresses all risk factors yields most benefit.

Elevated serum cholesterol is considered an independent risk factor for the development of CHD and a fasting lipid profile is recommended every 5 years for all individuals of 20 years and above, regardless of cardiovascular risk status.

Monitoring for Hyperlipidaemia

- Check fasting serum cholesterol prior to treatment
- Assessment should include Thyroid Stimulating Hormone (TSH) if dyslipidaemia is present
- Reassess fasting serum cholesterol 3 months after initiation of treatment
- Monitor as appropriate, depending on results and other risk factors
Classification of serum cholesterol levels

<table>
<thead>
<tr>
<th>Serum Lipid Concentration mmol/L</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low density lipoprotein- LDL</td>
<td></td>
</tr>
<tr>
<td>&lt; 2.59</td>
<td>Optimal</td>
</tr>
<tr>
<td>2.59 to 3.34</td>
<td>Near or above optimal</td>
</tr>
<tr>
<td>3.36 to 4.11</td>
<td>Borderline high</td>
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<tr>
<td>4.14 to 4.89</td>
<td>High</td>
</tr>
<tr>
<td>≥ 4.91</td>
<td>Very high</td>
</tr>
<tr>
<td>Total cholesterol- TC</td>
<td></td>
</tr>
<tr>
<td>&lt; 4.0</td>
<td>Desirable</td>
</tr>
<tr>
<td>≥ 4.0</td>
<td>High</td>
</tr>
<tr>
<td>High density lipoprotein- HDL</td>
<td></td>
</tr>
<tr>
<td>&lt; 1.0</td>
<td>Low</td>
</tr>
<tr>
<td>≥ 1.55</td>
<td>High</td>
</tr>
</tbody>
</table>

The risk for CHD should be calculated using an appropriate risk calculator (NICE) which in addition to current lipid levels takes account of other positive risk factors:

- Older age- 45 years and above in males, 55 years and above in female
- Smoking
- Obesity
- Hypertension- BP of or above 130/80 mmHg
- HDL concentration of less than 1.0 mmol/L in men or 1.2mmol/L in women
- Family history of premature heart disease
- Ethnicity
- Abnormal fasting blood glucose levels

Diabetes is a risk factor equivalent to CHD

The risk factor is individual to the patient and should be recorded with primary care consultation records.

People with the following pre-existing conditions do not require risk assessment as they meet the requirement for secondary treatment:

- CHD or angina
- Stroke or TIA
- Peripheral Vascular Disease

Risk equations should not be used for people who are at high risk of CVD due to the following conditions, as they have specific treatment considerations:

- familial hypercholesterolemia – treated by specialist management
- diabetes – treated under NICE management of type 2 diabetes (update) CG 66.

People older than 40 should have their estimate of cardiovascular (CVD) risk reviewed on an ongoing basis. Offer the patient information about the absolute risk of CVD and absolute benefits and harms of an intervention over a 10 year period- see www.npci.org.uk for decision aids. (NICE 2010)
Strategies for Minimisation of Hyperlipidaemia

- Use low association agent when possible
- Encourage lifestyle changes
- Monitor weight regularly and take appropriate action in cases of weight gain
- Monitor serum cholesterol at appropriate intervals

Management of Hypercholesterolemia

Lifestyle changes appropriate for the improvement of lipid profile include:
- Increase physical activity, consider exercise referral systems
- Weight reduction
- Decreased dietary intake of saturated fat and cholesterol
- A cardioprotective diet (including 5 portions of fruit and vegetables a day and 2 portions of oily fish a week as per NICE)

If lifestyle changes are insufficient then additional measures should be taken for an additional six weeks:
- Reinforcement of lifestyle changes
- Referral to a dietician
- Consider plant sterols and stanols (note NICE does not recommend routine use of these agents for primary prevention of CVD).

Before offering lipid modification therapy (statins) for primary prevention of CHD all other modifiable CVD factors should be considered and their management optimised if possible (NICE Lipid Modification 2010)

- Control BP: The NSF BP target of 140/85 mmHg to reduce risk is challenging, in practice it may not be possible to achieve this for every patient within high risk groups, hence audit criteria of 150/90 mmHg (also adopted by General Medical Service -GMS Quality and Outcomes Framework as a target for the CHD clinical domain)
- Smoking Cessation: Offer advice about how to stop smoking including advice on nicotine replacement therapy.
- Advice on other modifiable risk factors and personalised advice about how they can be reduced, including advice about physical activity, diet, alcohol consumption, weight and diabetes should be provided.

