Guideline aims:
The aim of this guideline is to provide information and guidance on the use of high dose antipsychotic therapy (HDAT) in line with the recommendations of the Royal College of Psychiatrists. We recommend that it is read in conjunction with the Royal College of Psychiatrists Consensus Statement on High-Dose Antipsychotic Medication (CR190).1

Background – see appendix 1

“High dose” definition1:
“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, and a total daily dose of two or more antipsychotics which exceeds the SPC or BNF maximum using the percentage method.”

Calculating antipsychotic dose using the percentage method
An antipsychotic dosage ready reckoner is the easiest way to calculate antipsychotic dose. It consists of a table of all the currently available antipsychotics which states the equivalent percentage of a dose. A copy can be found on the intranet – click on the picture on the right.

In the absence of a ready reckoner the antipsychotic percentage can be calculated by converting the dose of antipsychotic into a percentage of the BNF maximum recommended dose for that drug. E.g. the BNF maximum dose of olanzapine is 20mg, therefore 10mg of olanzapine constitutes 50% antipsychotic dose.

Example calculations:

**Example 1 - Adults**
Zuclopenthixol decanoate IM 600g once weekly (100% BNF max) + Olanzapine 10mg OD (50% BNF max)
Total AP dose = 150%
THIS IS A HIGH DOSE COMBINATION

**Example 2 - Adults**
Olanzapine 20mg OD (100% BNF max) + Haloperidol 5mg PO PRN max 15mg in 24 hours (75% BNF max)
Total AP dose = 175%
THIS IS A HIGH DOSE COMBINATION

**Example 3 - Adults**
Olanzapine 10mg OD (50% BNF max) + Haloperidol 5mg PO PRN maximum 10mg in 24 hours (50% BNF maximum)
Total AP dose = 100%
THIS IS NOT A HIGH DOSE COMBINATION

Prescribing principles:
- Do not start more than one antipsychotic at the same time in first episode psychosis or after a drug free period.
- Use oral doses only as a short term measure for patients on depot/long acting injections. Consult the Summary of Product Characteristics (SPC) for each drug and/or discuss with a member of the Pharmacy team.
- Switch medication when antipsychotic response is poor in preference to increasing doses above the BNF limits. Consult a member of the Pharmacy team for advice if necessary.
- Before resorting to high doses of antipsychotics, evidence based strategies for treatment resistant illness should be exhausted, including optimised use of clozapine. Clozapine should be considered in patients who do not respond to adequate trials of two different antipsychotics. Plasma clozapine levels can be used as a guide to treatment optimisation.4
- Escalate the dose in small increments and allow adequate time for response.
- Document in the Electronic Health Record (EHR) and explicitly state on the drug chart the indication for which any PRN antipsychotic is prescribed. Review PRN medication on a regular basis.
- Carry out a gradual stepwise dose reduction to the maximum licensed dose in the absence of improvement on high dose antipsychotics after the agreed period of time. Monitor for emergent adverse effects.
Before prescribing HDAT:

- Any decision to prescribe HDAT should involve an individual risk-benefit assessment by a trained psychiatrist in consultation with the clinical team, patient and patient’s family or advocate where possible (see page 3 for risk assessment information).
- Possible contraindications for prescribing a particular antipsychotic in high doses must be considered as well as potential drug interactions (see page 3). Drug interactions include *co-prescribing medications that prolong the QTc interval* and drugs that may increase antipsychotic plasma levels.
- Carry out a detailed personal and family history to assess cardiovascular risks.
- The decision to use HDAT must be documented in the EHR, including consent (see below).
- The aims of HDAT must be documented, including a description of the symptoms persisting at standard dose, an acknowledgement of the risks and desired benefits of using HDAT and the plan to assess for symptom reduction (assessments recommended at 6 weeks and 3 months). This must be agreed with the patient.
- Carry out baseline monitoring as indicated below and record the results on the monitoring form (see appendix 2).
- If a patient is found to have a prolonged baseline QTc interval, (men > 440 msec, women > 470 msec), halt the plan for high dose prescribing and seek further advice e.g. cardiology referral. If an ECG or other baseline tests are not conducted, the reason for this should be clearly documented in the notes. The Royal College of Psychiatrists recommends that ECGs should be performed every few days following initiation of HDAT or during a period of dose escalation until steady state is achieved. Thereafter, ECG and electrolyte assessment is recommended every few months, at times of acute illness and when potentially interacting drugs are introduced or a patient experiences symptoms that could be due to arrhythmia such as syncope or fits.

