

Guidelines on Choice and Selection of Antipsychotics for the Management of Psychosis and Schizophrenia in Adults

HPFT Guidelines

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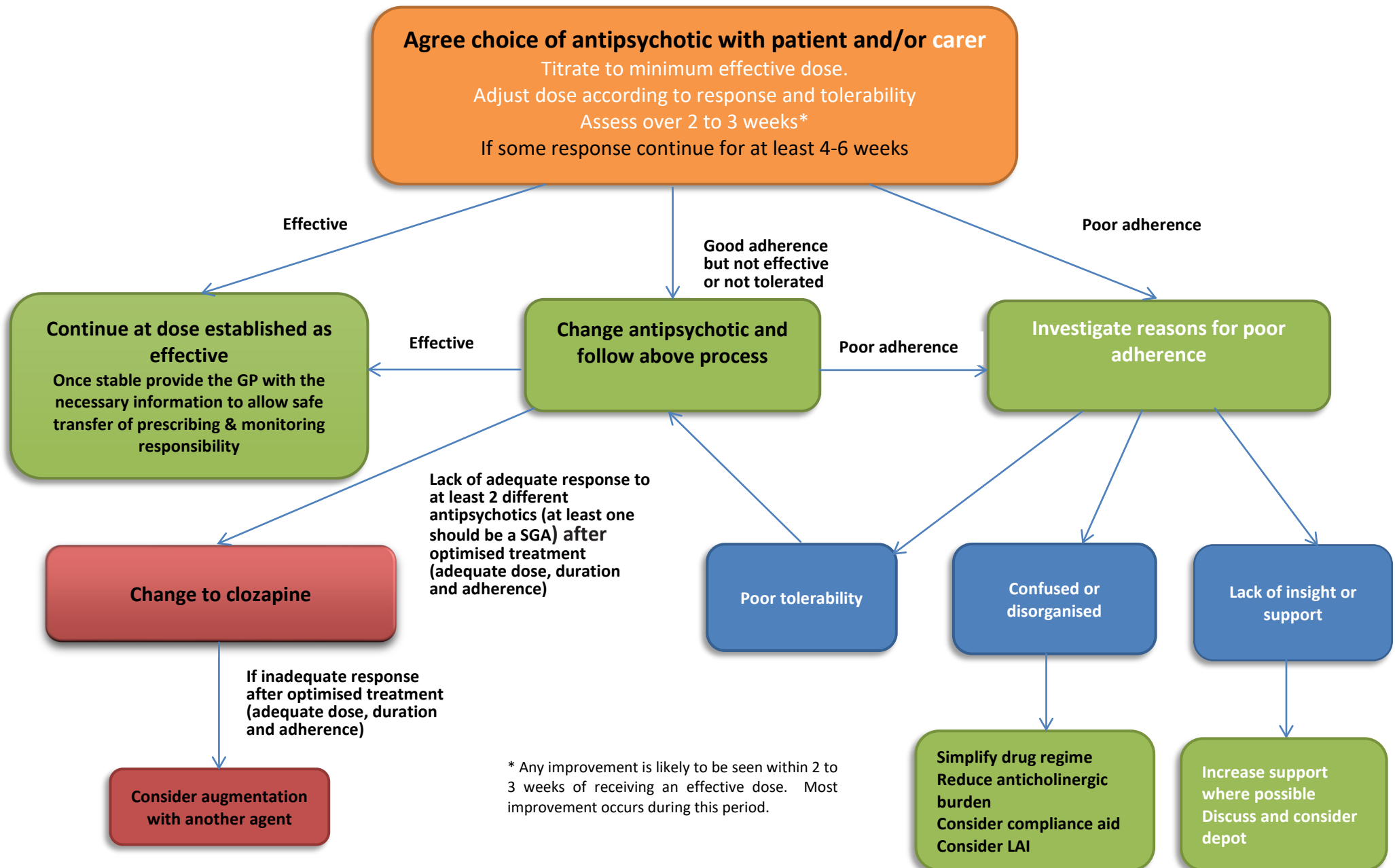
Title of document	Guidelines on Choice and Selection of Antipsychotics for the Management of Psychosis and Schizophrenia in Adults		
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Staff need to know about this guideline because (complete in 50 words)	These guidelines have been developed to provide clinical staff with clear guidance on prescribing antipsychotics for the management of psychosis / schizophrenia in adults to ensure safe and cost-effective care of service users in line with the current NICE guidance and trust formulary.		
Staff are encouraged to read the whole guideline, but I (the Author) have chosen three key messages from the document to share:	<p>1. No single antipsychotic has superior efficacy in the acute and maintenance treatment of schizophrenia and other psychotic disorders (excluding clozapine). Choice of treatment should be guided by individual service user factors.</p> <p>2. Rapid titration of LAIs should be avoided as there is a delay of several weeks in attaining peak plasma concentrations. This can help prevent long lived and severe adverse effects.</p> <p>3. There should be good and clear communication between the specialist and GP (especially when prescribing and monitoring is transferred to primary care) for the safe and effective management of service users.</p>		
Summary of significant changes from previous version are:	<p>Minor amendments:</p> <ul style="list-style-type: none"> References to Xeplion® LAI in the document changed to Paliperidone monthly LAI as generic version available 		

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N.B: Some links within this document will not be accessible to non-HPFT staff

1. Algorithm for the pharmacological management of schizophrenia



2. Introduction

Antipsychotics are the mainstay in the pharmacological management of schizophrenia and a range of other psychotic disorders¹. They are used to treat acute episodes and prevent relapses of the illness².

As per NICE guidelines service users with first episode psychosis, acute exacerbations and recurrence of psychosis or schizophrenia should be offered oral antipsychotic medication in conjunction with psychological interventions.

The aim of treatment is to reduce symptoms and improve social and cognitive functioning. Service users will often require long term treatment with antipsychotic medication.

The efficacy of currently available antipsychotic agents in the treatment of schizophrenia is broadly similar ^{3,4} (with the exception of clozapine's greater efficacy in treatment-resistant patients). Individual patient response can however vary². Antipsychotics also have important differences in the side-effects they cause. Service users differ in the side-effects they experience and the side-effects they are willing or not willing to tolerate^{1,2}.

Antipsychotics are most effective in ameliorating positive symptoms of schizophrenia, but less effective in treating negative and cognitive symptoms.

3. Purpose and Scope

This document provides guidance on the choice and selection of antipsychotic medication for the management of psychosis and schizophrenia in adults within Hertfordshire Partnership University NHS Foundation Trust (HPFT).

These guidelines are primarily based on [NICE CG 178 Psychosis and schizophrenia in adults](#) and cover pharmacological management and treatment of both first episode and subsequent episodes of psychosis. Psychological interventions are beyond the scope of this guideline.

The guidelines **do not** cover the management of psychoses and schizophrenia in:

- Children and adolescents [NICE CG 155 Psychosis and schizophrenia in children and young people](#)
- Pregnancy and lactation [NICE CG 192 Antenatal & postnatal mental health: clinical management and service.](#)

They also do not cover the use of antipsychotics in management of other disorders; please consult relevant national and/or local guidelines or contact Pharmacy for specific advice.

This document does not aim to provide full prescribing guidelines and other relevant sources of information and HPFT policies / guidelines (see section 19 below) should

be consulted for guidance on the safe and effective prescribing of antipsychotics. This is in addition to the NICE Clinical Guidelines.

4. Abbreviations

- BNF – British National Formulary
- CVD – Cardiovascular Disease
- CG – Clinical Guidelines
- ECG - Electrocardiogram
- EPR – Electronic Patient Record
- EPSEs – Extra Pyramidal Side Effects
- FGA – First Generation Antipsychotic
- GASS – Glasgow Antipsychotic Side-Effect Scale
- GP – General Practitioner
- HDAT – High Dose Antipsychotic Therapy
- IM - Intramuscular
- LAI – Long-Acting Injection
- NICE – National Institute of Health and Care Excellence
- NMS – Neuroleptic Malignant Syndrome
- SGA – Second Generation Antipsychotic
- SPC – Summary of Product Characteristics
- VTE – Venous Thromboembolism

5. Key principles of prescribing^{2,5}

- Apart from clozapine, the efficacy of all antipsychotics is very similar, and the initial choice should be based on several factors. These are listed under section 6 - “Choice of Antipsychotic”.
- Treatment with an antipsychotic medication should be considered an explicit individual therapeutic trial. The following should be recorded:
 - Indications and expected benefits and risks of oral antipsychotic medication.
 - Document the expected time for a change in symptoms and emergence of side-effects.
 - Discuss and record the side-effects that the person is most willing to tolerate.
- At the start of treatment, doses at the lower end of the licensed range should be used and gradually titrated upwards according to response and tolerability. Assess response (at optimum dosage) over 2 to 3 weeks, and if some response, continue for at least 4-6 weeks before considering a change of drug (see treatment algorithm on page 4).
- The lowest effective dose should be used. Doses should be within the maximum BNF or SPC dose limits.
- Lower doses are particularly appropriate for negative symptoms and first episode psychosis.
- Current evidence does not justify the routine use of HDAT. Justify and record the reasons for prescribing dosages outside the range given in the BNF or SPC. Refer to the [HPFT HDAT policy](#).
- Service users should only be treated with ONE regular antipsychotic at a time except in exceptional circumstances (e.g. clozapine augmentation or when cross-

tapering medication). Antipsychotic polypharmacy should be avoided due to increased risk of adverse effects such as extrapyramidal side effects (EPSEs), QT interval prolongation and sudden cardiac death⁶.

- Oral and parenteral doses of the same antipsychotic should be prescribed separately as they can vary in bioavailability.
- As required prescriptions should be reviewed regularly, ideally weekly, or as appropriate for clinical indication, frequency of administration, therapeutic benefits and side-effects. Prescriptions that are no longer required should be cancelled and doses of regular antipsychotics adjusted accordingly where appropriate. Check whether when required prescriptions have led to a dosage above the maximum daily dose specified in the BNF or SPC.
- The use of orodispersible tablets and liquid formulations should be regularly reviewed and changed to oral solid dosage formulations whenever possible to ensure cost-effective prescribing.
- Regular review of the medication regime should address the following and be documented in the EPR: This should also be clearly communicated to the GP especially when prescribing responsibility is to be transferred to primary care.
 - Response to treatment (including use of validated rating scales)
 - Side-effects (using validated rating scales)
 - Medication adherence
 - Overall physical health
 - Rationale for continuing, changing or stopping medication, and the effects of such changes
- There should be a clear plan in the service user's clinical records with all the relevant information (including diagnosis, indication for antipsychotic, target symptoms, adherence risks, relapse indicators, on-going prescribing and monitoring requirements (including physical health checks)). This should be clearly communicated to the GP when prescribing and monitoring responsibilities of oral antipsychotics are transferred to primary care.
- Note, the service user must be clinically stable prior to transferring prescribing and monitoring responsibilities to primary care.

6. Choice of antipsychotic^{2,5}

- Antipsychotics are effective in both the acute and maintenance treatment of schizophrenia and other psychotic disorders, however, no single antipsychotic has superior efficacy (excluding clozapine).
- The antipsychotics differ in their pharmacology, pharmacokinetics, overall efficacy/effectiveness and tolerability. More importantly, response and tolerability differ between service users. This variability of individual response means that there is no single antipsychotic is routinely recommended as first choice.
- The decision on which antipsychotic to prescribe should be made jointly by the prescriber and service user/carer(s) and should be guided by:
 - the service user's clinical presentation
 - any general medical/physical health conditions
 - any concurrent medication
 - the antipsychotics' side-effect profile including metabolic, extrapyramidal, cardiovascular, hormonal side-effects and other side-effects
 - service user's previous response to any antipsychotics

- service user's previous tolerance of any antipsychotics (including unpleasant subjective experiences)
 - side-effects the service user is most willing to tolerate
 - any contra-indications and cautions
 - service user preference
 - cost-effectiveness
- The '[Choice and Medication](#)' website has a number of 'Handy Charts' which may help the prescriber and service user/carer(s) decide which antipsychotic is the most suitable.
- When discussing treatment options with service users /carer(s), written information should be provided along with information about how to access further information if needed. Patient information leaflets are available from [Choice and Medication](#) website.