Should measures prove insufficient to reduce lipids and CHD risk then a change to a lower association atypical if possible, mental state should be monitored accordingly. If a change to a lower association agent is not possible pharmacological treatment for hypercholesterolemia may be necessary.
Pharmacological intervention

Statin therapy is recommended by NICE as part of the management strategy for primary prevention of CVD for adults who have a 20% or greater 10 year risk of developing CVD (equating to a 15% or greater CHD 10 year risk) regardless of lipid level. For secondary prevention (existing CVD/CHD) lipid modification therapy should be offered and not delayed by management of modifiable risk factors. Treatment for both primary and secondary CVD should be initiated with simvastatin 40 mg, if there are potential drug interactions or simvastatin 40 mg is contra-indicated a low dose or alternative preparation such as pravastatin may be chosen.

In secondary prevention consider increasing statin potency if a total cholesterol of less than 4mmol/L and an LDL cholesterol of less than 2 mmol/L is not attained, taking into account patient preference, co-morbidities, multiple drug therapies and benefits and risks of treatment. Allow 3 months after commencement of statin therapy and each potency increase before repeating lipid levels to assess benefit of treatment. Current GMS QOF contains a target of total serum cholesterol less than or equal to 5 mmol/L within the CHD clinical domain remaining unchanged.

Within primary prevention NICE does not suggest a target to attain but ongoing monitoring of cholesterol levels (annual) may promote adherence to lifestyle interventions and statin therapy.
Postural Hypotension

<table>
<thead>
<tr>
<th>Incidence/severity of hypotension</th>
<th>Amisulpride, aripiprazole, sulpiride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low</td>
<td>Fluphenazine, haloperidol, Olanzapine, quetiapine, zuclopenthixol</td>
</tr>
<tr>
<td>Low</td>
<td>Chlorpromazine, clozapine, paliperidone(^5), pimozide, risperidone, sertindole, trifluoperazine, zotepine</td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
</tr>
</tbody>
</table>

Background
Postural hypotension is associated with antipsychotics that block alpha\(_1\) adrenoreceptors. It is likely to be more problematic in the following groups:

- Older individuals
- Individuals with cardiovascular disease
- Individuals on antihypertensive medication

Individuals exhibit varying degrees of tolerance to falls in blood pressure. A drop in systolic pressure in the region of 20 to 30mmHg within 3 minutes of standing, with associated symptoms is adequate for the diagnosis of postural hypotension.

Symptoms associated with postural hypotension include:

- Feeling faint or fainting
- Neck pain
- Weakness or buckling of the legs
- Cognitive slowing
- Headache
- Seizures- usually clonic jerks
- Angina- particularly after food
- Light headedness

Monitoring for Postural Hypotension
- Morning sitting and standing blood pressure after initiation and dose increments
- More frequent monitoring if symptomatic of postural hypotension

Strategies for the Minimisation of Postural Hypotension
- Choose agents with lower propensity for causing postural hypotension where possible
- Use standardised titrations for dose increments
- Consider more cautious titration in higher risk individuals and those who experience symptoms suggestive of postural hypotension

\(^5\) Paliperidone is not approved for general use by HFT and is only available by application to the DTC on a named patient basis
Management of Postural Hypotension

Individual presents with symptoms suggestive of postural hypotension

Educate individual to minimise postural hypotension
- Plan activity before meals
- Consume largest meal at night
- Decrease alcohol intake
- Eat low carbohydrate foods
- Avoid large meals
- Drinking water may improve symptoms
- Avoid prolonged recumbency
- Avoid prolonged exercise
- Care during hot weather
- Keep shower or bath temperature moderate
- Raise head of bed 5 to 20°

Further education

Symptoms continue

Switch to lower association agent and monitor mental state

Resolution of symptoms
Other Cardiovascular Side Effects

Stroke

In elderly patients with dementia, antipsychotic drugs are associated with a small increased risk of mortality and an increased risk of stroke or transient ischemic attack. All older individuals should be assessed for risk factors for cerebrovascular events (e.g. hypertension, atrial fibrillation), prior to commencement of any antipsychotic drug.

It is recommended that:

- Antipsychotic drugs should not be used in elderly patients to treat mild to moderate psychotic symptoms.
- Initial doses of antipsychotic drugs in elderly patients should be reduced (to half the adult dose or less), taking into account factors such as the patient’s weight, co-morbidity, and concomitant medication.
- Treatment should be reviewed regularly
- Risperidone holds a licence for the short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer’s dementia unresponsive to non-pharmacological interventions and when there is a risk of harm to self or others.
- There is very limited evidence for the efficacy of atypical or typical antipsychotic drugs for the treatment of symptoms of psychosis in dementia.
- A clinically significant degree of improvement has only been demonstrated for aripiprazole, with NNT of 13.8

QTc Prolongation

Zotepine may cause significant prolongation of the QT<sub>C</sub> interval. The use of zotepine should be avoided in individuals with a history of:
- Coronary heart disease
- Cardiac failure
- Arrhythmia

Myocarditis and Cardiomyopathy

Potentially fatal myocarditis (usually occurring in the first 2 months of treatment) and cardiomyopathy (occurring at anytime) are rare serious effects of clozapine. Individuals who have a history suggestive of heart disease should be assessed by a specialist before commencing treatment with clozapine.
## Hyperglycaemia

