

Factsheet

Adult Antipsychotic Monitoring – 1st and 2nd Generation (Excluding Clozapine)

Start date: October 2022

Review date: October 2025

Document Control		
Date	Version	Action
March 2018	V1	Factsheet produced by Camden & Islington NHS Foundation Trust Agreed by NCL Medicines Optimisation Network: 6 March 2018 Ratified by NCL Joint Formulary Committee: 19 March 2018
January 2020	V1.1	Title amended for adult population only; Factsheet approved by NCL Shared Care Group via Chairs Action, Jan 2020
October 2020	V1.2	Table 5 amended to make clear referral pathways. Factsheet approved by NCL Shared Care Group: October 2020
October 2022	V2.0	Appendix 4. addition of prolactin flow chart Amendments to checklist and actions for GP Table 1 clinical monitoring amended Guideline updated Factsheet approved by NCL Shared Care Group: October 2022
January 2024	V2.1	Amendment to Appendix 4. – flowchart modified to reflect local services Update to contact details
<p>With thanks to the antipsychotics factsheet working group:</p> <ul style="list-style-type: none"> • David Rogalski, Lead Pharmacist, C&I (Lead author) • Dr Ruth Embaie, GP, Clinical Lead for Mental Health - Haringey, NCL CCG • Dr Chandni Pujara, ST4 General Adult Psychiatry Barnet, Enfield & Haringey Mental Health Trust • Isaac Quarm, Prescribing adviser, North Central London CCG North East Haringey Collaborative • Dr Abhishek Jha, Consultant Psychiatrist, C&I • Georgina Glass, Manager Medicines Advice Service/ Endocrinology Pharmacist, Royal Free • Dr Mark Cohen, Consultant Endocrinologist, Royal Free • Dr Bernard Khoo, Senior Clinical Lecturer in Endocrinology, UCL Medical School <p>With thanks to Rachel Hogan (Oxford Health NHS Foundation Trust) for use of the flow diagrams from the “Antipsychotic-induced hyperprolactinaemia” guideline</p>		

Disclaimer

Factsheets support GPs in taking full and ongoing responsibility for continuing a medicine initiated in secondary care. It differs from a shared care agreement where secondary cares retain a proportion of responsibility for ongoing care.

This document is intended for use by healthcare professionals to aid the treatment of patients within NCL. It should not be used for marketing purposes. If you identify information within this document that is inaccurate, please report to admin.ncl-mon@nhs.net.

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Factsheet – Antipsychotics – 1st and 2nd Generation (excluding clozapine)

Indication information

Refers to individual antipsychotic, 1st and 2nd Generation (excluding clozapine), for licensed indication: schizophrenia and other psychosis, mania, bipolar disorder, adjunctive treatment of depression.
Unlicensed use: Anxiety disorders, Emotionally Unstable Personality Disorder

Antipsychotic medication is usually initiated by a specialist. If initiated by a secondary care specialist, the patient should be stabilised prior to transfer and documentation sent to the GP.

Antipsychotic medications considered in scope are aripiprazole, amisulpride, sulpiride, risperidone, paliperidone, olanzapine, quetiapine, chlorpromazine, trifluoperazine, haloperidol, flupentixol and zuclopentixol

Check list and actions for GP:

1. Ensure documented communication has been received from a specialist including:
 - Indication for use
 - Dose and frequency of medication
 - Duration of treatment
 - Baseline investigations
 - Patient has been counselled on the antipsychotic (including side effects/risks/pregnancy)
2. Before continuation in primary care ensure that the patient meets criteria for continuation of treatment (i.e. antipsychotic treatment is initiated by a specialist and the patient is stabilised on treatment)
3. Conduct necessary blood test monitoring at agreed schedule (see **Clinical Monitoring** section) and communicate results to the mental health team if required
4. Prescribe routine supplies of antipsychotic
5. Monitor the patient's overall physical health and well-being
6. Discuss with a specialist or refer the patient back to the specialist if the patient:
 - Relapses
 - Is intolerant of side effects
 - Is non-compliant with medicines (or this is suspected)
 - Experiences adverse events
 - Has a change in circumstances affecting treatment (e.g. pregnancy)
7. If the patient is referred back to secondary care mental health services and the patient has a change in medication or the dose of medication, the responsibility of prescribing and carrying out monitoring tests will be under the specialist until the patient is stabilised on treatment.

Note: Clozapine is not included in this factsheet as it is a Red Listed medication not routinely prescribed in primary care

Dose and Administration

Refer to individual manufacturer's [Summary of Product Characteristics \(SPC\)](#) and also current BNF.

For local formulary position, please see the [NCL Joint Formulary website](#).

Renal impairment³:

No medication clearly preferred to another, however: Avoid sulpiride and amisulpride as primarily renally excreted
Avoid highly anticholinergic medication because they may cause urinary retention
For further information on renal impairment for specific antipsychotic medication see SPC/BNF.

Hepatic impairment³:

Most antipsychotics are hepatically metabolised and may require a dose reduction or be avoided (See Appendix 1 for choice in specific medication conditions).

Discontinuing treatment³:

The decision to stop antipsychotic medication requires a thorough risk-benefit analysis for each patient. Advice should be requested from a specialist. Withdrawal of antipsychotic medication after long-term treatment should be gradual and closely monitored. The relapse rate, in the first 6 months after abrupt withdrawal, is double that seen after gradual withdrawal (defined as slow taper down over at least 3 weeks for oral antipsychotics or abrupt stopping of depot preparations). Abrupt withdrawal may also lead to discontinuation symptoms (e.g. headache, nausea, insomnia) in some patients.