7. Antipsychotic Long-acting Injections (LAIs)

- The term long-acting injection (LAI) in these guidelines refers to both conventional oil-based depots which are predominantly FGAs and the newer SGA long-acting injections.
- LAIs are a useful option when concordance with oral antipsychotic treatment is unreliable.
- The FGA LAIs are licensed for the maintenance treatment of schizophrenia and other psychoses whereas the SGA LAIs are licensed for maintenance treatment of schizophrenia in those who have been stabilised with the oral formulation. (Paliperidone LAI can also be used in patients previously responsive to oral paliperidone or risperidone).
- Consider offering an antipsychotic LAI to people with psychosis or schizophrenia:⁵
 - who would prefer such treatment after an acute episode
 - where avoiding covert non-adherence (either intentional or unintentional) to antipsychotic medication is a clinical priority within the treatment plan
- It is preferable to maintain the same antipsychotic when switching from oral to LAI in those who have shown some response to the oral form, however not all antipsychotics are available as LAI and the clinical pharmacy team can be contacted for advice on alternative choices of LAI when required.
- As with oral antipsychotics, FGA LAIs have a higher propensity for EPSEs whilst SGA LAIs have a relatively lower propensity for this side-effect at therapeutic doses.
- There is no evidence of any greater benefit with SGA LAIs over FGA LAIs in preventing relapses or admission to hospital. There are however significant price differences between the two groups of LAIs. FGA LAIs should be considered first as they are significantly cheaper and only if not clinically appropriate or not tolerated should a SGA LAI be selected. A clear rationale for selecting a SGA over FGA must be documented.
- Due to their long half-life, any adverse effects that result from the administration of an LAI antipsychotic are likely to be long lived. Antipsychotic LAIs should be avoided in service users with a history of serious side effects that would warrant immediate discontinuation of treatment².

- When initiating therapy with FGA LAIs, service users should first be given a test-dose to assess sensitivity to EPSEs and to reveal any sensitivity to the base oil².
- There is a delay in achieving peak plasma levels, therapeutic effect and steady state plasma levels with antipsychotic LAIs compared with oral medication. Doses may be reduced if adverse effects occur, however, should only be increased after careful assessment over at least 1 month. At the start of therapy, plasma levels of antipsychotic released from a depot increase over several weeks to months without increasing the given dose. Dose increases during this time to steady-state plasma levels are therefore unnecessary².
- Antipsychotic LAIs should only be initiated by specialist secondary care mental health specialists. Prescribing and administration responsibility is to be retained by HPFT.
- Note, LAIs are not recommended for those who are antipsychotic naïve.
- Refer to appendices 2 - 5 for guidelines on prescribing and administration of the SGA LAIs.
- See [Guidance on the Administration to Adults of Oil-based Depot and other Long-Acting Intramuscular Antipsychotic Injections](#) and [HPFT injections procedure](#).

8. Side-effects of antipsychotics

- Antipsychotics have different side-effect profiles⁷ (see Appendix 7). The adverse effects of particular note are the propensity for FGAs to cause EPSEs including akathisia and the varying propensity for many of the FGAs and SGAs to cause weight gain, hyperprolactinaemia and metabolic sequelae such as diabetes and lipid disturbances.
- Not all service users experience EPSEs. Anticholinergic drugs should ideally be prescribed on a when required basis if EPSEs such as Parkinsonism and dystonias occur and should not be used to manage tardive dyskinesia as they can exacerbate this symptom. Most service users do not require anticholinergics long-term, and withdrawal should be attempted if the patient is no longer experiencing troublesome side-effects. It is important to avoid increasing the anticholinergic burden where possible, especially in older adults, as medicines with an anticholinergic effect can impair cognition, increase the risk of falls, as well as causing other side-effects⁸.
- Side-effects experienced should be assessed using validated rating scales (e.g. GASS /LUNTERS) and recorded in the electronic patient record (EPR). See appendix 1 for GASS template.
- SGAs may be preferable in the treatment of first episode psychosis due to lower propensity for EPSEs within BNF dose range.
- Persistent elevation of plasma prolactin is associated with sexual dysfunction, reductions in bone mass density, menstrual disturbances, breast growth and galactorrhoea and possible increase in risk of breast cancer. Prolactin elevating drugs should be avoided (if possible) in patients under 25 years of age i.e. before peak bone mass, with osteoporosis or with a history of hormone dependent breast

cancer. In symptomatic patients consider switching to an alternative antipsychotic (see table 1). If asymptomatic discuss implications with the service user and make a joint decision to stay on current treatment or switch to another antipsychotic.

- Antipsychotics also vary in the degree of cardiac risk including, arrhythmias, syncope, QT prolongation, Torsade de pointes (potentially life-threatening heart arrhythmia) and sudden cardiac death. In order to reduce the risk of QT prolongation the following is recommended:
 - Use minimum effective dose
 - Avoid polypharmacy
 - Avoid concomitant prescribing of more than one drug that prolongs QT interval
 - Avoid hepatic enzyme inhibitors
 - Correct any modifiable risk factors e.g. electrolyte imbalances
 - Perform baseline ECG prior to starting an antipsychotic medication if:
 - specified in the SPC
 - a physical examination has identified specific cardiovascular risk (such as diagnosis of high blood pressure)
 - there is a personal history of cardiovascular disease /disorder or
 - the service user is being admitted as an inpatient

- Neuroleptic malignant syndrome (NMS) is a rare but potentially fatal side-effect of all antipsychotic drugs. It is characterised by muscular rigidity, hyperthermia, altered consciousness, and autonomic dysfunction. Rises in creatinine kinase (CK) are fairly common. There is, however, considerable variability in clinical presentation. Risk factors include, but are not limited to, high potency FGAs, recent or rapid dose increase, rapid dose reduction, abrupt withdrawal of anticholinergic agents and antipsychotic polypharmacy.

All antipsychotics should be withdrawn and temperature, pulse, blood pressure monitored. Benzodiazepines, if not already prescribed, should be considered. Liaise with medical staff at the acute trust as a medical admission may be required. Re-starting antipsychotic treatment would be required in most cases. Allow time for symptoms of NMS to resolve first. An antipsychotic structurally unrelated to that previously associated with NMS or an antipsychotic with low dopamine affinity should be considered. Doses should be increased very gradually with close monitoring of physical and biochemical parameters. Antipsychotic LAIs of any kind and high potency conventional antipsychotics should be avoided².

- Antipsychotics are associated with a small but important risk of venous thromboembolism (VTE), resulting in an elevated incidence of pulmonary embolism, stroke and myocardial infarction, particularly in the early part of treatment. Risk appears to be greatest during the early part of treatment and in younger people and is likely to be dose related.

All patients (but especially younger patients) starting antipsychotic treatment should be closely monitored for signs of venous thromboembolism e.g. calf pain or swelling, breathing difficulties, signs of myocardial infarction or stroke.

To minimise the risk, the lowest therapeutic dose should be prescribed². Hydration and physical mobility should also be encouraged. Please also refer to the [HPFT VTE prophylaxis policy](#).

- Refer to the Maudsley Prescribing Guidelines for further information and guidance on the management of antipsychotic adverse effects.

Antipsychotic choice in certain situations

Service users will often experience intolerable side-effects from antipsychotics and the table below gives some suggestions on possible alternative choices of antipsychotics in these situations.

Table 1 Suggested choices of antipsychotics due to poor tolerability / side-effects²

Adverse effect	Suggested drugs	Alternatives
Acute extrapyramidal symptoms	Aripiprazole Olanzapine Quetiapine	Clozapine* Lurasidone**
Akathisia	Olanzapine Quetiapine	Clozapine*
Dyslipidaemia	Amisulpride Aripiprazole Lurasidone**	
Impaired glucose tolerance	Amisulpride Aripiprazole Lurasidone**	Haloperidol
Hyperprolactinaemia	Aripiprazole Lurasidone** Quetiapine	Clozapine* Olanzapine
Postural hypotension	Amisulpride Aripiprazole Lurasidone **	Haloperidol Sulpiride Trifluoperazine
QT prolongation	Lurasidone**	Low dose monotherapy of any drug not formally contra-indicated in QT prolongation (with ECG monitoring)
Sedation	Amisulpride Aripiprazole Risperidone Sulpiride	Haloperidol Trifluoperazine
Sexual Dysfunction	Aripiprazole Lurasidone ** Quetiapine	Clozapine*

Tardive Dyskinesia	Clozapine*	Aripiprazole Olanzapine Quetiapine
Weight gain Lifestyle advice and support	Amisulpride Aripiprazole Lurasidone**	Haloperidol Trifluoperazine

N.B: Cariprazine has not been added to the table above as it is non-formulary at HPFT.

*Clozapine is only an option if lack of satisfactory clinical response to at least two different antipsychotics (at least one should be a SGA) after optimised treatment (adequate dose, duration and adherence).

** Approved with an Amber Initiation status – see HPFT antipsychotic formulary (section 15) for further information.

9. Interactions

The impact of antipsychotic interactions with other medicines should be considered when making treatment decisions.

Note, the hydrocarbons from cigarette smoking can induce certain liver enzymes (particularly CYP1A2 and to a lesser extent CYP2C19 and CYP3A4). Smoking can therefore significantly affect plasma levels of certain antipsychotics, particularly clozapine, olanzapine and haloperidol. Smoking significantly reduces drug plasma levels and higher doses are required than in non-smokers. When people stop smoking, plasma levels of affected drugs will then rise, and dose reduction may be necessary. Close monitoring of plasma levels (where useful), clinical progress and adverse effects are essential. N.B: Nicotine replacement or vaping have no effect on this process². Please also refer to [HPFT Nicotine Replacement Policy](#) and the Maudsley Prescribing Guidelines for further information and guidance on managing the impact cigarette smoking and changes in smoking habit can have on antipsychotic plasma levels. Other important drug interactions are listed in Appendix 9.

10. Clozapine

- Clozapine should be introduced at the earliest opportunity in service users with evidence of treatment resistant schizophrenia i.e. those whose illness has not responded adequately to treatment despite the sequential use of adequate doses of at least two different antipsychotic drugs. At least one of these drugs should be a second-generation antipsychotic⁵. Measuring plasma clozapine levels can be a useful tool to monitor adherence and maximise efficacy and minimise side-effects.
- Augmenting clozapine with another agent occasionally needs to be considered when there has been a poor or inadequate response to clozapine alone. The evidence base supporting augmentation is limited and at best shows a marginally improved response. Augmentation should only be considered once clozapine

treatment has been optimised, ensuring adequate dose, duration of treatment and adherence. Efficacy of clozapine augmentation should be assessed using recognised scales and clozapine should be discontinued if there is an unsatisfactory response after a suitable trial period e.g. 3 to 6 months⁹. Contact the Pharmacy department for advice on options to augment clozapine treatment.

- Refer to the [Clozapine Policy](#) for further guidance and information on prescribing and management of clozapine.

11. Monitoring

- Baseline physical health monitoring should be performed at the start of antipsychotic treatment as outlined in the HPFT [Physical Health Policy](#) (see appendix 8) and as recommended in the SPC.
- When prescribing maintenance therapy, prescribers should ensure that on-going physical health is monitored in accordance with [HPFT Physical Health Policy](#) and SPC. Prescribers must respond to any abnormal results appropriately (see appendix 8). [The Lester Adaptation of the Cardiometabolic Health Resource](#) provides clinicians with a simple assessment and intervention framework to protect the cardiovascular and metabolic health of service users with severe mental illness receiving antipsychotic medication.

12. Switching / Stopping

- Antipsychotics may need to be switched for a variety of reasons or they may even need to be stopped altogether. There are risks associated with switching or stopping antipsychotics, such as cholinergic rebound, withdrawal dyskinesias, relapse or destabilisation⁷. How this is managed will very much depend on the reason for the change as well as the antipsychotics involved and individual patient factors. Please refer to the latest editions of the Psychotropic Drug Directory and / or The Maudsley Prescribing Guidelines in Psychiatry for further information. Alternatively, contact the Pharmacy Team for specific advice on this.

13. Older Adults (>60 years)

NICE CG guideline 178 covers the treatment and management of psychosis and schizophrenia and related disorders in adults (18 years and older) with onset before 60 years. Antipsychotics, however, are often required for the management of such disorders in people aged over 60. Due to changes in pharmacodynamic sensitivity and pharmacokinetics, older adults are more sensitive to the side-effects of medicines. This may result in an increase in the incidence and severity of adverse effects². The balance of risks and benefit should be considered before prescribing antipsychotic drugs for older adults.