<table>
<thead>
<tr>
<th>SPC reported incidence of hyperglycaemia/risk of developing/exacerbating diabetes mellitus</th>
<th>Level of evidence</th>
<th>Not reported in SPC</th>
<th>Limited data</th>
<th>Sulpiride, fluphenazine, trifluoperazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not known (reports exist)</td>
<td>Limited data</td>
<td>Not assessed</td>
<td>Limited data</td>
<td>Aripiprazole, flupentixol, pipotiazine, pimozide, zuclopenthixol</td>
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<tr>
<td>Not assessed</td>
<td>Limited data</td>
<td>Rare (≥ 1/10,000 to &lt;1/1,000)</td>
<td>Limited data</td>
<td>Clozapine olanzapine, quetiapine, risperidone</td>
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<tr>
<td>Common (≥ 1/100 to &lt; 1/10)</td>
<td>Limited data</td>
<td>Amisulpride</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very common (≥ 1/10)</td>
<td>Limited data</td>
<td>Other sources</td>
<td></td>
<td></td>
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<tr>
<td>Conflicting</td>
<td>Limited data</td>
<td>Consensus conference</td>
<td>Clozapine, olanzapine</td>
<td></td>
</tr>
<tr>
<td>Report of hypoglycaemia frequency unknown</td>
<td>Limited data</td>
<td>Haloperidol</td>
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### Background
The prevalence of diabetes mellitus among individuals with schizophrenia is around twice that in the general population. Traditional and atypical antipsychotics may further increase the risk of developing diabetes. Much of the information about the risk of hyperglycaemia is based on retrospective analyses of large databases. The difficulty in adjusting for confounding factors and there is a clear need for more robust evidence to assess the relative risks of individual antipsychotics. Most, but not all, analyses have suggested an increased risk with atypical antipsychotics as a group. Known risk factors for hyperglycaemia include:
- Age of 45 or more
- Positive family history
• Pre-existing obesity - ≥ 20% above desired body weight or BMI ≥ 25
• Physical inactivity
• Ethnic factors- African, Asian, Afro-Caribbean origin
• Impaired glucose tolerance- fasting plasma glucose of ≥ 5.55mmol/L but < 6.99mmol/L
• Hypertension- BP ≥ 140/90mmHg
• HDL cholesterol less than 0.9 and or triglycerides more than 2.82mmol/L
• History of gestational diabetes or delivery of baby weighing > 4kg
• Polycystic ovary syndrome or history of vascular disease

It is suggested that the risk of developing diabetes during therapy is cumulative and not associated with initial therapy alone.

**Monitoring for Hyperglycaemia**

• Baseline random or fasting plasma glucose prior to initiation
• Serum glucose concentration 3 to 4 monthly for first year to check for hyperglycaemia- glucose concentration ≥ 8.9mmol/L but < 11.0mmol/L
• Subsequently for high risk individuals- check serum glucose concentration 6 monthly
• Individuals with no additional risk factors- check serum glucose concentration 12 monthly

**Strategies for the Minimisation of Hyperglycaemia**

• Use low association agent wherever possible
• Advise individuals on prophylactic lifestyle changes when prescribing an atypical antipsychotic particularly those associated with weight gain or hyperglycaemia
• Advise individual to report first signs of polyuria (excess urination) and polydipsia (excess drinking)
Management of Hyperglycaemia

Monitoring indicates signs of hyperglycaemia

Encourage lifestyle changes

Switch to atypical with lower association with hyperglycaemia

IN EFFECTIVE

YES

Monitor mental state

Already on low association agent or switch would adversely affect mental state

Consider use of oral hypoglycaemic agent

LEVELS MAINTAINED WITHIN NORMAL LIMITS

EFFECTIVE
## Monitoring Parameters for Antipsychotics

<table>
<thead>
<tr>
<th>Patient Name:</th>
<th>Date of Birth:</th>
<th>NHS Number:</th>
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<tbody>
<tr>
<td>Agent Prescribed:</td>
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<td></td>
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<tr>
<td>Date:</td>
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</table>

### Height (m) | Amisulpride | Aripiprazole | Clozapine | Olanzapine | Quetiapine | Risperidone | Zotepine | Typical Agents | Date: | Baseline | Repeat (min annually) |
<table>
<thead>
<tr>
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**FPG/ HbA1c**  
*If Random Plasma Glucose (RPG) elevated*

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<th><strong>Prolactin</strong></th>
<th><strong>LFTs</strong></th>
<th><strong>TFTs</strong></th>
<th><strong>U&amp;Es</strong></th>
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<td>B</td>
<td>B</td>
</tr>
</tbody>
</table>

*SM = specific monitoring is required under the terms of the SPC  
N = no requirement for monitoring this parameter  
B = best practice  
Y = monitoring required*