Adverse Effects

If concerned about side effects the [Glasgow antipsychotic side effect scale \(GASS\) \(Appendix 5\)](#) is a helpful tool to assess and monitor side effects. Consider referral to a specialist for patients scoring >22 (moderate side effects). Adverse effects vary between individual antipsychotics.

Significant adverse effects related to antipsychotics⁴: Extrapyramidal side-effects (EPS), Weight gain, Hypertension, Postural hypotension, Sedation, Sexual dysfunction, Hyperprolactinaemia, Impaired glucose tolerance, Dyslipidaemia.

Serious adverse effects⁴: Psychotropic-related QTc prolongation, Neuroleptic Malignant Syndrome (NMS)
For further information on side effects for specific antipsychotic medication see [SPC/BNF](#). Healthcare professionals are asked to report any suspected adverse reactions using the [Yellow Card Scheme](#).

Contra-indications: Hypersensitivity to the active substance or to any of the excipients.

Special Warnings and Precautions for Use: Antipsychotics can have an influence on the ability to drive and use machines due to potential nervous system and visual effects.

Pregnancy and Breastfeeding⁴: When consideration is given to prescribing psychotropics to any woman of childbearing age, appropriate counselling regarding contraception and the risks of pregnancy (including relapse, risks associated with stopping or changing medication and risk to foetus) should be given. (See **Appendix 1**)

Note: when switching from medicines known to raise prolactin to one which reduces prolactin a change in fertility can occur which can result in an unplanned pregnancy (see page 7 for details of effect on prolactin).

Drug Interactions - See Appendix 2

Please refer to SPC/BNF for full information on interactions with drug name and how to manage these interactions.

Clinical monitoring Table 1: Clinical Monitoring⁵

Frequency Parameter	Baseline	Weekly for the first 6 weeks		at 12 weeks	at 6 months	at 1 year	Annual Check-up	Comments:
Glycosylated haemoglobin (HbA1c) and/or fasting glucose	✓	✗		✓	✓	✓	✓	Increase frequency if evidence of elevated levels. As changes in glycosylated haemoglobin (HbA1c) occur only after a few weeks, fasting glucose tests should be carried out in preference to HbA1c after treatment initiation.
Blood Lipids (Total cholesterol, non-HDL, HDL, triglycerides)	✓	✗		✓	✓	✓	✓	Increase frequency if evidence of elevated levels. Non-fasting samples are satisfactory for most measurements except for triglycerides
FBC	✓	✗		✗	✗	✗	✓	Repeat FBC if there are signs and symptoms of a blood dyscrasia
LFTs	✓	✗		✗	✗	✗	✓	Repeat LFTs if there are signs of liver toxicity
U&Es & Renal Function	✓	✗		✗	✗	✗	✓	
TFTs		Baseline and annual check-up only required for patients with bipolar affective disorder & 6 monthly for rapid-cycling bipolar affective disorder. Quetiapine is associated with small clinically insignificant decreases in thyroid hormones so annual monitoring may be advisable						
CPK	✓	✗		✗	✗	✗	✗	Repeat if there are signs and symptoms of NMS
Prolactin	✓		Only required if antipsychotic known to cause a sustained rise in prolactin. Amisulpride, Risperidone and the Typical Antipsychotics are associated with hyperprolactinaemia. Repeat if there are signs of raised prolactin. See Appendix 4 for more information					
ECG	✓		Where possible offer all patients an annual ECG, especially where other risk factors exist. Baseline ECG for all patients especially if there are specific CV risk factors e.g. high BP. During therapy the need for ECG monitoring should be assessed on an individual patient basis.					
BP & Pulse	✓		See comments				✓	Monitor BP during titration if there are risk factors for postural hypotension e.g. older adults
Weight & BMI	✓	✓		✓	✗	✓	✓	Patients should be encouraged to weigh themselves and keep a record which can be discussed at each contact.
Smoking Status	✓		May interact with antipsychotic metabolism; patients should inform the healthcare professional if their smoking status changes.					
Side Effects	✓		Side effects should be discussed at every patient contact. If concerned about side effects, an optional tool to determine if the patient is suffering from excessive side effects from antipsychotic medication is the Glasgow antipsychotic side effect scale (GASS) (Appendix 5)					

Where a patient refuses any monitoring, an explanation should be given to them of the purpose of monitoring and the risks involved with continuing treatment without monitoring. The decision to continue treatment without monitoring should be discussed with the patient and specialist. Patients who refuse any monitoring should be reoffered monitoring at regular opportunities.

The clinical monitoring guidance above should be used in conjunction with the intervention framework ([Lester UK adaptation](#)) for monitoring physical health⁶. If a person has rapid or excessive weight gain, abnormal lipid levels or problems with blood glucose management, consider a referral to a specialist.

Glucose and diabetes monitoring⁵

Increases in glucose occur early on after initiating treatment with antipsychotics and may be difficult to reverse. As changes in glycosylated haemoglobin (HbA1c) occur only after a few weeks, fasting glucose tests should be carried out in preference to HbA1c after treatment initiation. In the long-term blood glucose control can be monitored using HbA1c (as this is more feasible to arrange for patients), however fasting glucose together with HbA1c is preferred at all time-points to determine immediate and long-term impact on blood glucose. Where there is concern about the validity of the HbA1c reading (e.g. in HIV or sickle cell disease) then fasting glucose should always be used. Where a patient also has HIV, discuss concerns about blood glucose levels with their HIV consultant

Increased frequency of testing should be considered for patients at risk of diabetes or where results are high. Medicines that are high risk for causing diabetes include **clozapine and olanzapine**.