### HDAT prescribing

- Risk-benefit assess
- Assess cardiovascular risks
- Consider drug interactions
- Document the decision
- Obtain consent
- Document the follow up plan with timescales
- Carry out and record baseline monitoring
- Place green sticker on front of drug chart (see p3)
- Carry out ECGs every few days during dose escalation
- Repeat physical monitoring every 3 months
- Gradually reduce the dose to within BNF limits if no improvement
- If patient refuses monitoring, document clearly on form + in notes

### BASELINE TESTS:

- ECG
- Pulse
- Blood pressure
- Temperature
- FBC
- LFTs
- U&Es
- Ca
- Mg

### DURING DOSE ESCALATION:

- Repeat ECG every few days

### EVERY 3 MONTHS*:

- ECG
- Pulse
- Blood pressure
- Temperature
- FBC
- LFTs
- U&Es
- Ca
- Mg

*unless a greater frequency is clinically indicated
**Factors known to increase risk:**

- Electrolyte imbalance, especially hypokalaemia, hypocalcaemia, & hypomagnesaemia
- Hepatic impairment
- History of alcohol intake or substance use
- Hyperlipidaemia
- Ischaemic heart disease (including hypertension)
- Malnourishment
- Obesity
- Older age
- Renal impairment
- Sedentary lifestyle
- Smoking

**IMPORTANT NOTES**

- If HDAT is in use and the need for rapid tranquillisation to manage agitated behaviour arises or a decision is made that administration of zuclopenthixol acetate (Acuphase®) is required, it is particularly important that the routine monitoring of a sedated patient is carried out, with particular attention to regular checks of pulse, blood pressure, respiration, temperature and hydration. Please refer to the Rapid Tranquilisation policy and the Acuphase Guideline as appropriate.

- A green HIGH DOSE sticker (see right) must be placed on the front of the prescription chart by pharmacy, nursing or medical staff indicating the need for monitoring.

**DOCUMENTATION**

- Use the monitoring form in appendix 2.
- The information should be completed before initiating high dose treatment and then as an ongoing monitoring record for both inpatients and outpatients.
- Upload a copy of the baseline data into the Electronic Health Record (EHR) when HDAT is initiated.
- Complete the form at 3 monthly intervals as per the guideline and record that monitoring has been completed in the EHR under the heading HDAT.
- The monitoring form should be kept with the patient’s prescription chart, for in-patients.
- If a patient is discharged on HDAT, the AMHT should be advised of the need for continued monitoring.
- The AMHT should access the copy of the chart held on the EHR for continued monitoring. High dose monitoring should be reviewed and documented at every CPA.

**TOTAL ANTIPSYCHOTIC DOSE ABOVE BNF MAXIMUM**

Please refer to High Dose Antipsychotic Therapy Guideline OTI

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Signed: Date: Profession: High Dose Monitoring Initiated (date):

**Other considerations:**

- **Side effects:** There may be an increased incidence of side effects such as tachycardia, postural hypotension, sedation, seizures, hyperprolactinaemia, extrapyramidal side effects (EPSE), and akathisia.
- **Interactions:** Higher doses or additional antipsychotics may increase the likelihood of and risks from drug-drug interactions:
  - Pharmacodynamic interactions - combining antipsychotics with drugs that prolong the QT interval e.g. other antipsychotics, TCAs, citalopram
  - Hepatic enzyme inhibitors e.g. Erythromycin, ketoconazole - may ↑ antipsychotic plasma concentrations
  - Antidepressants e.g. some SSRIs - may ↑ antipsychotic plasma concentrations
  - Tricyclic antidepressants – antipsychotics ↑ plasma concentrations
  - Diuretics – ↑ risk of electrolyte abnormalities
  - Antihypertensives – ↑ risk of postural hypotension
  - Antiarrhythmics - ↑ cardiac risks

- **Increased mortality:** It is thought that high dosage antipsychotic prescribing may contribute towards ventricular tachycardia and sudden death although there is no consensus on whether a true causal association exists.
- **Higher than necessary doses:** Without careful review, patients could end up on total doses of single or combined antipsychotics that are unnecessarily high, putting the patient at greater risk from the problems mentioned above.
- **Non-adherence:** Making drug regimens more complicated, or the development of side effects can lead to a reduction in adherence.
- **Difficulty with determining cause and effect**
- **Lack of supporting evidence**
- **Potential for increased cost**