In people with dementia, antipsychotic drugs are associated with a small increased risk of mortality and an increased risk of stroke or transient ischaemic attack¹⁰. See [HPFT Guidelines for the Pharmacological Management of Dementia](#). Furthermore, older adults are particularly susceptible to postural hypotension which can lead to falls.

To reduce drug related risk it is recommended that²

- Antipsychotic drugs should only be used in older adults when absolutely necessary.
- Initial doses of antipsychotic drugs in older adults should be reduced (to half the adult dose or less), taking into account factors such as the service user's weight, co-morbidity, and concomitant medication.
- Avoid (if possible) drugs that block alpha1 adrenoceptors, have anticholinergic side-effects, are very sedative, have a long half-life or are potent inhibitors of hepatic metabolising enzymes.
- Treatment should be reviewed regularly.

Older adults often receive multiple medicines for their multiple conditions, and this can greatly increase the risk for drug-drug and drug-disease interactions.

14. Transfer of oral Antipsychotic Drug prescribing to GPs

Service users must be stabilised on an antipsychotic drug before requesting the GP to take over prescribing responsibility. The following minimum information must be provided to enable the GP to safely take on the continued prescribing for the service user:

- **Choice of antipsychotic medication:** including formulation and dose.
- **Rationale for choice of antipsychotic:** The rationale for continuing, changing or stopping medication. Where relevant include details of antipsychotics that have already been tried and why they were discontinued or not appropriate.
- **Monitoring requirements:** as per [physical health policy](#).
- **Date of next review**
- **Prescriber contact details:** in case GP has any queries or concerns.

Clinicians must ensure all the above information is included in correspondence to GPs to ensure the smooth and safe transfer of prescribing responsibility.

N.B: Primary care may prescribe branded generics for certain antipsychotics. Brands may be switched according to primary care recommendations.

15. HPFT antipsychotics formulary

Table 2 lists the antipsychotics and the formulations available on the Trust formulary. If a clinician wishes to use an antipsychotic or a formulation of an antipsychotic which is not listed, then a [new drug / non-formulary medicine request](#) will need to be made to either include this on the formulary if it is to be used more widely, or for named patient use only.

Table 2: HPFT Formulary – oral and short acting IM antipsychotics

First Generation	Available Formulations	Comments
Chlorpromazine	25mg, 50mg and 100mg tablets	▪ Can cause skin photosensitivity

	25mg/5ml and 100mg/5ml oral solution	
Flupentixol (dihydrochloride)	500microgram, 1mg and 3mg tablets	<ul style="list-style-type: none"> Last dose to be taken before 4pm (500 microgram and 1mg tablets only licensed for depressive illness)
Haloperidol	500microgram capsules/tablets 1.5mg, 5mg, 10mg, tablets 1mg/ml and 2mg/ml oral solution 5mg/ml injection	<ul style="list-style-type: none"> Baseline ECG is recommended See DTC recommendation on haloperidol and ECG monitoring Injection for HPFT prescribing only
Sulpiride	200mg and 400mg tablets 200mg/5ml oral solution	<ul style="list-style-type: none"> Caution in aggressive, agitated or excited patients (even low doses aggravate symptoms)
Trifluoperazine	1mg and 5mg tablets 1mg/5ml and 5mg/5ml oral solution	<ul style="list-style-type: none"> EPSEs more frequent especially at doses above 6mg daily All formulations very costly (£67.45 for 56 x 5mg) compared to SGA formulations
Zuclopenthixol (dihydrochloride)	2mg and 10mg and 25mg tablets	
Second Generation	Formulation	Comments
Amisulpride	50mg, 100mg, 200mg 100mg/ml oral solution	<ul style="list-style-type: none"> 400mg tablets are significantly more expensive than 200mg tablets Significantly higher cost than other SGA generic solid dose forms
Aripiprazole	5mg ,10mg, 15mg, 30mg tablets 10mg and 15mg orodispersible tablets 1mg/1ml oral solution 7.5mg/ml injection	<ul style="list-style-type: none"> Orodispersible tablets are restricted for use in those with swallowing difficulties or problems with concordance Oral solution is very expensive - only to be used when titrating doses or for doses less than 5mg. Transfer to plain or orodispersible tablets where possible Injection for HPFT prescribing only
Clozapine	25mg and 100mg tablets only 50mg/ml oral suspension	<ul style="list-style-type: none"> Prescribing to remain within HPFT Suspension can settle on standing - risk of uneven distribution of clozapine and inaccurate dosing if bottle is not shaken thoroughly before measuring dose Only to be used in those with swallowing difficulties or poor compliance with tablets

		<ul style="list-style-type: none"> See HPFT Clozapine Policy
Lurasidone	18.5mg, 37mg and 74mg tablets	<ul style="list-style-type: none"> Approved with an Amber Initiation status: for use within its licensed indication (i.e. for schizophrenia) for adult patients (aged 18 years and over) once aripiprazole has either failed to manage the service user's condition or is not suitable due to a contraindication or intolerance Initiation, clinical stabilisation (assessment of efficacy and side effects) and dose stabilisation to be carried out by specialist (usually at least 3 months), with continuation in primary care
Olanzapine	2.5mg, 5mg, 7.5mg, 10mg, 15mg, 20mg tablets 5mg, 10mg, 15mg, 20mg orodispersible tablets RESTRICTED USE Velotabs® 5mg, 10mg, 15mg, 20mg Olanzapine 10mg injection (unlicensed)	<ul style="list-style-type: none"> Orodispersible tablets should be reserved for use in those unable to swallow solid dose forms or problems with concordance There are slight variations in the speed at which generic orodispersible tablets dissolve in the mouth It may be necessary to prescribe Velotab® brand if there is a problem with a service user removing generic orodispersible tablets from their mouth Velotabs® are significantly more costly than generic tablets or orodispersible tablets Injection for HPFT prescribing only
Quetiapine	25mg, 100mg, 150mg, 200mg, 300mg tablets (immediate release) RESTRICTED USE 50mg, 150mg, 200mg, 300mg, 400mg XL (modified release tablets)	<ul style="list-style-type: none"> XL tablets are significantly more costly than the immediate release (IR) XL tablets should only be prescribed for: <ul style="list-style-type: none"> ➤ acutely unwell patients for first 3 days after which IR tablets should be prescribed ➤ those who cannot tolerate the switch to IR tablets once or twice a day ➤ those in whom it would be clinically inappropriate to use or switch to IR tablets – a valid reason must be provided See quetiapine briefing

Risperidone	500micrograms, 1mg, 2mg, 3mg, 4mg tablets 500micrograms, 1mg, 2mg, 3mg, 4mg orodispersible tablets 1mg/ml oral liquid	<ul style="list-style-type: none"> ▪ Dose response studies suggest doses above 6mg daily generally provide no additional benefit but increased risk of side effects such as EPSEs and raised prolactin ▪ Orodispersible should be reserved for use in those unable to swallow solid dose forms or problems with concordance
Antipsychotics that require a named patient request		
Clozapine IM	125mg/5ml injection	<ul style="list-style-type: none"> ▪ Named patient request only ▪ For inpatient use only ▪ See HPFT Guidelines for the use of IM clozapine for further information
Antipsychotics that have NOT been approved		
Asenapine sub-lingual tablets		
Cariprazine capsules		
Paliperidone tablets		

Table 3: HPFT Formulary - Antipsychotic Long-acting injections

First Generation	Formulation	Comments
Flupentixol decanoate	20mg/ml, 40mg/2ml, 100mg/ml, and 200mg/ml injection ampoule	Every 2 to 4 weeks <ul style="list-style-type: none"> ▪ Avoid in excitable and overactive patients
Haloperidol decanoate	50mg/ml and 100mg/ml	Every 4 weeks <ul style="list-style-type: none"> ▪ Baseline ECG is recommended. See DTC recommendation on haloperidol and ECG monitoring
Zuclopenthixol decanoate	200mg/ml and 500mg/ml	Every 1 to 4 weeks <ul style="list-style-type: none"> ▪ May be more suitable in agitated /aggressive patients
Second Generation	Formulation	Comments
Aripiprazole (Abilify Maintena®)	300mg and 400mg powder and solvent for suspension for injection vials or pre-filled syringe	Monthly <ul style="list-style-type: none"> ▪ See appendix 4 for guidelines on prescribing and administration ▪ Good choice of treatment for

		<ul style="list-style-type: none"> ➤ when FGA LAI or paliperidone LAI cannot be used (e.g. not tolerated or contra-indicated) ➤ first episode psychosis ➤ metabolic disturbance with previous antipsychotics ▪ Check for drug interactions which may require dose adjustment
Paliperidone palmitate monthly	50mg, 75mg, 100mg and 150mg pre-filled syringes	<p>Monthly</p> <ul style="list-style-type: none"> ▪ See appendix 2 for guidelines on prescribing and administration ▪ Consider when FGA LAI is not tolerated or is not clinically appropriate ▪ May increase prolactin levels and has a similar side-effect profile to risperidone
Paliperidone palmitate 3-monthly (Trevicta®)	175 mg, 263 mg, 350 mg, 525 mg prolonged release suspension for injection	<p>3 monthly.</p> <p>(NAMED PATIENT REQUEST: for evaluation of patient experience – see appendix 3)</p> <ul style="list-style-type: none"> ▪ Consider in those who are adequately treated with 1-monthly paliperidone palmitate injectable and on a stable dose for a minimum of 6 months or more at the same dose ▪ See appendix 3 for guidance on prescribing and administration)
<p>Note:</p> <ul style="list-style-type: none"> • Risperidone LAI (Risperdal Consta) is no longer included in the trust medicines formulary as there are no clinical or practical advantages of using this over paliperidone LAI. Existing service users can remain on this preparation. Any new service users for whom formulary LAI choices are not suitable and risperidone LAI is deemed to be the most appropriate choice then an application to use this on a named patient basis must be made by the consultant. • Olanzapine embonate LAI – named patient request only (see appendix 5 for further information) 		

16. Cost of Antipsychotics

Drug costs must not be viewed in isolation as their benefit in preventing relapse can significantly outweigh the cost associated with management and treatment of a relapse.

16.1 Oral antipsychotics

- All antipsychotics should be prescribed by generic name, unless there is a clinical reason to prescribe olanzapine orodispersible as Velotabs® which should be documented as described in table 2.
- Orodispersible and liquid formulations are significantly more expensive than standard tablet or capsule formulations and therefore should be reserved for use in those unable to swallow solid dose forms or problems with concordance. Their use should be reviewed regularly.

Table 4: Oral antipsychotic costs (approximate) for 28 days treatment* (from Drug Tariff November 2022). Based on commonly used doses

Oral Antipsychotic	Dose	Formulation	Cost / 28 days (£)
Risperidone	6mg/day (2x3mg)	Tablets	£2.24
		Orodispersible tablets	£87
Quetiapine	600mg/day (2x300mg)	Immediate release tablets	£3.91
		Modified release tablets	£170
Olanzapine	20mg/day (1x20mg)	Tablets	£1.47
		Orodispersible tablets	£79.98
		Zyprexa Velotab	£174.79
Aripiprazole	5mg/day (1mg/ml)	Liquid (150ml)	£98.67
Aripiprazole	15mg/day (1x15mg)	Tablets	£1.35
		Orodispersible tablets	£56.95
Lurasidone	37mg/day (1x37mg)	Tablets	£39.60
	148mg/day (2x74mg)	Tablets	£79.20

Clozapine (Denzapine)	450mg/day (4x100mg + 2x25mg)	Tablets	£99.79
Clozapine (Denzapine)	450mg/day (50mg/ml)	Liquid	£133.75
Amisulpride	800mg/day (2x400mg)	Tablets	£69.21
Amisulpride	800mg/day (4x200mg)	Tablets	£14.74
Haloperidol	10mg/day (1x10mg)	Tablets	£16.06
	10mg/day (2x5mg)	Tablets	£4.84
Haloperidol	10mg/day (10mg/5ml)	Liquid	£11.38

16.2 Antipsychotic Long-acting injections

Table 5: Annual cost (approximate) of antipsychotic LAIs (from Drug Tariff November 2022)

Antipsychotic depot / LAI	Dose	Annual cost (£)
Paliperidone monthly (Xeplion)	50mg monthly	£2207.04
	150mg monthly	£4711.08
Paliperidone 3-monthly (Trevicta)	175mg every 3 months	£2207.04
	525mg every 3 months	£4711.08
Risperidone (Risperdal Consta)	25mg every 2 weeks	£2071.94
	50mg every 2 weeks	£3711.76
Aripiprazole Maintena	400mg monthly	£2644.92
Zuclopenthixol decanoate	200mg weekly (1x200mg/ml)	£163.85
	600mg weekly (2x500mg/ml)	£773.34
Haloperidol decanoate	50mg every 4 weeks (1x50mg/ml)	£49.56
	300mg every 4 weeks (3x100mg/ml)	£101.04

Flupentixol decanoate	40mg weekly (1x40mg/2ml)	£132.03
	400mg weekly (2x200mg/ml)	£2029.87

NOTE: Some of the links in this document may not be accessible to non-HPFT staff. Please contact the Pharmacy department for access to these.