All patients should be given dietary and lifestyle advice to help prevent the development of diabetes. Management of high glucose should be in line with NICE guidance “type 2 diabetes in adults: management.” <https://www.nice.org.uk/guidance/ng28>

[Diabetes UK](#) provides guides on diet and diabetes.

Further diabetes guidelines by NCL JFC can be found at: <http://ncl-mon.nhs.uk/faq/guidelines/>

The [Lester UK adaptation tool](#) for monitoring physical health provides further advice on threshold values used in blood glucose monitoring.

Cholesterol and Lipid monitoring⁵

Increases in cholesterol and triglycerides can occur after initiating antipsychotics and may continue to increase over the longer term if they are not managed. Increased cholesterol is an established risk factor for cardiovascular disease and intervention to treat dyslipidaemia is known to reduce morbidity and mortality.

Patients with high cholesterol should be given dietary advice and may need treatment in line with NICE guidance on “cardiovascular disease: risk assessment and reduction, including lipid modification”

<https://www.nice.org.uk/guidance/cg181>

Patients with diabetes in particular may need aggressive treatment to lower cholesterol.

Further advice on the management of antipsychotic induced dyslipidaemia is available in the British Association of Psychopharmacology guideline on the management of weight gain, metabolic disturbances and cardiovascular risk associated with psychosis and antipsychotic treatment: https://www.bap.org.uk/pdfs/BAP_Guidelines-Metabolic.pdf

The NHS provides information on cholesterol including information on how to reduce cholesterol: <http://www.nhs.uk/Livewell/Healthyhearts/Pages/Cholesterol.aspx>

Further statin prescribing and lipid modification guidelines by NCL JFC can be found at: <http://ncl-mon.nhs.uk/faq/guidelines/>

The [Lester UK adaptation tool](#) for monitoring physical health provides further advice on threshold values used in blood lipid monitoring.

Weight Gain and Weight monitoring⁵

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. Patients should be encouraged to weigh themselves and keep a record which can be discussed at each contact.

Medicines that are High Risk for causing weight gain include **clozapine** and **olanzapine**. **Quetiapine** and **risperidone** have a moderate risk of causing weight gain. Haloperidol has a low risk of causing weight gain and to a low extent.

All patients should be given dietary and lifestyle advice to prevent weight gain. Lifestyle interventions are first line for reversing weight gain.

The NHS provides a range of resources on healthy eating and weight loss. <http://www.nhs.uk/livewell/healthy-eating/Pages/Healthyeating.aspx>

The [Lester UK adaptation tool](#) for monitoring physical health provides further advice on threshold values used in weight monitoring.

Management of abnormal results

QTc prolongation^{3,4}

The QT interval broadly relates to the duration of cardiac repolarisation. Some antipsychotics are linked to prolongation of the cardiac QT interval, a risk factor for the ventricular arrhythmia torsade de pointes, which is often fatal. Overall risk is probably dose-related. Medicine interactions (involving enzyme inhibition) are important (See **Appendix 2** for medication interactions).

See **Appendix 3** for risk factors for QT prolongation.

Table 2: Management of QT prolongation in patients receiving antipsychotic medicines^{3,4}.

QTc	Action	Refer to cardiologist
<440msec (men) or <470msec (women)	None unless abnormal T-wave morphology	Consider if in doubt
>440msec (men) or > 470msec (women), but < 500msec	Consider referral to specialist to reduce dose or switching to a medicine of lower effect; repeat ECG	Consider
>500msec	Repeat ECG. Stop suspected causative medicine(s) and refer to specialist to switch to a medicine of lower effect	Immediately - Same day
Abnormal T-wave morphology	Review treatment. Refer to specialist to consider reducing dose or switching to a medicine of lower effect.	Immediately - Same day
Correct electrolyte disturbances (potassium and magnesium) if present		

Hyperprolactinaemia^{3,4}

Dopamine inhibits prolactin release and so dopamine antagonists can be expected to increase prolactin plasma levels. All antipsychotics cause measurable increases in prolactin but some do not increase prolactin above the normal range at standard doses.

Hyperprolactinaemia is often superficially asymptomatic and there is some evidence that Hyperprolactinaemia does not affect subjective quality of life. Persistent elevated levels of plasma prolactin are associated with sexual dysfunction, reductions in bone mineral density, menstrual disturbances, breast growth, galactorrhoea, suppression of the hypothalamic-pituitary-gonadal axis, and a possible increase in the risk of breast cancer.

Table 3: Antipsychotics that affect the prolactin level

Antipsychotics that reduce prolactin level	Aripiprazole
Antipsychotics that increase prolactin level	Amisulpride, sulpiride, risperidone, paliperidone and first generation antipsychotics
Antipsychotics not usually associated with hyperprolactinaemia	Aripiprazole, asenapine*, clozapine, lurasidone*, olanzapine, quetiapine and ziprasidone*

*Non-formulary in NCL

See **Appendix 4** for Antipsychotic-induced hyperprolactinaemia flow chart for identification, monitoring, and management.

Extrapyramidal side effects (EPSE)

Including Dystonia (uncontrolled muscular spasm), Pseudo-parkinsonism (tremor etc.), Akathisia (restlessness), Tardive dyskinesia (abnormal movements) should be considered for a referral to the mental health specialist for review.

Neuroleptic malignant syndrome (NMS)^{3,4}

Neuroleptic malignant syndrome is a rare, but potentially serious or even fatal adverse effect of all antipsychotics. It is a syndrome of muscular rigidity and sympathetic hyperactivity occurring as a result of dopaminergic antagonism in the context of psychological stressors and genetic predisposition.