*check BNF/ clinical pharmacist/ medicines information service (ext: 4365)
A NOTE ABOUT PRN PRESCRIBING:

CONCERNS

In 2006 a working party with medical, nursing, pharmacy and service user involvement produced some good practice guidance due to the concerns about prn prescribing. These concerns include:

- Lack of dosage intervals indicating poor understanding of the drugs’ pharmacokinetics e.g. time to peak, half-life, and cumulative side effects.
- Lack of maximum doses per 24 hours or cumulative maximum doses where a drug is prescribed by more than one route.
- Lack of clarity about the exact indication for a prn with nursing staff interpreting prescriptions differently.
- A lack of cross referencing prn antipsychotics to the patient’s regular prescription when calculating maximum & cumulative doses given.
- New admissions prescribed prn antipsychotics without a full assessment of a patient’s needs.
- Prn prescriptions often remain in place when they are no longer necessary without an appropriate medication review.
- Route entered as IM/oral on the same prescription entry with insufficient consideration being given to whether the same dose is appropriate both IM and orally and inadequate recording of the route of administration.

RECOMMENDATIONS

- Antipsychotic prn should only be used for agitation due to psychosis. Lorazepam is the first line drug of choice for agitation.
- Do not prescribe prn medication routinely on admission.
- Only prescribe for patients assessed as likely to exhibit disturbed behaviour or with history of disturbed behaviour or violence.
- During the assessment period use only section for non-emergency oral treatment and review. Consider whether patient is neuroleptic-naive and potential adverse effects of prn.
- State frequency, maximum dose and indication clearly
- Write IM & oral doses separately- NICE considers oral and IM should be prescribed in different situations.
- All prn medicines should be prescribed with reference to regular antipsychotics and whether they constitute high dose prescribing.
- Special note should be taken of haloperidol doses prescribed. Generally oral maximum daily doses of 10mg and, if necessary, 5mg of IM should be adequate initially. If prn are given these doses can be reviewed. In Rapid Tranquilisation situations refer to the Oxford Health NHS FT Rapid Tranquilisation policy. For the use of Zuclopenthixol Acetate (Acuphase), refer to Oxford Health NHS FT Guidelines.
- Prn procyclidine should always be prescribed when haloperidol IM is prescribed.
- All patients on high doses should be monitored as per high dose guidelines.
- All doses given should be recorded in patient’s notes with details of efficacy and any adverse effects.
- All prn medicines should be reviewed regularly and also in Multidisciplinary Team meetings. Discontinue if no longer required.

References

6. Oxford Health NHS Foundation Trust Rapid Tranquilisation Guidelines CP042015
7. Guidelines for the use of Zuclopenthixol Acetate (Clopixol Acuphase) Injection 2014
Background information

In 1993 the Royal College of Psychiatrists produced the first consensus statement\(^1\) on the use of high dose antipsychotic medication (updated in 2014) as a result of a possible link between high doses of antipsychotics, ventricular tachycardia, sudden death and the increased incidence of side effects.

In addition, the National Patient Safety Agency report on patient safety incidents in mental health\(^12\) stated that high dose antipsychotic prescribing needed to be reviewed within trusts because of the increased potential for adverse effects which includes the unclear contribution towards ventricular tachycardia and sudden death.

Audits of high dose antipsychotic prescribing conducted by the Prescribing Observatory for Mental Health have consistently shown that high dose antipsychotic use is common in practice and that it usually results from the use of multiple antipsychotics and PRN prescribing. The 2012\(^13\) audit showed that 25% of sample of 9,537 patients were prescribed high dose antipsychotics. The National Audit of schizophrenia 2014\(^14\) also found that in approximately 10% of prescriptions examined, antipsychotics were prescribed at higher than the BNF maximum.