17. Version control for the Procedural Document Management System

Version	Date of Issue	Author	Status	Comment
V1	September 2016	Harsha Patel	Principal Clinical Pharmacist	New guidelines
V1.1	September 2018	Harsha Patel	Principal Clinical Pharmacist	Minor amendment to V1
V2	November 2022	Darshni Haria	Principal Clinical Pharmacist	<p>Full review and update of guidelines</p> <p>Update of relevant resources</p> <p>Update of HPFT Antipsychotic Formulary and cost of antipsychotics</p> <p>Appendices added:</p> <ul style="list-style-type: none"> • GASS side effect rating scale • Guidance for prescribing and administration of second-generation LAI antipsychotics • Guidance on monitoring plasma concentrations for toxicity of Antipsychotics
V2.1	January 2024	Darshni Haria	Principal Clinical Pharmacist	Minor amendments to V2

18. Relevant Standards

1. NICE Psychosis and schizophrenia in adults: prevention and management CG178 Feb 2014 (updated March 2014)
2. NICE Quality Standard [QS80] Psychosis and Schizophrenia in adults (published 12 February 2015)

19. Associated Documents

1. British National Formulary (BNF)
2. Summary of product characteristics (SPC)
3. Maudsley Prescribing Guidelines in Psychiatry
4. Psychotropic Drug Directory
5. HPFT Clozapine Policy

6. HPFT Guidelines for the use of intramuscular clozapine treatment for inpatients
7. HPFT High Dose Antipsychotic Therapy (HDAT) Policy
8. HPFT Physical Health Policy
9. HPFT Rapid Tranquillisation Policy
10. HPFT Management of Behavioural and Psychological Symptoms of Dementia
11. HPFT Medicines Policy
12. HPFT Medicines Adherence Policy
13. HPFT Nicotine Replacement Policy
14. HPFT VTE Prophylaxis Policy
15. Guidelines - Administration of oil-based depots and other long-acting IM antipsychotic injections 7th Edition
16. HPFT Injection Procedure
17. HPFT Standard Operating Procedure – Polar Speed Community Delivery

20. Supporting References

1. Stroup TS, Gray N. Management of common adverse effects of antipsychotic medications. *World Psychiatry*. 2018 Oct;17(3):341-356. doi: 10.1002/wps.20567. PMID: 30192094; PMCID: PMC6127750.
2. Taylor D, Barnes T, Young A. *The Maudsley Prescribing Guidelines in Psychiatry*, 14th Edition
3. Jones P.B, *et al*. Randomised controlled trial of the effect on quality of life of second-vs. first-generation antipsychotic drugs in schizophrenia. Cost utility of the latest antipsychotic drugs in schizophrenia study (CUtLASS-1). *Arch Gen Psychiatry* 2006; 63: 1079-87.
4. Lieberman J., Stroup T.S, McEvoy J., *et al*. (Clinical Antipsychotics Trials of Intervention Effectiveness [CATIE] Investigators). Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 2005; 353(12): 1209-23.
5. NICE Clinical Guideline 178. Psychosis and schizophrenia in adults: treatment and management. (2014)National Institute for Health and Care Excellence (NICE).
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8. Fox C, Richardson K, Maidment ID, *et al*. Anticholinergic medication use and cognitive impairment in the older population; the Medical Research Council Cognitive Function and Ageing Study. *Journal of the American Geriatrics Society* 2011;59:1477– 83.
9. Clozapine Handbook. S Bleakley, D Taylor 1st Edition Lloyd-Reinhold Communications
10. Banerjee S. The use of antipsychotic medication for people with dementia: time for action. A report for the Minister of State for Care Services London: Department of Health, 2009.

21. Consultation

The Consultation section of the Policy Management System advises on the types of people

Job Title of person consulted
Pharmacy and Medicines Optimisation Team
Drugs and Therapeutics Committee members

Part 3 Appendices

Appendix 1: Glasgow Antipsychotic Side-Effect Scale (GASS)

Appendix 2: Paliperidone monthly LAI: Guidance for prescribing and administration

Appendix 3: Paliperidone 3-monthly LAI: Guidance for prescribing and administration

Appendix 4: Aripiprazole Maintena LAI: Guidelines for prescribing and administration

Appendix 5: Olanzapine Pamoate LAI: Guidelines for prescribing and administration

Appendix 6: Monitoring Plasma Concentrations for Toxicity of Antipsychotics
(excluding clozapine)

Appendix 7: Antipsychotic relative side-effects table.

Appendix 8: Recommended Routine Physical Health Monitoring for Service Users.

Appendix 9: Important drug interactions with antipsychotics.

Appendix 1

Glasgow Antipsychotic Side-Effect Scale (GASS)

Glasgow Antipsychotic Side Effect Scale (GASS) [Waddell L and Taylor M. Journal of Psychopharmacology 2008; 22:238-243]

Name:	Age:	Sex: M / F	Date of completion:
Please list current medication and total daily dose			

This questionnaire is about how you have been recently. It is being used to see if you are suffering from side effects from your antipsychotic medication.

Please place a tick in the column which best indicates the degree to which you have experienced the following side effects. Also, when you have had a side effect, please indicate a number on the last box between 1 – 10 to show how distressing that was for you.

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

Tick yes or no for the last <u>three months</u>	No	Yes	Level of distress 1= not at all 10= very much
21. Women only: I have noticed a change in my periods			
22. Men and women: I have been gaining weight			

Staff Information

1. Ask people to fill in the questionnaire themselves. All questions relate to the previous week.

2. Scoring

For questions 1 to 20 award the following:

- 1 point for the answer “once”
- 2 points for the answer “a few times”
- 3 points for the answer “everyday”.
- Zero points for an answer of “never”.

For questions 21 and 22 award the following:

- 3 points for “yes”
- 0 points for “no”

Total score for all questions = _____

3. For completed questionnaires (male & female), scores indicate the following side effect severity:

- 0-21 absent/mild side effects
- 22-42 moderate side effects
- 43-63 severe side effects

4. Side effects covered include:

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

The column relating to the level of distress experienced with a particular side-effect is not scored but is intended to inform the clinician of the person’s views and condition.

Appendix 2

PALIPERIDONE PALMITATE monthly – Long-acting injection (LAI) Guidance for prescribing and administration

Paliperidone monthly long-acting injection has been approved for use in the Trust.

The licensed indications are:

- maintenance treatment of schizophrenia in adult patients stabilised with *paliperidone or risperidone
- in selected adult patients with schizophrenia and previous responsiveness to oral *paliperidone or risperidone, paliperidone injection may be used without prior stabilisation with oral treatment if psychotic symptoms are mild to moderate and a long-acting injectable treatment is needed

*Oral paliperidone has **NOT** been approved for use in the Trust, due to the lack of apparent clinical benefit and its significantly greater cost when compared with oral risperidone.

The following criteria also apply:

1. Service users starting paliperidone should have demonstrated a response to and tolerability of risperidone
2. Service users currently established on a depot antipsychotic should not be switched to paliperidone unless there is a clear indication to do so (e.g. poor tolerability due to extra-pyramidal effects of a typical depot)

Paliperidone injection has the following advantages over risperidone injection (Risperdal Consta):

1. There is no need to provide supplementation with an oral antipsychotic during initiation, as is the case with risperidone injection
2. For maintenance treatment, the injection is administered monthly (not 4 weekly). This equates to 12 injections per year
3. The injection does not require refrigeration
4. The injection is supplied in a pre-filled syringe (i.e. reconstitution prior to administration is not required)

Paliperidone is the major active metabolite of risperidone. Paliperidone injection has been shown to be more effective than placebo and as effective as risperidone long-acting injection (Risperdal Consta). The cost of treatment with paliperidone injection is broadly comparable with risperidone long-acting injection, but greater than for typical depots.

DOSING INFORMATION

Initiation (loading) doses

Day		Dose (mg)	Site of administration
1	1 st dose	150	Deltoid muscle
8	2 nd dose	100	Deltoid muscle

Previous oral risperidone / paliperidone can be discontinued at the time of initiation of treatment with Xeplion. Some patients may benefit from gradual withdrawal.

Maintenance doses

Day		Dose (mg)	Site of administration
36 and monthly thereafter not 4 weekly	3 rd dose and subsequent doses	50 – 150	*Gluteal or deltoid muscle

*Continuation with deltoid injections for the first 6 months may be considered in some patients who switch from higher doses of oral paliperidone or risperidone.

Suggested maintenance doses – summary of approximate dose equivalences

Dose		
Risperidone oral (mg/day)	Risperidone injection (Consta) (mg/2 weekly)	Paliperidone palmitate injection (mg/monthly)
2	25	50
3	37.5	75
4	50	100
6	-	150

Switching from other oral antipsychotics to paliperidone injection (see criteria above):

- Always take into consideration the pharmacological properties of the oral antipsychotic
- Advice from the manufacturer of paliperidone injection is that the oral risperidone / paliperidone can be discontinued when treatment with paliperidone injection is initiated.
- It is however worth considering reducing the dose of the oral drug over 1-2 weeks following the first injection of paliperidone
- Give the two initiation doses (loading doses), followed by the maintenance dose

Switching from a depot antipsychotic to paliperidone injection (see criteria above):

- Start paliperidone injection (at the maintenance dose) when the next injection is due
- No initiation (loading) doses of paliperidone is required.

For further guidance on switching from other oral antipsychotics / other LAIs to Xeplion, please refer to Maudsley Prescribing guidelines.

Administering paliperidone injection

- Each pack of paliperidone injection contains two different sized needles (1.5 inch, 22 gauge and 1.0 inch, 23 gauge). The choice of needle is determined by the site of administration and the service user's weight. See table below:

Site of administration	Service user weight	Needle size
Deltoid muscle	Less than 90 kilograms	1.0 inch, 23 gauge
Deltoid muscle	90 kilograms or more	1.5 inch, 22 gauge
Gluteal muscle	Any weight	1.5 inch, 22 gauge

Supply

For service users in the community, paliperidone monthly LAI should be ordered through Polarspeed by the Community Depot Clinic staff. Refer to the [Polarspeed Delivery SOP](#)

For further information refer to the SPC for Paliperidone monthly LAI via [Home - electronic medicines compendium \(emc\)](#)

Appendix 3

PALIPERIDONE (TREVICTA) 3 MONTHLY - Long-acting injection (LAI) Guidance for Prescribing and Administration

Paliperidone 1- monthly long-acting injection

This is included in the Trust medicines formulary for the maintenance treatment of schizophrenia in:-

- Adult patients stabilised with risperidone or paliperidone (oral paliperidone is not included in HPFT medicines formulary).
- Selected adult patients with schizophrenia and previous responsiveness to oral risperidone (or paliperidone), paliperidone LAI may be used without prior stabilisation with oral treatment if psychotic symptoms are mild to moderate and a long-acting injectable treatment is required.

See Appendix 1 for prescribing guidance for Paliperidone monthly LAI

Paliperidone 3-monthly long-acting injection (Trevicta®)

This is now available and is licensed for the maintenance treatment of schizophrenia in adult patients who are clinically stable on paliperidone 1- monthly LAI

Paliperidone 3- monthly LAI (Trevicta®) has been approved for use in HPFT on a named patient basis where all the following criteria are met:-

- Is currently receiving paliperidone 1-monthly
- Has received at least six paliperidone 1-monthly injections at the same dose*
- Patient is clinically stable with well controlled symptoms and a dose change is unlikely to be necessary
- Paliperidone 1-monthly is well tolerated

A named patient request and data collection form (see below) should be completed and submitted to hpft.medsmanagement@nhs.net prior to changing a service user over to paliperidone 3 monthly LAI. A 12 month follow up will be completed (see 12 month follow up questionnaire below).