Signs and symptoms (Presentation varies considerably): Fever, diaphoresis, rigidity, confusion, fluctuating consciousness, fluctuating blood pressure, tachycardia, elevated creatinine kinase, leucocytosis, altered liver function tests.

Risk factors for NMS:

- high potency first generation antipsychotics
- recent or rapid dose increase
- rapid dose reduction
- abrupt withdrawal of anticholinergics
- antipsychotic polypharmacy
- agitation
- dehydration
- psychosis
- organic brain disease
- alcoholism
- Parkinson's disease
- hyperthyroidism
- psychomotor agitation
- mental retardation

If Neuroleptic malignant syndrome suspected the patient must be sent to A&E

High Dose Antipsychotic Therapy⁴

High dose antipsychotic therapy (HDAT) is defined as a total daily dose of a single antipsychotic which exceeds the upper limit stated in the SPC or BNF with respect to the age of the patient and the indication being treated or a total daily dose of two or more antipsychotics which exceeds the SPC or BNF maximum using the percentage method. The percentage method requires converting the dose of each medicine into a percentage of the BNF maximum recommended dose for that medicine and adding these together (See [Antipsychotic Dosage Ready Reckoner](#)). A cumulative dose of more than 100% is high dose antipsychotic prescribing.

Doses of antipsychotics prescribed above the maximum licensed dosages are off-label. The GP must be informed of the off-label use of the medicine and be willing to accept clinical and legal responsibility for prescribing. The specialist is responsible for ensuring that appropriate information is provided to the GP and the GP must agree to accept prescribing responsibility before the patient care is transferred to primary care. If the GP does not wish to continue the prescription this needs to be discussed with the specialist recommending treatment.

High doses of antipsychotics might worsen already compromised cognitive function in their patients (particularly older people). High dose antipsychotics have a greater liability for extrapyramidal side effects for which anticholinergic/anti-Parkinsonism medicines might be required which also may worsen cognitive function. Dose-related side effects include extrapyramidal side effects, tachycardia, postural hypotension, sedation, seizures, and hyperprolactinaemia.

Additional monitoring will be advised by the specialist. All patients on HDAT should have regular ECGs (baseline, when steady state serum levels have been reached after each dosage increment and then every 6 to 12 months). Additional biochemical/ECG monitoring is advised if medicines that are known to cause electrolyte disturbances or QTc prolongation are subsequently co-prescribed (Appendix 3 Risk factors for QT prolongation)

Contact Details and Further Information:

Camden and Islington NHS Foundation Trust

Mental Health Advice and Assessment Team

Address: 4 St Pancras Way, St Pancras Hospital, London, NW1 0PE, United Kingdom

Phone number: 0203 317 7300

Islington Core Mental Health Team: islington.MHCT@candi.nhs.uk Phone Number:

Camden Core Mental Health Team: camden.MHCT@candi.nhs.uk Phone Number:

Opening hours Monday - Friday 9.00am - 5.00pm

Other specialist contact –Crisis Resolution Team: Phone number 0800 917 3333

This number is available 24 hours a day, 7 days a week.

Barnet, Enfield and Haringey Mental Health NHS Trust

Crisis Resolution and Home Treatment Team (CRHT) service

Urgent outreach service, assessing service users 24 hours a day, 7 days a week.

Borough	Address	Telephone
Barnet	1st floor, Dennis Scott Unit, Edgware	0208 702 4040
Enfield	Ivy House, Chase Farm Hospital	0208 702 3800
Haringey	Lea Unit, St. Ann’s Hospital	0208 702 6700

GP Advice Line

An advice line is available for GPs who would like to speak to a consultant about any mental health issue.

Telephone number: 0208 702 3997

Phone line operational Monday - Friday 9am – 5pm

Calls received by 12.45pm will be responded to by a consultant between 1pm and 2pm on the same day. Calls taken after 12.45pm will result in a call back the following day.

<http://www.beh-mht.nhs.uk/gps-and-referrers/>

To find a Summary Product Characteristics: <https://www.medicines.org.uk/emc/>

The [Choice and Medication Website](#) is a patient friendly website which can be provided to patients. Leaflets on medications, including in different languages and formats and fact sheets on a number of areas including weight gain, hyperprolactinaemia, EPSEs and metabolic adverse effects.

[Headmeds](#) is a unique new website about mental health medication for young people aged 13-25. It has been created by YoungMinds and funded by Comic Relief and the Nominet Trust as part of the Innovation Labs project which has developed a range of digital projects to improve young people's mental health

References

1. Summary of Product Characteristics, <https://www.medicines.org.uk/emc/>
2. BNF, <https://bnf.nice.org.uk/>, Last updated: 10 November 2021
3. Taylor D., Barnes T., Young A. The South London and Maudsley NHS Foundation Trust. Oxleas NHS Foundation Trust. Prescribing Guidelines. 14th Edition. London. Wiley Blackwell (2021).
4. Antipsychotic Prescribing Guideline (PHA35), Camden and Islington NHS Foundation Trust, December 2018
5. Summary of Physical Health Monitoring with Mood Stabilisers & Antipsychotics, Central and North West London NHS Foundation Trust, Updated August 2016 (Version 04.0.0)
6. Positive cardio metabolic health resource, Lester UK Adaptation, 2014 update www.rcpsych.ac.uk/quality/NAS/resources
7. Antipsychotic-induced hyperprolactinaemia - Trust guideline for identification, monitoring and management, Oxford Health NHS Foundation Trust, January 2014 V2, <http://www.oxfordhealthformulary.nhs.uk/docs/AntipsychoticinducedhyperprolactinaemiaguidelineJuly2015.pdf>