Why do clinicians prescribe high dose antipsychotics?
The use of high dose antipsychotics in clinical practice is common. The following are some of the factors contributing to the use of high dose antipsychotics:

- Poor response to standard treatment
- Management of challenging symptoms such as violence and aggression
- Limited pharmacological knowledge of the prescriber and scepticism about prescribing algorithms.
- The use of combination antipsychotics for augmentation purposes e.g. clozapine and amisulpride
- The use of augmenting antipsychotics such as aripiprazole to reduce hyperprolactinaemia
- Inadvertent prescribing e.g. due to prn antipsychotic or during rapid tranquilisation

What is the evidence base regarding the prescribing of high dose antipsychotics?

- There is no evidence that high dose antipsychotics use is beneficial for patients with first episode psychosis.\(^1\)
- For the majority of people with acute psychotic illness the target dose for effective treatment is likely to be below the licensed maximum.\(^1\)
- There does not seem to be any justification in the published literature for the use of high dose antipsychotic medication for relapse prevention in schizophrenia, nor is there convincing evidence that maintaining the higher dose of antipsychotic initiated during a period of relapse provides better relapse prevention in the long term.\(^1\)
- There is no justification in published literature for high dose antipsychotics in the treatment of persistent aggression.\(^1\)
- There is no convincing evidence that antipsychotic dosage higher than the maximum licensed dose is more effective than the standard dosage for treatment resistant schizophrenia.\(^1\)
- There is evidence that most antipsychotic drugs are associated with a small but definite increase in the frequency of QTc prolongation, torsade de pointes and sudden cardiac death. The risk increases with higher doses.\(^1\)
- There is evidence that high dose antipsychotic use is detrimental to cognitive functioning.\(^1\)
- The efficacy of combining two or more first generation antipsychotics or adding a first generation antipsychotic to a second generation drug and vice versa has not been established, and there is evidence for an increased risk of adverse effects and pharmacokinetic interactions.\(^5\)
HIGH DOSE ANTIPSYCHOTIC MONITORING FORM

This form should be completed in accordance with Oxford Health NHSFT High Dose Antipsychotic Monitoring Guidelines for all patients prescribed High Dose Antipsychotic doses i.e. > 100% BNF Maximum

### HIGH DOSE DETAILS

<table>
<thead>
<tr>
<th>Start Date</th>
<th>Antipsychotic</th>
<th>Route (po, IM, depot/ LAI)</th>
<th>Dose and frequency (include whether regular or PRN)</th>
<th>% BNF max.</th>
<th>Cumulative % BNF max. dose</th>
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*Please note that for any change in antipsychotic treatment e.g. dose increase, addition of another antipsychotic or change of antipsychotic, where continued HDAT monitoring is required, a new form must be completed with a new baseline ECG.*

### Baseline Monitoring Checklist - please circle. Where risk factors are noted complete *section below

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<th>Obesity</th>
<th>Heavy Smoker</th>
<th>High Alcohol Intake</th>
<th>Age over 70 yrs</th>
<th>Age under 18 yrs</th>
<th>Family history of cardiovascular disease</th>
<th>Current Cardiovascular disease</th>
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### Initial Tests

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*Limited evidence that cardiac risk is greater if QTc >440ms for men; 470ms for women. Stronger evidence links QTc values >500ms to arrhythmia-risk

*If there are any contraindications highlighted please state the reasons why high dosage therapy is to continue and state risk management plan:

### Previous treatment: Please circle as relevant

Has the patient been non-responsive to two different classes of antipsychotic prescribed at maximum dosage for suitable time period? **Y/N**

### Consent: Please circle as relevant

- **Informal Patient** - consent documented in Electronic Health Record **Y/N** Date:
- **Patient detained under Mental Health Act:** Form T2: **Y/N** Date: Form T3: **Y/N** Date:
- **High Dose therapy documented on Form:** T2/T3 **Y/N** If “N”, S62 form completed: **Y/N** Date:

Signature: __________________________ Print Name: __________________________ Date: __________________________

Designation: **CONSULTANT ONLY**
HIGH DOSE ANTIPSYCHOTIC MEDICATION MONITORING.
REPEAT TESTS AT 3-MONTHLY INTERVALS.
Complete chart with date of relevant results & ✓ if results within normal range or x if results abnormal & document below. Enter signature by result.
If test is offered and refused write REF and document in EHR under HDAT.
Results to be recorded in the electronic records every 3 months under heading HDAT RESULTS.

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ABNORMAL RESULTS - please provide details and REVIEW RISK/BENEFIT OF HIGH DOSE ANTIPSYCHOTIC PRESCRIBING

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