Service users, who may particularly benefit, include those who are difficult to engage, erratic nonattenders, those with injection site reactions or those who are keen to have a less frequent injections.

As paliperidone 3-monthly LAI has a slow-release profile, it is not proposed for acutely unwell patients or those transitioning from oral or other long-acting antipsychotic injections.

*The license for paliperidone palmitate 3-monthly states that it can be used after 4 or more injections of 1-monthly, however the DTC have made a decision that patients must have received a minimum of 6 months treatment at the same dose before changing over to Trevicta. This is to allow clinicians to assess for response and tolerability.

Assessing response and tolerability before starting paliperidone 3-monthly LAI

It is important to assess that an adequate response has been achieved with paliperidone 1-monthly as dose adjustments with paliperidone 3-monthly can only be made every 3 months and patient response may therefore not be apparent for several months.

Paliperidone plasma levels can be detected for an average of 18 months from the last paliperidone 3 monthly injection. It is therefore essential to assess tolerability to reduce risk of adverse effects before switching to paliperidone 3-monthly LAI. Tolerability should be assessed once steady state is achieved with paliperidone 1- monthly LAI (8 to 12 weeks).

Other considerations

- Since paliperidone has been detected in plasma up to 18 months after a single dose of the 3 monthly formulation, its use in women of childbearing age who could become pregnant should be considered carefully.
- If paliperidone 3- monthly is discontinued, its prolonged release characteristics must be considered.

To avoid confusion with 1-monthly paliperidone LAI prescribe by 3 monthly paliperidone LAI by brand name TREVICTA.

Presentation

Trevicta is presented as a pre-filled syringe with 2 needles (a 22G 1½-inch safety needle [0.72 mm x 38.1 mm] and a 22G 1-inch safety needle [0.72 mm x 25.4 mm]).

Dosing recommendations

Give the first dose of Trevicta when the next dose of 1-monthly paliperidone (Xeplion) would have been due, as per the recommendations below.

If the last dose of paliperidone 1-monthly was	Initiate Trevicta at the following dose	Volume of Trevicta
50mg	175mg	0.875ml
75mg	263mg	1.315ml
100mg	350mg	1.75ml
150mg	525mg	2.625ml

The last 6 doses of paliperidone 1- monthly should be the same strength before starting Trevicta. The first dose of Trevicta can be given 7 days before or after the 1-monthly paliperidone due date.

Dosing interval

Administer Trevicta every 3 months (can be given 2 weeks before or after the 3 monthly due date).

Supply

For service users in the community, Trevicta should be ordered through Polarspeed by the Community Depot Clinic staff. Only one dose per patient should be ordered at a time. Refer to the [Polarspeed Delivery SOP](#)

Administration

- Administer intramuscularly into either the deltoid or gluteal muscle.
- Select appropriate needle depending on administration site and patient weight. 22G 1½ needles must be used for gluteal administrations regardless of body weight.
- **IMPORTANT: Vigorously shake** the syringe with a loose wrist for at least **15 seconds** within the 5 minutes prior to administration. This is to ensure homogeneous suspension and prevention of incomplete administration.
- If more than 5minutes pass before administering the injection, then shake vigorously again for at least 15 seconds to resuspend.

What if a dose of Trevicta is missed?

If the scheduled dose is missed and the time since last injection is:	Action
> 3½ months up to 4 months	Trevicta should be administered as soon as possible and then resume the 3-monthly injection schedule.
4 months to 9 months	Use the recommended re-initiation regimen shown in the table below.

> 9 months	Re-initiate treatment with 1-monthly paliperidone palmitate injectable as described in the prescribing information for that product. Trevicta can then be resumed after the patient has been adequately treated with 1-monthly paliperidone palmitate injectable preferably for four months or more.
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Recommended re-initiation regimen after missing 4 to 9 months of TREVICTA

If the last dose of TREVICTA was:	Administer 1-monthly paliperidone palmitate injectable, two doses one week apart (into deltoid muscle)		Then administer TREVICTA (into deltoid or gluteal muscle)
	Day 1	Day 8	1 month after day 8
175 mg	50 mg	50 mg	175 mg
263 mg	75 mg	75 mg	263 mg
350 mg	100 mg	100 mg	350 mg
525 mg	100 mg	100 mg	525 mg

Pharmacokinetics

The release of the active substance starts as early as day 1 and lasts for at least 18 months.

Trevicta is the palmitate ester prodrug of paliperidone. It has an extremely low solubility in water and therefore, dissolves slowly after intramuscular injection before being hydrolysed to paliperidone and absorbed into the systemic circulation. Following a single intramuscular dose, the plasma concentration of paliperidone gradually rises to reach maximum plasma concentrations at a median of 30-33 days.

Storage

Store in a locked medicines cupboard. Trevicta does not need refrigeration.

For further information refer to the SPC for Trevicta via [Home - electronic medicines compendium \(emc\)](#)

Paliperidone 3 monthly Long-Acting Injection (LAI) Named Patient Request and Data Collection Form

The named patient request form for Paliperidone 3 monthly LAI has been adapted in order to gather information that will support a short clinical audit.

The aims of this short clinical audit are to evaluate:

- Any factors that contributed to the decision making on prescribing Paliperidone 3 monthly LAI
- The number of patients remaining on Paliperidone 3 monthly LAI 12 months after initiation and any factors leading to discontinuation

1. REQUESTING CONSULTANT DETAILS			
Consultant name		Clinic name	
Clinic address		Telephone No.	
Email address			
2. SERVICE USER DETAILS			
Service user name		D.O.B	
PARIS I.D.		Gender	
3. SERVICE USER'S CURRENT MEDICATION			
a.	What is the service user's current Paliperidone monthly dose?		
b.	Have they received the current Paliperidone monthly dose for at least 6 months?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
c.	Is the service user tolerating the Paliperidone monthly LAI	Yes <input type="checkbox"/>	No <input type="checkbox"/>
d.	Is the service user prescribed any additional antipsychotic medication	Yes <input type="checkbox"/>	No <input type="checkbox"/>
	If yes, please specify medication:		
4. PALIPERIDONE 3-MONTHLY REQUEST			
a.	What are the factors that have led to the choice of Paliperidone 3-monthly as the preferred option in this service user?	Tick all that apply	
	Service user is stable and 3-monthly injections is a good option		
	Service user is difficult to engage		
	Service user is erratic at attending depot clinic appointments		
	Service user suffers from injection site reactions		
	Service user is keen to have less frequent injections		
	Other (please specify)		
b.	Has the service user been involved in the decision making to prescribe Paliperidone 3-monthly LAI	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Please return completed form hpft.medicinesmanagement@nhs.net
Questionnaire post 12 months

At 12 months, the consultant will be contacted and PARIS notes reviewed to ascertain:

Service user name		D.O.B	
PARIS I.D		Gender	
Paliperidone 3-monthly LAI dose service user initiated on			
		Yes	No
1.	Is the service user still on Paliperidone 3-monthly LAI		
	If yes, please go to Q2.		
	If not, what antipsychotic medications are they prescribed currently (if any):		
	If not, what were the reasons for discontinuing Paliperidone 3-monthly LAI:	Tick applicable reasons	
	Service users mental state deteriorated		
	Service user missed appointments		
	Injections are too far apart and unable to maintain contact with the service user		
	Other (please specify):		
		Yes	No
2.	If yes, is the service user maintained on the same dose as when initiated		
	If not, please state the current dose of Paliperidone 3-monthly LAI		
	If not, please specify reasons the dose was changed:		

Appendix 4

ARIPIPRAZOLE MAINTENA (ABILIFY) Long-acting injection (LAI) Guidance for prescribing and administration

Aripiprazole long-acting injection has been approved for use in the Trust

The licensed indications are:

- maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole.

Service users must have demonstrated response and tolerability to oral Aripiprazole prior to initiating treatment with Aripiprazole LAI.

Service users should be stabilised on oral aripiprazole for at least 14 days before initiating aripiprazole LAI, if they do not have a recent history of tolerability and response to the drug.

Initiating Aripiprazole LAI

Aripiprazole LAI does not require dose titration. The starting dose can be administered by following one of two regimens:

- One injection start: On the day of initiation, administer one injection of 400 mg Abilify Maintena and continue treatment with 10 mg to 20 mg oral aripiprazole per day for 14 consecutive days to maintain therapeutic aripiprazole concentrations during initiation of therapy.
- Two injection start: On the day of initiation, administer two separate injections of 400 mg Abilify Maintena at separate injection sites (see method of administration), along with one 20 mg dose of oral aripiprazole.

N.B: The two-injection start must be used with caution due to the increased risk of side-effects and therefore, may not be appropriate for use in the community.

After the one-injection + oral starting regimen, peak plasma levels are seen 7 days after the injection and trough levels at four weeks. At steady state, peak plasma levels are up to 50% higher than the first dose peak and trough plasma levels only slightly below the first dose peak. Dose adjustments should take this into account. A population pharmacokinetic modelling study indicated that the two-injection start regimen would produce comparable aripiprazole plasma concentrations to the one injection start method.

Dosing Information

The recommended starting and maintenance dose of Abilify Maintena is 400 mg. Aripiprazole LAI should be administered once a month as a single injection (no sooner than 26 days after the previous injection). If there are adverse reactions with the 400 mg dosage, reduction of the dose to 300 mg once monthly should be considered.

In service users who are known to be CYP2D6 poor metabolisers:

- One injection start: The starting dose should be 300 mg Abilify Maintena and continue treatment with the prescribed dose of oral aripiprazole per day for 14 consecutive days.
- Two injection start: The starting dose should be 2 separate injections of 300 mg Abilify Maintena along with one single dose of the previous prescribed dose of oral aripiprazole.

In service users who are known to be CYP2D6 poor metabolisers and concomitantly use a strong CYP3A4 inhibitor:

- The one injection start: The starting dose should be reduced to 200 mg and continue treatment with the prescribed dose of oral aripiprazole per day for 14 consecutive days.
- Two injection start is not to be used in patients who are known to be CYP2D6 poor metabolisers and concomitantly use a strong CYP3A4 inhibitor.

After the injection start, see table below for the recommended maintenance dose of Abilify Maintena. Abilify Maintena should be administered once monthly as a single injection (no sooner than 26 days after the previous injection).

Maintenance dose adjustments due to interactions with CYP2D6 and/or CYP3A4 inhibitors and/or CYP3A4 inducers

Maintenance dosage adjustments should be made in patients taking concomitant strong CYP3A4 inhibitors or strong CYP2D6 inhibitors for more than 14 days. If the CYP3A4 inhibitor or CYP2D6 inhibitor is withdrawn, the dosage may need to be increased to the previous dose. In case of adverse reactions despite dose adjustments of Abilify Maintena, the necessity of concomitant use of CYP2D6 or CYP3A4 inhibitor should be reassessed.

Concomitant use of CYP3A4 inducers with Abilify Maintena should be avoided for more than 14 days because the blood levels of aripiprazole are decreased and may be below the effective levels

Maintenance dose adjustments of Abilify Maintena in patients who are taking concomitant strong CYP2D6 inhibitors, strong CYP3A4 inhibitors, and/or CYP3A4 inducers for more than 14 days

	Adjusted dose
Patients taking 400 mg of Abilify Maintena	
Strong CYP2D6 or strong CYP3A4 inhibitors	300 mg
Strong CYP2D6 and strong CYP3A4 inhibitors	200 mg*
CYP3A4 inducers	Avoid use
Patients taking 300 mg of Abilify Maintena	
Strong CYP2D6 or strong CYP3A4 inhibitors	200 mg*
Strong CYP2D6 and strong CYP3A4 inhibitors	160 mg*
CYP3A4 inducers	Avoid use

* 200 mg and 160 mg can be achieved via adjustment of the injection volume only by using Abilify Maintena powder and solvent for prolonged-release suspension for injection.