Appendix 1: Choice of medication in specific medical conditions^{3,4}			
Medical condition	Suggested antipsychotic	Avoid if possible	Comments
Epilepsy	Trifluoperazine haloperidol, sulpiride, amisulpride	Clozapine Chlorpromazine (avoid completely) Depot antipsychotics Lurasidone (experience limited)* Asenapine (experience limited)*	Consider referral to specialist and neurologist The majority of antipsychotics decrease the seizure threshold. Clozapine – very epileptogenic. Approximately 5% who receive more than 600mg/day develop seizures. Sodium valproate or lamotrigine are the anticonvulsants of choice as they have a lower incidence of leucopenia than carbamazepine. None of the depot preparations currently available are thought to be epileptogenic. The kinetics of depots are complex (seizures may be delayed). If seizures do occur, the offending medicines may not be easily withdrawn. Depots should be used with extreme care. Beware pharmacokinetic interactions with anticonvulsants (see Appendix 4).
Pregnancy	Chlorpromazine (constipation and sedation may occur) Trifluoperazine, Haloperidol, Olanzapine Quetiapine, Clozapine (gestational diabetes may be a problem with all atypical antipsychotics). There is most experience with the above, although safety not fully established	Depot antipsychotics (Anticholinergics)	Consider referral to specialist perinatal services. Discuss with the patient the absolute and relative risks associated with treating and not treating the mental disorder during pregnancy and the postnatal period. If patient established on another antipsychotic, the most up-to-date advice should always be obtained. A change in treatment may not be necessary or wise.

Appendix 1: Choice of medication in specific medical conditions ^{3,4}			
Medical condition	Suggested antipsychotic	Avoid if possible	Comments
Breastfeeding	Olanzapine	Clozapine	Consider referral to specialist perinatal services. The benefits of breastfeeding to the mother and infant must be weighed against risk of medicine exposure in the infant. Infant exposure can be decreased by timing feeds to avoid peak medicine levels.
Renal impairment	No agent clearly preferred to another. However for typical antipsychotic, suggest haloperidol 2-6mg/day; for atypical agent, suggest olanzapine 5mg/day	Sulpiride Amisulpride Depot antipsychotics Medicines known to prolong QTc interval Highly anticholinergic agents (risk of urinary retention)	Consider referral to specialist. Olanzapine and clozapine may cause or aggravate diabetes, a common cause of renal disease. Avoid medicines known to prolong QTc interval. In established renal failure, electrolyte changes are common so it may be best to avoid antipsychotics with the greatest risk of QTc prolongation. Weight gain (a risk with antipsychotics) may predispose to diabetes which can cause rhabdomyolysis and renal failure. Be vigilant for dystonias and NMS (as the resulting rhabdomyolysis can cause or worsen renal failure). Rhabdomyolysis can occur without symptoms of NMS.
Hepatic impairment	Low dose Haloperidol, Sulpiride (no dosage reduction required if renal function is normal) Amisulpride (no dosage reduction required if renal function is normal) Paliperidone: if a depot is required.	Sedative or constipating medicines, e.g. chlorpromazine, clozapine (risk of hepatic encephalopathy). Avoid medications hepatotoxic in their own right e.g. MAOIs, chlorpromazine, clozapine. Avoid medicines with a long-half life or those that need to be metabolised to render them active. Depot antipsychotics.	Consider referral to specialist. Monitor Liver function tests (LFTs) weekly, at least initially. If LFTs deteriorate after a new medicine is introduced, consider switching to another medicine. One third of patients who are prescribed antipsychotics have at least one abnormal LFT and in 4% at least one LFT is elevated three times above the upper limit of normal. Transaminases are mostly affected and this generally occurs within 1-6 weeks of treatment initiation. Only rarely does clinically significant hepatic damage result.

Appendix 1: Choice of medication in specific medical conditions^{3,4}			
Medical condition	Suggested antipsychotic	Avoid if possible	Comments
Atrial fibrillation	Aripiprazole Lurasidone*	Clozapine Olanzapine Paliperidone Avoid QT-prolonging medicines in ischaemic heart disease, and those which increase heart rate.	Consider referral to specialist. In permanent AF with rate control medicine choice is less crucial, but probably best to avoid medicines with potent effects on the ECG (ziprasidone, pimozide, sertindole) and those which increase the heart rate. Avoid QT-prolonging medicines in ischaemic heart disease. Beware arrhythmogenicity of psychotropics, their effect on ventricular rate (some induce reflex tachycardia via postural hypotension, others e.g. clozapine, quetiapine directly increase heart rate). Risk of interaction with co-prescribed antiarrhythmics or rate-controlling drugs.
HIV	Atypical antipsychotics (risperidone most widely used). Quetiapine, aripiprazole and olanzapine may also be used.	Clozapine not routinely recommended but may be helpful in low doses in patients with higher CD4 counts who are otherwise medically stable. May be helpful in HIV-associated psychosis with medicine-induced parkinsonism. It is not known whether patients with HIV have a greater risk of agranulocytosis, extremely close monitoring of the white cell count is recommended.	Liaise closely with HIV specialists and MDT team. Beware interaction between antipsychotics and antiretrovirals. Idiosyncratic interactions between risperidone and ritonavir have been reported. Patients may be more susceptible to extrapyramidal side-effects, NMS and tardive dyskinesia.

*Non-formulary in NCL

Appendix 2: Interactions with antipsychotic medication^{3,4}

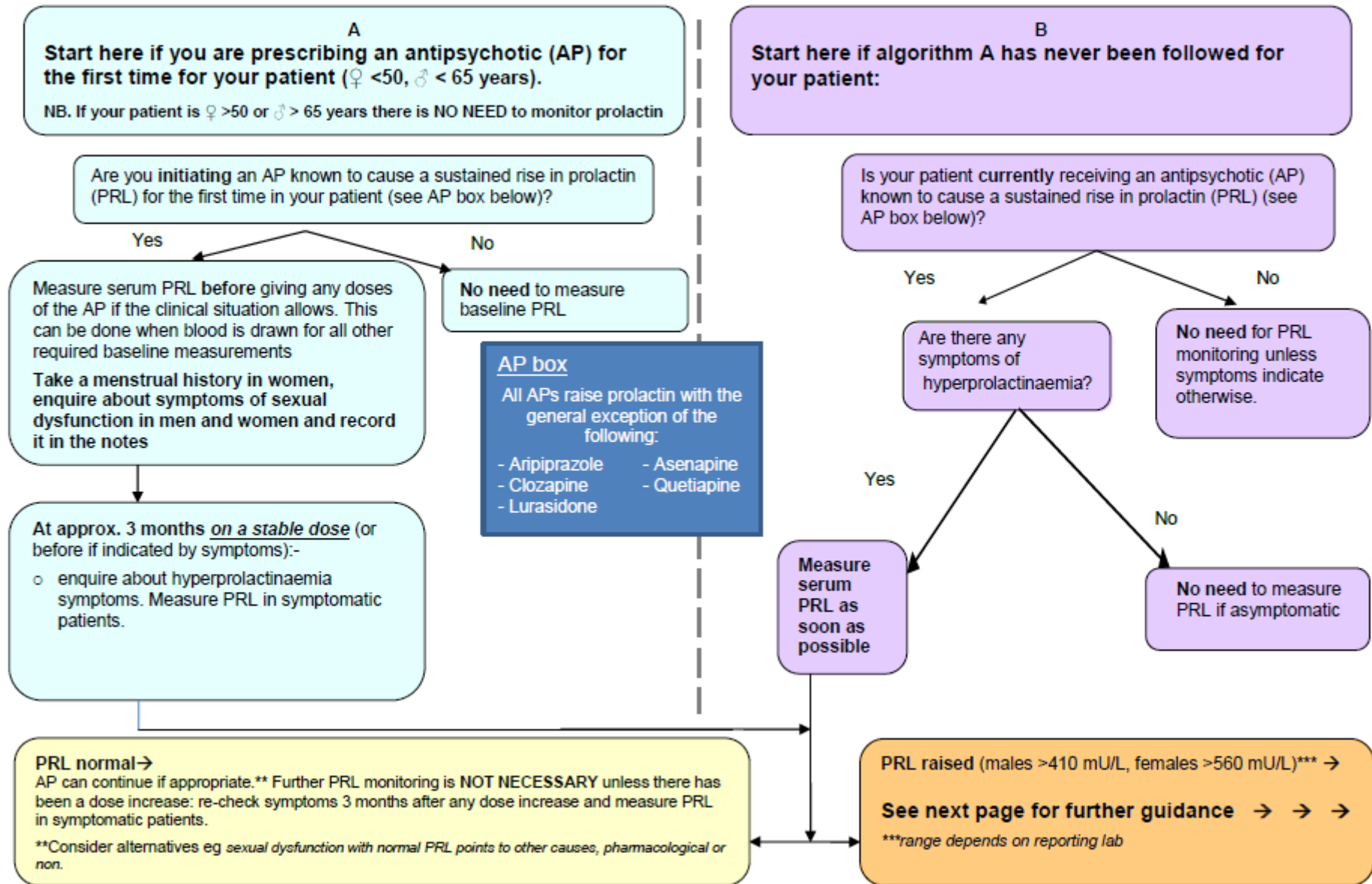
Medication	Interaction
angiotensin converting enzyme (ACE) inhibitors, angiotensin-II receptor antagonists or calcium channel blockers	Postural hypotension
Antiarrhythmic medicines	Increased risk of ventricular arrhythmia with anti-arrhythmic medicines that prolong the QT interval such as amiodarone, bretylium, quinidine, sotalol, procainamide, quinidine, disopyramide.
Antibacterials	Erythromycin possibly increases plasma concentration of clozapine. Ciprofloxacin can possibly increase the plasma levels of olanzapine. Increased serum levels may result in an increase in seizures. Plasma concentrations of quetiapine are possibly increased by macrolides e.g. erythromycin. The following antibacterials have been associated with QT prolongation and so could have synergistic effect- erythromycin, clarithromycin, ampicillin, co-trimoxazole, pentamidine and some 4-quinolones.
Antidepressants	Increased risk of arrhythmia with tricyclic antidepressants. Fluoxetine and venlafaxine increase the plasma concentration of haloperidol. Severe EPSEs have been reported with fluoxetine and haloperidol.
Antiepileptics	Carbamazepine lowers the plasma concentration of aripiprazole, chlorpromazine, fluphenazine, haloperidol, olanzapine, paliperidone, quetiapine, risperidone. Phenytoin lowers the plasma concentration of aripiprazole, haloperidol, phenothiazines, quetiapine and risperidone, Phenytoin serum levels are increased by phenothiazines. The risk of neutropenia is increased if clozapine or olanzapine is given with valproate. Valproate possibly increases plasma concentration of quetiapine. Valproate plasma concentration is increased by risperidone. Phenobarbital decreases the plasma concentration of aripiprazole, chlorpromazine, haloperidol, promethazine and quetiapine
Antimalarials	The following antimalarials have been associated with QT prolongation and so could have a synergistic effect – chloroquine, mefloquine, quinine.