Reconstituted volumes to inject using 400mg vial

Dose	Volume
400mg	2ml
300mg	1.5ml
200mg	1ml
160mg	0.8ml

Method of administration

- Abilify Maintena is only intended for intramuscular use and should not be administered intravenously or subcutaneously. It should only be administered by a healthcare professional.
- The suspension should be injected slowly as a single injection (doses must not be divided) into the gluteal or deltoid muscle. Care should be taken to avoid inadvertent injection into a blood vessel.
- If initiating with the two-injection start, inject into two different sites i.e. in two different muscles. DO NOT inject both injections concomitantly into the same deltoid or gluteal muscle. For known CYP2D6 poor metabolisers administer in either two separate deltoid muscles or one deltoid and one gluteal muscle. DO NOT inject into two gluteal muscles.
- Ensure the appropriate needle size is selected depending on the administration site and whether the patient is classed as obese.
- Full instructions for use and handling of Abilify Maintena are provided in the package leaflet (information intended for healthcare professionals).

For guidance on switching from other oral antipsychotics / other LAIs to Abilify Maintena, please refer to Maudsley Prescribing guidelines.

Supply

For service users in the community, Abilify Maintena should be ordered through Polarspeed by the Community Depot Clinic staff. Refer to the [Polarspeed Delivery SOP](#)

For further information refer to the SPC for Aripiprazole Maintena via [Home - electronic medicines compendium \(emc\)](#)

Appendix 5

OLANZAPINE PAMOATE (ZYPADHERA) Long-acting injection (LAI) Guidance for prescribing and administration

Introduction/Background

Olanzapine LAI is a licensed medication for the maintenance treatment of adult patients with schizophrenia sufficiently stabilised during acute treatment with oral olanzapine. The product gained a marketing authorisation in 2010, however its use in the United Kingdom is somewhat limited due to safety concerns and consequent monitoring requirements post administration.

Safety Concerns

During pre-marketing clinical studies, reactions that presented with signs and symptoms consistent with olanzapine overdose were reported in patients following an injection of olanzapine LAI. This “post injection syndrome” occurred in <0.1% of injections and approximately 2% of patients. Most of these patients developed symptoms of sedation (ranging from mild in severity up to coma) and/or delirium (including confusion, disorientation, agitation, anxiety and other cognitive impairment). Other symptoms noted include extrapyramidal symptoms, dysarthria, ataxia, aggression, dizziness, weakness, hypertension and convulsion. In most cases, initial signs and symptoms related to this reaction appeared within 1 hour following injection, and in all cases full recovery was reported to have occurred within 24 - 72 hours after injection. Reactions occurred rarely (<1 in 1,000 injections) between 1 and 3 hours, and very rarely (<1 in 10,000 injections) after 3 hours.

As a result of these adverse reactions, when discussing initiation, patients should be advised about this potential risk and must agree to the need to be observed for 3 hours in a healthcare facility each time olanzapine LAI is administered. Post-marketing reports of post-injection syndrome since the marketing authorization of olanzapine LAI are generally consistent with the experience seen in clinical studies.

Use within Hertfordshire Partnership University Foundation NHS Trust (HPFT)

Olanzapine LAI is **NOT** approved for routine use within HPFT primarily due to the safety concerns identified above. A non-formulary request **must** be made to the Drugs and Therapeutic Committee (DTC) by the Consultant for use on a patient-by-patient basis. For those patients maintained on olanzapine LAI who are transferred to HPFT, the treatment plan should be reviewed and if olanzapine LAI is considered to be drug of choice for that individual patient, a non-formulary request must be made to DTC by the Consultant.

Before considering prescribing olanzapine LAI, the Consultant must be assured that:

- Patients have a history of response and tolerability to oral olanzapine
- Patients have demonstrated adherence problems with long-term oral medication
- Patients have been advised about the potential risks of olanzapine LAI post-injection syndrome, the requirement for them to be observed for three hours in a healthcare facility after each administration of injection and that they should not drive or operate machinery for the rest of the day. If it is felt that the patient might not comply with these requirements, olanzapine LAI must not be initiated.
- A care plan has been agreed with the Consultant and nursing staff that will undertake the post administration observation within a healthcare facility in the community.

Prescribing Olanzapine LAI

- All patients must have a history of response and tolerability to oral olanzapine before olanzapine LAI is prescribed.
- Recommended dose scheme when transferring patients from oral olanzapine to olanzapine LAI is detailed below:

Target oral olanzapine dose	Recommended starting dose of Olanzapine LAI	Maintenance dose after 2 months of treatment
10 mg/day	210 mg/2 weeks or 405 mg/4 weeks	150 mg/2 weeks or 300 mg/4 weeks
15 mg/day	300 mg/2 weeks	210 mg/2 weeks or 405 mg/4 weeks
20 mg/day	300 mg/2 weeks	300 mg/2 weeks

- Olanzapine LAI is to be administered by deep intramuscular gluteal injection
- The maximum licensed dose of olanzapine LAI is 300mg 2-weekly or 405mg 4-weekly
- Patients should be monitored carefully for signs of relapse during the first one to two months of treatment
- Supplementation with oral olanzapine was not authorised in double-blind clinical studies. If oral olanzapine supplementation is clinically indicated, then the combined total dose of olanzapine from both formulations should not exceed the corresponding maximum oral olanzapine dose of 20 mg/day.
- Olanzapine LAI has not been studied in elderly patients and therefore is not recommended for this treatment population unless a well-tolerated and effective dose regimen using oral olanzapine has been established. A lower starting dose (150 mg/4 weeks) is not routinely indicated, however should be considered for those 65 and over when clinical factors warrant. Olanzapine LAI is not recommended to be started in patients >75 years.
- Olanzapine LAI is **not licensed** for use in patients aged less than 18 years of age
- In renal and hepatic impairment a lower starting dose (150 mg every 4 weeks) should be considered. In cases of moderate hepatic insufficiency (cirrhosis, Child-Pugh class A or B), the starting dose should be 150 mg every 4 weeks and only increased with caution.
- Clinicians prescribing olanzapine LAI must review the ZypAdhera Product Training Slides which are available through the manufacturer <https://www.zypadhera.co.uk/SignIn.aspx>
- Clinicians must prescribe Olanzapine LAI on the trust depot chart

Obtaining supplies of Olanzapine LAI

All Olanzapine LAI administered from community settings must be ordered from Kingfisher Court Pharmacy dispensary as it is a named patient medicine.

Administration

Due to the “post injection syndrome” adverse reactions described above, Olanzapine LAI must be administered by **deep intramuscular gluteal injection**:

- By a Dr or Nurse who have been trained in the administration of depot injection technique
- In a location where at least 3 hours of observation of the patient can take place
- Where rapid access to medical (or paramedical) care, if needed, (to include dialling 999 if a doctor is not on the premises), must be available throughout the observation period.

Post injection syndrome observation

The staff member undertaking the observation must be vigilant for any signs and symptoms consistent with olanzapine overdose such as:

- sedation and delirium (disorientation, confusion, agitation, anxiety and other cognitive impairment)
- extrapyramidal symptoms
- dysarthria (slurred speech)
- ataxia (staggering, uneven gait)
- aggression
- dizziness

- weakness
- hypertension
- convulsion

Post injection syndrome usually occurs within three hours of olanzapine depot. The risk of post injection syndrome does NOT decrease. It remains the same at EVERY injection. The three hour observation period should be extended as clinically appropriate for patients who exhibit any signs or symptoms consistent with olanzapine overdose, until signs/symptoms resolved.

Within HPFT the post injection monitoring of Olanzapine LAI can be undertaken by a nurse, nursing associate or health care assistant (HCA) however the HCA must be supported by a member of the nursing team as follows:

- The nurse administering the Olanzapine LAI and delegating the post injection syndrome monitoring to the HCA must have completed the online training available through the manufacturers <https://www.zypadhera.co.uk/SignIn.aspx> and read through this guidance document fully.
- Explain to the HCA the symptoms to be vigilant for that are consistent with olanzapine overdose (as above)
- Explain how to undertake the post injection syndrome observations and complete the monitoring form in Appendix 1.
- The nurse must be on site if the HCA has any queries/concerns/need to escalate issues

Following observation period

The nurse should discharge the patient and ensure that:

- Patients must be advised to be vigilant for signs and symptoms of olanzapine overdose (secondary to post-injection adverse reactions) for the remainder of the day following administration of olanzapine LAI.
- Assurance must be sought that they will remain in a position to obtain assistance if needed and that they will not drive or operate machinery.
- All patients must be issued with a copy of the Zypadhera® patient information card before they leave the unit / clinic if they are not already carrying one. The card contains important safety information for the patient on post-injection adverse events.

If the patient refuses to adhere to the post injection monitoring schedule it should be escalated to the Consultant in charge of the patient.

For further information refer to the SPC for Zypadhera via [Home - electronic medicines compendium \(emc\)](#)

Olanzapine LAI Post injection syndrome observation form

Patient name: _____ NHS/Paris number: _____ D.O.B _____

Name of nurse/nursing associate/HCA conducting observation: _____

Sign/Symptoms to observe: Sedation and delirium (disorientation, confusion, agitation, anxiety and other cognitive impairment), extrapyramidal symptoms, dysarthria (slurred speech), ataxia (staggering, uneven gait), aggression, dizziness, weakness, hypertension and convulsion.

Physical monitoring: At hourly intervals undertake, blood pressure and heart rate monitoring

Medical/Emergency support: If post injection syndrome symptoms appear, contact medical staff immediately including dialling 999 if necessary. Additionally monitor BP, HR, Temp and Respiratory Rate.

Time	Observations	Nurse/HCA Signature
Date/Time of starting observation: Baseline BP _____ Baseline Heart Rate _____		
15 min post administration	No signs of weakness, dizziness, general malaise <input type="checkbox"/> Alert <input type="checkbox"/> Orientated <input type="checkbox"/> No signs and symptoms of olanzapine overdose <input type="checkbox"/>	
30 min post administration	No signs of weakness, dizziness, general malaise <input type="checkbox"/> Alert <input type="checkbox"/> Orientated <input type="checkbox"/> No signs and symptoms of olanzapine overdose <input type="checkbox"/>	
45 min post administration	No signs of weakness, dizziness, general malaise <input type="checkbox"/> Alert <input type="checkbox"/> Orientated <input type="checkbox"/> No signs and symptoms of olanzapine overdose <input type="checkbox"/>	
60 min post administration	No signs of weakness, dizziness, general malaise <input type="checkbox"/> Alert <input type="checkbox"/> Orientated <input type="checkbox"/> No signs and symptoms of olanzapine overdose <input type="checkbox"/> Blood Pressure _____ Heart Rate _____	
1hr 30 min post administration	No signs of weakness, dizziness, general malaise <input type="checkbox"/> Alert <input type="checkbox"/> Orientated <input type="checkbox"/> No signs and symptoms of olanzapine overdose <input type="checkbox"/>	
2hr post administration	No signs of weakness, dizziness, general malaise <input type="checkbox"/> Alert <input type="checkbox"/> Orientated <input type="checkbox"/> No signs and symptoms of olanzapine overdose <input type="checkbox"/> Blood Pressure _____ Heart Rate _____	
2hr 30 min post administration	No signs of weakness, dizziness, general malaise <input type="checkbox"/> Alert <input type="checkbox"/> Orientated <input type="checkbox"/> No signs and symptoms of olanzapine overdose <input type="checkbox"/>	
Prior to leaving	No signs of weakness, dizziness, general malaise <input type="checkbox"/> Alert <input type="checkbox"/> Orientated <input type="checkbox"/> No signs and symptoms of olanzapine overdose <input type="checkbox"/> Blood Pressure _____ Heart Rate _____	

Monitoring End Time: _____

Please scan completed monitoring form into PARIS

Appendix 6

Monitoring Plasma Concentrations for Toxicity of Antipsychotics (excluding clozapine)

Background

The Medicines and Healthcare Products Regulatory Agency (MHRA) Drug safety report of August 2020 highlighted that plasma level monitoring of other antipsychotics for toxicity may be helpful in certain circumstances. The example given is to consider taking plasma levels in the event of symptoms suggestive of toxicity. It goes on to add, however, that assay levels should not be used to determine whether to take action in suspected toxicity. If toxicity is suspected, immediate action should be taken, in response to the symptoms displayed or when concomitant medicines may interact to increase antipsychotic plasma levels.¹

Plasma level monitoring of antipsychotics, when appropriately used, is of considerable help in optimising treatment and assuring adherence. However, plasma level determinations are frequently undertaken without good cause and results acted upon inappropriately. In other instances, therapeutic drug monitoring is underused.³

Before taking a blood sample for plasma concentration assay, make sure that the following criteria are satisfied:^{3,4}

- Is there a clear reason for plasma level determination that cannot be determined by clinical observation to other biochemical monitoring parameters?
Only the following reasons are valid:
 - To confirm compliance
 - If toxicity is suspected
 - If a pharmacokinetic drug interaction is suspected
 - If clinical response is difficult to assess directly (and where a target range of plasma levels has been established)
 - If the drug has a narrow therapeutic index and toxicity concerns are considerable.
- Is there a clinically useful assay method available?
Only a minority of antipsychotic drugs have available assays (see table below). The assay must be clinically validated and results available within a clinically useful timescale.
- Will the level have any inherent meaning?
Is there a target range of plasma levels? If so, then plasma levels (from samples taken at the right time) will usefully guide dosing. If there is not an accepted target range, plasma levels can only indicate adherence.
Target ranges have their limitations: patients may respond to lower levels than the quoted range and tolerate levels above the range; also, range quoted by different laboratories can vary, sometimes widely, often without explanation.