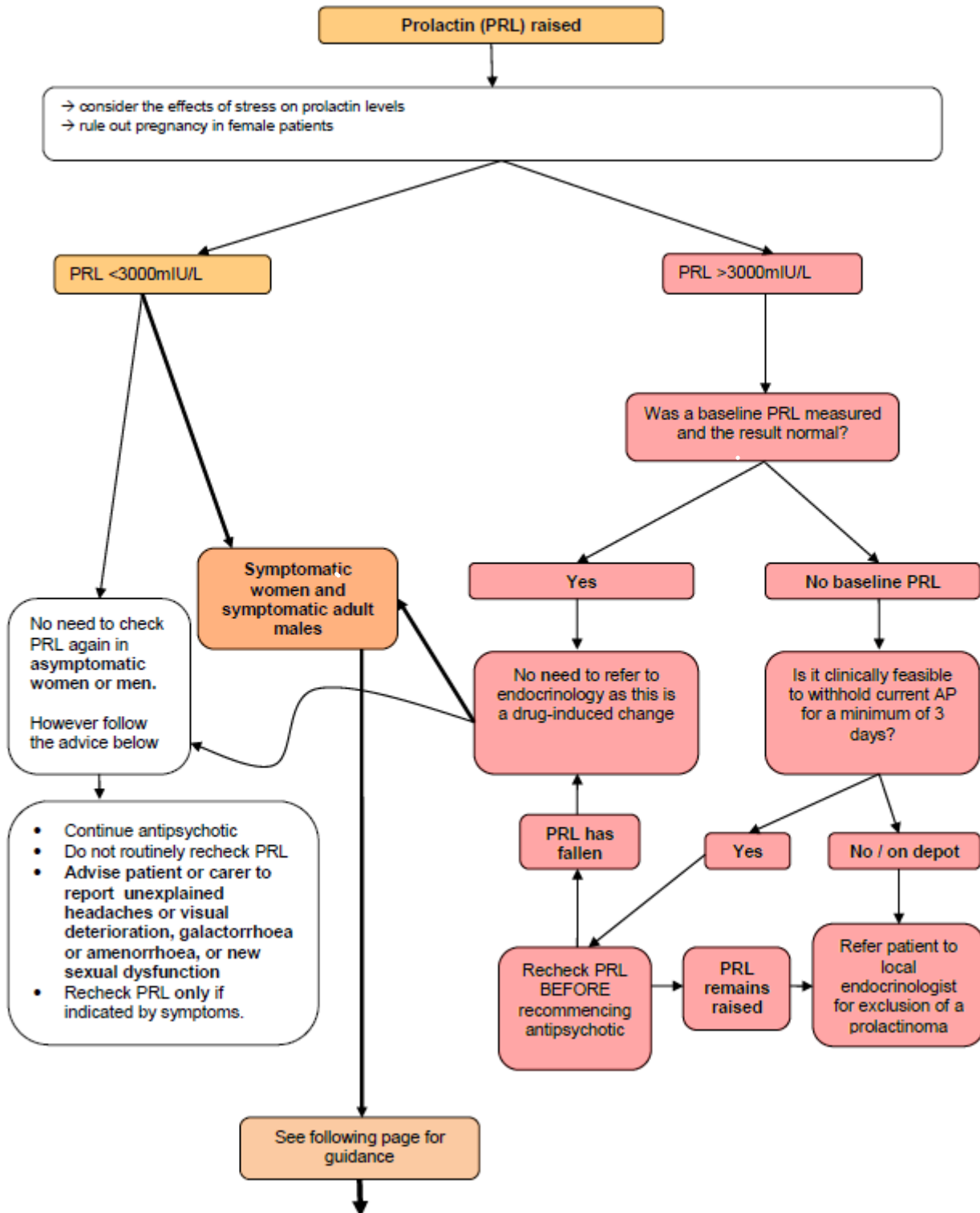
Medication	Interaction
Antivirals	<p>The effect of anti-retrovirals on antipsychotics is unpredictable.</p> <p>Plasma concentration of olanzapine reduced by ritonavir (may need to increase dose).</p> <p>Plasma concentration of aripiprazole possibly reduced by efavirenz and nevirapine. Metabolism of aripiprazole possibly inhibited by amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir (reduce dose of aripiprazole). Plasma concentrations of antipsychotics possibly increased by ritonavir.</p> <p>There is an increased risk of coma when ritonavir is prescribed concomitantly with risperidone.</p> <p>Lopinavir + ritonavir decrease levels of olanzapine. Use of risperidone decreases the effect of these two antiretrovirals, Can lead to reversible coma and increases propensity for extrapyramidal side effects.</p> <p>Increased risk of ventricular arrhythmias when haloperidol or phenothiazines are given with saquinavir – avoid concomitant use.</p>
Atomoxetine	Increased risk of ventricular arrhythmias when antipsychotics that prolong the QT interval are given with atomoxetine.
Beta-blockers	Increased risk of ventricular arrhythmias particularly when sotalol is given with zuclopenthixol, haloperidol, amisulpride, phenothiazines and risperidone.
Lithium	Increasing lithium levels has a direct neurotoxic effect, including increased risk of neuroleptic malignant syndrome (NMS), particularly with haloperidol and phenothiazines, flupentixol, zuclopenthixol. Possible risk of toxicity when given with olanzapine or sulpiride.
Other medicines	The following medicines have been associated with QT prolongation and could have synergistic effect- amantadine, ciclosporin, diphenhydramine, hydroxyzine, nifedipine, tamoxifen.
Smoking	Smoking can reduce psychotropic medication effects by enhancing metabolism. Where patients start or stop smoking this may have an impact on their treatment therefore patients should be asked about their smoking status and encouraged to report any changes in their smoking patterns to their team. The use of nicotine replacement therapy does not compensate for this interaction