When to take blood sample for plasma levels:

- Is the drug at 'steady state'?
Plasma levels are usually meaningful only when samples are taken after steady-state levels have been achieved (see table below). This takes 4-5 drug half-lives.
A clear exception to this advice is suspected overdose; in such situations attainment of steady state is of no relevance. But assay levels should not be used to determine whether to take action in suspected toxicity. If toxicity is suspected, immediate action should be taken, in response to the symptoms displayed or when concomitant medicines may interact to increase antipsychotic plasma levels.

- Is the timing of the sample correct?

Sampling time is vitally important for antipsychotics (see table below).

If recommended sampling time is, say, 12 hours post dose, then the sample should be taken 11-13 hours post dose if possible; 10-14 hours post dose, if absolutely necessary.

For trough or 'pre-dose' samples, take the blood sample immediately before the next dose is due.

Do not, under any circumstances, withhold the next dose for more than 1 or (possibly) 2 hours until the sample is taken.

As an absolute minimum, prescribers should always record the time of sampling and time of last dose.

Interpreting sample results:

The basic rule for sample level interpretation is to act upon assay results only in conjunction with reliable clinical observation (*'treat the patient, not the level'*).

For example, if a patient is responding adequately to a drug but has a plasma level below the accepted target range, then the dose should not normally be increased.

If a patient has intolerable adverse effects but a plasma level is within target range, then a dose decrease may be appropriate.

Where a plasma level result is substantially different from previous results, a repeat sample is usually advised. Check dose, timing of dose and recent compliance but ensure, in particular, the correct timing of the sample. Many anomalous results are the consequence of inaccurate sampling time.

Interpreting Sample results and Comments ^{2,3,4}

Drug	Target range (micrograms/L)	Sample timing	Time to steady state	Comments
Amisulpride	200-320 20-60 (elderly)	Trough	3 days	Adverse effects are usually well managed by dose adjustment alone. However, Plasma level monitoring is best reserved for those in whom clinical response is poor, adherence is questioned or drug interactions or physical illness may make adverse effects more likely.
Aripiprazole	150-210	Trough	15-16 days	Plasma level monitoring not advised in routine practice as for assay sample, as it requires to measure the metabolites plus the parent drug and only adherence prompt the need for an assay.
Clozapine	Please refer to Trust Clozapine Policy on The Hive			
Olanzapine	20-40	12 hours	1 week	Dose of olanzapine should be largely governed by response and tolerability. Plasma level determinations might be useful for those suspected of non-adherence, those showing poor tolerability or those not responding to the maximum licensed dose. Changes in dose give proportionate changes in plasma levels.

Paliperidone	20-60 (9-OH risperidone)	Trough	2-3 days oral 2 months depot	No obvious reason to suspect range should be any different from risperidone. The relation between clinical improvement, risk of extrapyramidal symptoms, increased prolactin levels and plasma concentration is not linear hence plasma level monitoring is not recommended.
Quetiapine (IR)	Around 50-500?	Trough?	2-3 days oral	Target range not defined. It has an established dose-response relationship and appears to be well tolerated at doses well beyond the licensed dose range. In practice, dose adjustment should be based on patient response and tolerability hence plasma level monitoring is not recommended.
Risperidone	20-60 (active moiety – risperidone + 9-OH risperidone)	Trough	2-3 days oral 6-8 weeks injection	Plasma level monitoring is not recommended because dose-response is well described except where compliance is in doubt; in such cases measurement of prolactin will give some idea of compliance.

Local availability of testing:

E&N Herts Trust:

- Samples can be sent via E&N lab (Lister Hospital) to a laboratory based in Birmingham
- Cost per sample is between £20 and £50 each.
- Minimum turnaround time is 14 days for each request.
- Contact Biochemistry on 01438 284690 to request forms as this is only an ad-hoc service not available to order directly via E&N ICE.

West Herts Hospitals Trust:

- Samples requests and results can be accessible via West Herts ICE (Watford or Hemel Hempstead Hospital) which will then sent to Kings Path lab, London for analysis.
- Cost per sample will be £63.89 each
- Minimum turnaround time is 10+ days for each request.

References:

1. MHRA Drug Safety Update, Volume 14, Issue 1 August 2020.
Accessible via: <https://www.gov.uk/government/publications/drug-safety-update-monthly-newsletter>
2. Summaries of Product Characteristics Accessible via: <https://www.medicines.org.uk/emc>
3. The Maudsley Prescribing Guidelines in Psychiatry, 13th edition, 2018 pages 731-738
4. Urban AE and Cubala WJ. Therapeutic drug monitoring of atypical antipsychotics. Psychiatr.Pol. 2017; 51(6): 1059-1077. Accessible via:
http://psychiatriapolska.pl/uploads/images/PP_6_2017/ENGver1059Urban_PsychiatrPol2017v51i6.pdf

Appendix 7

Antipsychotics relative side-effects⁷

The following table can be used by prescribers in conjunction with patients to help guide choice of antipsychotic. Alternatively, the [Choice and Medication](#) website provides information for patients on medicines used in mental health. The [handy chart](#) comparing medicines used for psychosis is a more service user friendly resource which may be helpful when discussing potential benefits and harms of individual antipsychotics with patients. Please note the Choice and Medication website may include information on medicines that have not been approved in Hertfordshire.

FGA	Anticholinergic effects	Cardiac	EPSE	Hypotension	Sedation	Weight gain	Prolactin elevation	Proconvulsant
Chlorpromazine	●●	●●	●●	●●●	●●●	●●●	●●●?	●●●
Haloperidol	●	●●	●●●	●	●	●	●●●	●?
Flupentixol	●●	○	●●	○	●	●	●●?	●?
Sulpiride	●	○	●	○	●	●	●●	○?
Trifluoperazine	●●●	●●	●●	●	●	?	●●●?	●
Zuclopenthixol	●●	●	●●●	●	●●	?	●●?	○?
SGA	Anticholinergic effects	Cardiac	EPSE	Hypotension	Sedation	Weight gain	Prolactin elevation	Proconvulsant
Amisulpride	●●	○	●	○	○	●	●●	●?
Aripiprazole	○	●	●	○	○	●	○	○
Clozapine	●●	●●●	○	●	●●●	●●●	○	●●●
Lurasidone	○	○	●	○	●	○	○	○
Olanzapine	●	○	○	○	●●	●●●	●	●●
Quetiapine	●	●	○	●	●●	●	●	●
Risperidone	●	○	●	●	●?	●	●●	○
FGA Depot injections	Anticholinergic effects	Cardiac	EPSE	Hypotension	Sedation	Weight gain	Prolactin elevation	Proconvulsant
Flupentixol decanoate	●●	○	●●	○	●	●	●●?	●?
Haloperidol decanoate	●	●●	●●●	●	●	●	●●●	●
Zuclopenthixol	●●	●	●●●	●	●●	?	●●?	○?
SGA Long-acting	Anticholinergic	Cardiac	EPSE	Hypotension	Sedation	Weight gain	Prolactin	Proconvulsant
Aripiprazole	○	●	●	○	○	●	○	○
Paliperidone (monthly + 3-monthly)	○	○	●	●	●	●	●●	○
Olanzapine LAI	●	○	○	○	●●	●●●	●	●●

●●● marked effect ●● moderate effect ● mild/ transient effect ○ little or minimal effect ? no information available or little reported

Reference: Stephen Bazire – Psychotropic Drug Directory 2020/21

Appendix 8

Recommended Routine Physical Health Monitoring for Service Users

See [HPFT Physical Health Policy V.6.1](#)

Table 1

		Baseline	3 months if antipsychotic initiated	6 months if antipsychotic initiated	Annual Review/ Health check
a	Personal and Family History	✓			
b	Smoking	✓	✓	✓	✓
c	Alcohol and Drug Use	✓	✓	✓	✓
d	Allergies/Drug sensitivities	✓	✓	✓	✓
e	Exercise and dietary habits	✓	✓	✓	✓
f	Dental Health	✓			✓
g	Weight (BMI/Waist circumference) Ideally plotted on a chart	✓	✓ *	✓	✓
h	Blood pressure	✓	✓	✓	✓
i	Blood lipid profile and fasting plasma glucose /HbA _{1c} Consider other relevant blood tests or investigations required (see Table 2 below)	✓	✓	✓	✓
j	Sexual Health and contraception. Consider the need for a pregnancy test	✓			✓
k	Check engagement with Primary Care	✓			✓
l	Screen for Side Effects (including sexual)		✓	✓	✓
m	Offer information about medication	✓	✓	✓	✓
n	Health Promotion and Signposting where appropriate	✓			✓

*NICE CG 178 for Schizophrenia recommends measuring weight weekly for first 6 weeks (plotted on a chart)

Frequency of review: As a minimum review those prescribed a new antipsychotic at baseline, at least once after 3 months, at 6 months and annually thereafter. For some medicines more frequent monitoring may be required. See table 2 for details on monitoring for specific drugs. Health checks should take place at least 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.

See [Positive Cardiometabolic Health Resource](#) for monitoring individuals commenced on antipsychotics.

*The Cardiometabolic Health Resource supports the recommendations relating to monitoring physical health in the NICE guidelines on psychosis and schizophrenia in adults. In addition, it also supports the statement about assessing physical health in the NICE quality standard for [psychosis and schizophrenia in adults](#).

Diagnosis/Psychotropic Drugs Requiring Specific Tests

In addition to the monitoring outlined in table 1 some drugs require more specific tests/monitoring. The recommendations below are best practice guidelines.

Table 2

DIAGNOSIS	BASELINE	MAINTENANCE
Serious Mental Illness (e.g. psychosis/bipolar disorder)	Full Blood Count (FBC) Urea and Electrolytes (U&Es) Renal function (serum creatinine or e-GFR) Liver Function Tests (LFTs) Fasting blood glucose (if possible), HbA _{1c} Blood lipid profile (fasting if possible) Prolactin level ECG if clinically indicated BP, weight, waist circumference	Annual health check (see appendix 8, table 1) FBC annually U&Es annually Renal Function (serum creatinine or e - GFR) annually LFTs annually Fasting (if possible) blood glucose, HbA _{1c} annually Blood lipid profile (fasting if possible) annually
DRUG		
Antipsychotics	BASELINE AND INITIAL	MAINTENANCE
Amisulpride Aripiprazole Lurasidone Olanzapine Quetiapine Risperidone First generation antipsychotics Clozapine (see below) Refer to High Dose Antipsychotic Therapy (HDAT) policy for monitoring those on high dose antipsychotics	FBC Blood glucose (fasting if possible), baseline then at 3 months and 1 year (olanzapine also at 1 month and 6 month) HbA _{1c} baseline and 3 months Blood lipid profile baseline then at 3 months and 1 year (olanzapine 3 monthly for first year then annually) LFTs U&Es Prolactin ECG if clinically indicated (and after target dose is reached during in-patient admission and before discharge if drug regimen has changed) (mandatory prior to haloperidol) - see appendix 9 of the Physical Health policy Blood pressure/ pulse baseline and frequently during dose titration then at 12 weeks and 1 year Weight baseline, weekly for 6 weeks (if possible) then at 12 weeks, 6 months and 1 year (plotted on a chart) (olanzapine, weekly for 6 weeks then at 12 weeks and every 3 months for first year, then annually) Waist circumference (plotted on a chart)	Annual health check (see appendix 8, Table 1) FBC annually Blood glucose (fasting if possible) annually HbA _{1c} annually Blood lipid profile - annually LFTs - annually U&Es - annually Prolactin level annually for antipsychotics likely to cause a rise in prolactin or if signs or symptoms of raised prolactin. See clinical notes. ECG if clinically indicated e.g. high dose antipsychotic (refer to HDAT policy) or presence of cardiovascular risk (see Appendix 9 of the Physical Health policy) Blood pressure / pulse annually Weight annually (plotted on a chart) Waist circumference annually (plotted on a chart) GASS (see appendix 1) / LUNSERs/ Barnes Akathisia Rating Scale for side-effect monitoring.
Clozapine	FBC	Annual health check (see appendix 1)