Appendix 3: Risk factors for QT prolongation^{3,4}

Effects of antipsychotics on QTc interval		
High effect	A medicine/combination of medicines exceeding the 100% BNF limits	Extensive average QTc prolongation (usually > 20msec at normal clinical doses).
Moderate effect	Amisulpride Chlorpromazine Haloperidol Levomepromazine Quetiapine Ziprasidone	Observed to prolong QTc by > 10msec on average when given at normal clinical doses or where ECG monitoring is officially recommended in some circumstances.
Low effect	Clozapine Flupentixol Fluphenazine Perphenazine Prochlorperazine Olanzapine Paliperidone Risperidone Sulpiride	Severe QTc prolongation has been reported only following overdose or where only small average increases (<10msec) has been observed at clinical doses.
No effect	Aripiprazole	QT prolongation has not been reported either at therapeutic doses or in overdose.
Unknown effect	Loxapine Pipothiazine Trifluoperazine Zuclopenthixol	
Non-psychotropics associated with QT prolongation		
Antibiotics	Erythromycin, clarithromycin, ampicillin, co-trimoxazole, pentamidine, some 4-quinolones	
Antimalarials	Chloroquine, mefloquine, quinine	
Antiarrhythmics	Quinidine, disopyramide, procainamide, sotalol, amiodarone, bretylium	
Others	Amantadine, cyclosporin, diphenhydramine, hydroxyzine, methadone, nicardipine, tamoxifen	
Physiological risk factors		
Cardiac	Long QT syndrome Bradycardia Ischaemic heart disease, Myocardial infarction Myocarditis Left ventricular hypertrophy	
Metabolic	Hypokalaemia Hypomagnesaemia Hypocalcaemia	
Others	Extreme physical exertion Stress or shock Anorexia nervosa Extremes of age Female gender	

Appendix 4: Antipsychotic-induced hyperprolactinaemia (Modified excerpt from [Oxford Health NHS Foundation Trust Guideline](#))⁷







STEP 1: Consider a dose reduction or a switch to an antipsychotic with a lower potential to elevate PRL to alleviate symptoms if clinically appropriate (but see **NOTES** section below and **notes for primary care**)

STEP 2: Follow the recommendations below to identify if your patient requires further investigation

- **Men age 18-65*** → Measure serum testosterone (**9 am sample**).
If 9 am testosterone is less than the lower limit of normal (<8.4 nmol/L) or borderline (8.4-12 nmol/L) repeat the level at least a week later. If both levels are below the lower limit of normal or borderline refer for further assessment; If testosterone is above 12 nmol/L there is no need for further follow up of testosterone or prolactin levels unless the patient develops headache, deterioration in vision, or galactorrhoea. Recheck PRL only if indicated by symptoms and refer as appropriate.
- **Women age 18-50* with amenorrhoea for 3 months or longer** → discuss with local endocrinology service to determine whether telephone advice is sufficient or if a referral appointment is necessary

**a raised prolactin after the age of 50 in women and after the age of 65 in men will have no additional health consequences on bone health beyond those of age alone.*

NOTES

1. Side effects must be balanced against the benefits of treatment. It may not be possible or appropriate to stop/switch existing antipsychotic treatment. Each case should be considered individually.
2. Other risk factors for osteoporosis should be addressed e.g. smoking, sedentary lifestyle, vitamin D deficiency and alcohol intake.
3. A decrease in prolactin may result in the return of fertility even before the reappearance of periods: contraceptive advice may be needed and recorded in the notes.
4. Prolactin levels should fall within days after dose reductions or switches, but a return to normal may take several weeks. Recheck prolactin monthly until normal.
5. Adjunctive aripiprazole could be used in some patients to reduce prolactin when switching to a prolactin-sparing antipsychotic is unwarranted.

Notes for primary care

GPs should refer patients to mental health services for a review of their antipsychotic medication if a dose reduction or switch is indicated. If appropriate, the mental health specialist will also initiate referral for further investigation, liaising with the GP about blood tests. If the patient is not under a secondary care mental health service the mental health team may advise the GP to initiate referral for further investigations.

Appendix 5 – Glasgow Antipsychotic Side-effect Scale (GASS)

Name: _____

Age: _____

Sex: M / F

Please list current medication and total daily doses below:

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

Please place a tick in the column which best indicates the degree to which you have experienced the following side effects.

Also tick the **end or last** box if you found that the side effect was distressing for you.

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<i>Over the past <u>week</u>:</i>	<i>Never</i>	<i>Once</i>	<i>A few times</i>	<i>Everyday</i>	<i>Tick this box if distressing</i>
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					

<i>Tick yes or no for the last <u>three months</u></i>	<i>No</i>	<i>Yes</i>	<i>Tick this box if distressing</i>
21. Women only: I have noticed a change in my periods			
22. Men and women: I have been gaining weight_			

Staff Information

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

For questions 1-20 award 1 point for the answer “once”, 2 points for the answer “a few times” and 3 points for the answer “everyday”.

Please note zero points are awarded for an answer of “never”.

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

Total for all questions=

3. For male and female patients a score of:
 - 0-21 absent/mild side effects
 - 22-42 moderate side effects
 - 43-63 severe side effects
4. Side effects covered include:
 - 1-2 sedation and CNS side effects
 - 3-4 cardiovascular side effects
 - 5-10 extra pyramidal side effects
 - 11-13 anticholinergic side effects
 - 14 gastro-intestinal side effects
 - 15 genitourinary side effects
 - 16 screening question for diabetes mellitus
 - 17-21 prolactinaemic side effects
 - 22 weight gain

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