(Refer to HPFT clozapine policy for more details)	Blood glucose (fasting if possible) baseline then at 1, 3, 6 and 12 months HbA _{1c} baseline and at 3 months Blood lipid profile baseline, then at 3, 6 and 12 months LFTs at baseline and then at 6 months U&Es at baseline ECG Blood pressure and pulse baseline, frequently during dose titration then at 3 months and 12 months Weight at baseline, weekly for 6 weeks (if possible) then at 12 weeks, 6 months and 1 year (plotted on a chart) Waist circumference baseline then at 12 weeks and 1 year (plotted on a chart) Assessment of bowel movements	FBC as per monitoring guidelines Fasting blood glucose (if possible) and HbA _{1c} every 6 months U&Es - annually LFTs – annually Blood lipid profile – annually ECG annually if high dose >600mg/day or otherwise indicated. Blood pressure and pulse – minimum 6 monthly Weight minimum 6 monthly (plotted on a chart) or at each review. Waist circumference annually (plotted on a chart) C-GASS – 6 monthly Bowel movements at each review
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CLINICAL NOTES

WEIGHT: Weight gain occurs early on after initiating treatment with antipsychotics and is difficult to reverse. It is therefore important to monitor weight closely during initiation and intervene promptly where weight gain occurs. Target = 18.5-24.9 kg/m² (18.5-22.9 kg/m² in South Asian or Chinese). Waist circumference > than 94cm (men) and 80 cm (women) is a predictive factor for developing metabolic syndrome. Weight gain of > 5kg over 3 months and/or high BMI over target require action (medication review/lifestyle advice)

Medicines that are high Risk for causing weight gain include **clozapine** and **olanzapine**. **Quetiapine** and **risperidone** have a moderate risk of causing weight gain.

BLOOD PRESSURE: In those aged less than 80 years old reduce clinic BP to < 140/90 mmHg and in those aged 80 and above reduce clinic BP to <150/90. Use clinical judgement for people with frailty or multimorbidity. Refer to appropriate clinician for investigation or management if indicated.

GLUCOSE: Increases in glucose occurs early on after initiating treatment with antipsychotics and may be difficult to reverse. As changes in glycosylated haemoglobin (HbA_{1c}) occur after a few weeks, fasting glucose tests should be carried out in preference to HbA_{1c} after treatment initiation. In the long-term blood glucose control can be monitored using HbA_{1c} (as this is more feasible to arrange for patients), however fasting glucose together with HbA_{1c} is preferred at all time-points to determine immediate and long-term impact on blood glucose. Increased frequency of testing should be considered for patients at risk of diabetes or where results are high. If fasting blood glucose (FBG) is impractical, then random blood glucose (RBG) can be measured and interpreted accordingly. People with FBG of 5.5-6.9mmol/L or HbA_{1c} 42 - 47mmol/mol (6.0% – 6.4%) are at high risk of diabetes and should be supported to change their diet and lifestyle.

LIPIDS: If fasting samples are impractical then non-fasting samples are satisfactory for most measurements except LDL and triglycerides. Follow NICE CG 181 CVD: risk assessment and reduction, including lipid modification. Use QRISK 3 for assessing CVD risk for primary prevention. Provide advice on lifestyle modification for prevention of CVD. Refer to GP for advice where appropriate.

FULL BLOOD COUNT: Stop suspect drug if neutrophils <1.5 x 10⁹ and refer to medical specialist if <0.5 x 10⁹. Note high frequency of benign ethnic neutropenia in some ethnic groups.

PROLACTIN: A prolactin level is useful at baseline as it can be repeated if sexual or reproductive system abnormalities are reported. Drugs reported to cause raised prolactin: amisulpride, sulpiride, risperidone, paliperidone and first-generation antipsychotics. (Aripiprazole, clozapine, olanzapine and quetiapine have minimal effect on prolactin levels). Normal range of prolactin levels are

men 0 – 424 mIU/L (0 -20 ng/ml) and women 0 – 530 mIU/L (0 – 25ng/ml).

Prolactin levels should be taken one hour after waking and before eating. Hyperprolactinaemia should not be diagnosed on the basis of a single blood test. Other causes would need to be ruled out. Stress, such as venepuncture, can itself increase prolactin levels. Measure macroprolactin (inactive form of prolactin) if prolactin levels are high but no associated signs or symptoms.

ECG: The need for a baseline ECG should always be considered. An ECG should be performed if there are cardiovascular risk factors (including a strong family history of CVD), if drugs which cause ECG abnormalities such as haloperidol are prescribed (refer to the SPC) or on HDAT, if there are metabolic/electrolyte abnormalities or other factors (see appendix 9 of the [Physical Health policy](#)). Inpatients should have a baseline ECG if they are prescribed antipsychotic drugs. People on high dose antipsychotic regimes should have repeat ECGs during periods of dose escalation and/or after steady state is reached during the initiation phase. Once stabilised on high-dose treatment, perform ECG every 12 months or sooner if clinically indicated.

ANTIPSYCHOTICS: All antipsychotics are associated with neutropenia, especially in high doses. Cardiovascular mortality is high in patients on antipsychotics, especially those on high doses and combinations. Some antipsychotics are associated with QTc prolongation, enhanced by hypokalaemia, or other QTc prolonging medication. Consider an ECG if risk factors are identified for QTc prolongation or arrhythmias (see Appendix 9 of the [Physical Health policy](#)). Hyperglycaemia and induction of diabetes are associated with atypical antipsychotics. If random or fasting blood glucose is raised, an oral glucose tolerance test should be performed. Weight gain is more common with certain antipsychotics (see above under weight gain). Hyperlipidaemia is common in people on antipsychotics. Hyperprolactinaemia is most likely to be associated with certain antipsychotics (see above under prolactin).

OLANZAPINE: Weight gain. Transient LFT increase. Significant association with increased lipids, increased blood glucose and risk of diabetes: Hyperglycaemia is not dose dependent and is reversible on cessation. Olanzapine levels are reduced by tobacco smoking – important to check changes in smoking habit.

QUETIAPINE: can cause dose related decrease in thyroid hormone levels within 2-4 weeks of initiation that is reversible on stopping the drug. There is no evidence of clinically relevant hypothyroidism. Use with caution and monitor in patients with pre-existing thyroid disease.

CLOZAPINE: Blood dyscrasias: Risk of neutropenia 2.7% and agranulocytosis 0.8%. Seizures: Risk increases with levels above 0.6mg/L. Raised body temperature common during initiation, but fever should be investigated. Refer to [clozapine policy](#) for full information. Hypersensitivity, myocarditis and cardiomyopathy. Exacerbation of pre-existing liver disease. Impaired glucose tolerance and/or development or exacerbation of diabetes mellitus. As many as a third of patients might develop diabetes after 5 years of treatment. Many cases are noted in the first 6 months and may occur within 1 month. Increased risk of hyperlipidaemia, weight gain, hypersalivation, constipation and potentially fatal intestinal obstruction, faecal impaction and paralytic ileus. Use other drugs that cause constipation cautiously e.g. antimuscarinics or history of colonic disease or bowel surgery. Monitor for constipation and prescribe laxative if required. Clozapine levels are reduced by tobacco smoking – important to check changes in smoking habit.

Appendix 9

Important drug interactions with antipsychotics

Interacting drug or drug class	Effect of interaction	Risk-reduction measures
ACE inhibitors and angiotensin-II receptor antagonists	Increased hypotensive effect	Monitor blood pressure and ask about signs and symptoms of postural hypotension
Alcohol	Increased risk of CNS depression – impaired concentration, judgement, sedation and lethargy	Warn patient of excessive sedation and of psychomotor impairment
Amphotericin	Hypokalaemia increases risk of adverse effects of QT-interval prolongation	Ensure any hypokalaemia is corrected
Anaesthetics, general	Increased hypotensive effect	Monitor blood pressure and ask about postural hypotension
Anti-arrhythmics with QT-interval prolonging properties (e.g. amiodarone, disopyramide, flecainide, and sotalol)	Increased risk of QT-interval prolongation	Preferably avoid concomitant use of drugs that prolong QT interval
Antibacterials	Some antibacterials (e.g. clarithromycin, erythromycin, moxifloxacin) increase risk of QT-interval prolongation Macrolides (e.g. clarithromycin and erythromycin) may increase plasma levels of some antipsychotics e.g. quetiapine, clozapine Ciprofloxacin may increase plasma levels of clozapine and olanzapine	Preferably avoid concomitant use of drugs that prolong QT interval Monitor closely for adverse effects
Antidepressants	Increased risk of arrhythmias with tricyclic antidepressants. Phenothiazine antipsychotics may increase levels of tricyclics SSRIs inhibit various P450 enzymes to different degrees and may cause significant increases in plasma levels of some antipsychotics. Citalopram and escitalopram increase risk of QT-interval prolongation	Preferably avoid concomitant use of drugs that prolong QT interval
Antiepileptics	Antipsychotics lower seizure threshold and thus may antagonise anticonvulsant action Carbamazepine, Phenytoin and Phenobarbital are known P450 inducers and reduces plasma levels of many antipsychotics	Choose a lower risk antipsychotic, and use minimum effective doses
Antihistamines, sedative	Increased sedation	Select non-sedative antihistamine; warn patient of excessive sedation and of psychomotor impairment
Anxiolytic and hypnotic drugs (e.g. benzodiazepines)	Increased risk of CNS depression – impaired concentration, judgement, sedation and lethargy	Warn patient of excessive sedation and of psychomotor impairment

Atomoxetine	Increased risk of QT-interval prolongation	Preferably avoid concomitant use of drugs that prolong QT interval
Beta-blockers	Increased hypotensive effect Increased risk of ventricular arrhythmias particularly when sotalol is given with zuclopenthixol, haloperidol, amisulpride, phenothiazines and risperidone.	Monitor blood pressure and ask about postural hypotension
Calcium-channel blockers	Increased hypotensive effect	Monitor blood pressure and ask about postural hypotension
Clonidine	Increased hypotensive effect	Monitor blood pressure and ask about postural hypotension
Corticosteroids	Hypokalaemia increases risk of adverse effects of QT-interval prolongation Increased risk of metabolic effects such as weight gain and diabetes	Ensure any hypokalaemia is corrected
Diuretics (loop and thiazide)	Hypokalaemia increases risk of adverse effects of QT-interval prolongation Increased hypotensive effect	Ensure any hypokalaemia is corrected Monitor blood pressure and ask about postural hypotension
Dopamine agonists (e.g. drugs used for Parkinson's disease)	Antipsychotics inhibit antiparkinsonian effects of dopamine agonists	
Lithium	Increased risk of neuroleptic malignant syndrome, extrapyramidal side effects and CNS toxicity. Increased risk of QT-interval prolongation	If concomitant administration necessary, adjust dose so plasma-lithium concentration is at minimum effective level; monitor closely for side effects
Metoclopramide	Increased risk of extrapyramidal effects	
Opioid analgesics and methadone	Increased hypotensive effect Increased risk of CNS depression – impaired concentration, judgement, sedation and lethargy Methadone also increases risk of QT interval prolongation	Monitor blood pressure and ask about signs and symptoms of postural hypotension; warn patient of excessive sedation and of psychomotor impairment Preferably avoid concomitant use of drugs that prolong QT interval

N.B: This is not an exhaustive list. Please refer to the BNF, specific SPCs and the Stockley's Drug Interactions for further information, including interactions between specific drugs.

	<i>we are...</i>	<i>you feel...</i>
Our Values	Welcoming	✓ Valued as an individual
	Kind	✓ Cared for
	Positive	✓ Supported and included
	Respectful	✓ Listened to and heard
	Professional	✓ Safe and confident

Our  values
 Welcoming Kind Positive Respectful Professional