

Guidelines for Antipsychotic Medication Switches

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General Principles

There are no published controlled trials on switching antipsychotics, therefore clinicians should use these guidelines to aid their practice but may depart from them when clinical need warrants the need to do so. Any decision to depart from these guidelines should be documented in the patient's notes with a rationale for the decision. Much of the information on antipsychotic medication switches is based on case reports and pharmacokinetic/ pharmacodynamic principles.

NICE Recommendations on Antipsychotics (NICE CG1 Dec 2002)

- ◆ The choice of antipsychotic drug should be made jointly by the individual and the clinician based on informed discussion on the relative benefits and side effects which is recorded in the notes
- ◆ A risk assessment should be performed by the clinician responsible for treatment and the multidisciplinary team regarding compliance with medication. Depot preparations should be prescribed when appropriate
- ◆ An advance directive regarding choice of treatment is documented in the individual's care programme where possible
- ◆ Oral atypical medications are recommended for individuals who despite adequate control with conventional agents are suffering unacceptable side effects and those in relapse who have experienced unsatisfactory management or unacceptable side effects. Oral atypical antipsychotic monotherapy is recommended as first line therapy for first episode schizophrenia
- ◆ In individuals with treatment resistant schizophrenia (TRS) clozapine should be introduced at the earliest opportunity. TRS is suggested by lack of clinical improvement following sequential use of at least two antipsychotics for 6-8 weeks, at least one of which should be an atypical
- ◆ When full discussion is not possible, for example in an acute psychotic episode, the oral atypical antipsychotics should be considered treatment options of choice because of lower risk of extrapyramidal side effects (EPS). The individual's carer or advocate should be consulted where possible and appropriate

Indications for Switching Antipsychotics

- ◆ Persistent positive or negative symptoms
- ◆ Relapse despite proven compliance
- ◆ Persistent distressing adverse drug reactions
- ◆ Change of formulation to assist concordance e.g. switch to depot

Risks Associated with Antipsychotic Switches

- ◆ Relapse or destabilisation, should the replacement drug be less effective than the former. If the side effect profile experienced by the individual remain unacceptable there are further risks of discontinuation
- ◆ Reduced compliance due to worsening of mental state and/or adverse drug reactions
- ◆ Deterioration in physical condition due to adverse drug reactions and/or other concomitantly prescribed medication
- ◆ Exacerbation of condition due to stress and anxiety from the switch
- ◆ Potential medication errors during the cross over
- ◆ Cholinergic rebound, where the second drug has less cholinergic activity. Symptoms may be severe but relatively brief and predictable- nausea, vomiting, restlessness, anxiety, insomnia, fatigue, malaise, myalgia, diaphoresis, rhinitis, paraesthesia, GI distress, headaches and nightmares.
- ◆ Withdrawal dyskinesia, rebound akathisia, rebound dystonia and worsening of tardive dyskinesia may in part be related to cholinergic rebound.
- ◆ Combined adverse drug reactions (ADRs)
- ◆ Other discontinuation reactions
- ◆ Neuroleptic malignant syndrome (NMS) has been reported during many antipsychotic switches

Issues for consideration

- ◆ Advise individual that switch of medication is associated with increased risk of relapse
- ◆ Additional support and monitoring should be in place for individuals during the switch. Where applicable this should be via the Care Program Approach process
- ◆ Where switching is considered while in primary care additional support and monitoring should be in place
- ◆ Formulate relapse prevention strategy
- ◆ Involve carer if appropriate
- ◆ Ensure full care plan in place to support and monitor individual during and post switch
- ◆ Allow at least 3 months at full therapeutic dose to assess full impact, unless reasons dictate otherwise e.g. serious deterioration in mental state or risk issues, serious side effects etc
- ◆ Differentiate change in presentation that may be due to reduction in side effects from increased antipsychotic effect- particularly over first six weeks
- ◆ If no improvement at all after six weeks exclude non- compliance, substance misuse and inadequate dosage
- ◆ Gradually discontinue anticholinergic or antiakathisia medication in the second month post switch
- ◆ Normalisation of raised prolactin can take over 3 months- especially important to women due the implications for advice on contraception

Switching Antipsychotic Drugs

Approaches to switching medication vary in the rate of change and extent of any overlap of agents. Pharmacokinetically and pharmacologically the lowest risk strategy for switching is to have a drug free interval. In practice the aim is to avoid additive effects of the agents that may result in unpredictable toxicity while at the same time ensuring adequate antipsychotic cover. The advantages and disadvantages of the various approaches to switching antipsychotics are summarised:

Option	Advantages	Disadvantages
Drug free interval	<ul style="list-style-type: none"> Minimal potential for combined adverse drug reactions Minimal potential for drug interactions Clarity between side effects of second drug and discontinuation effects from first drug Anticholinergic /antiakathisia medication can be titrated independently Reduces potential for additive myelosuppression when switching to clozapine Low risk of medication errors 	<ul style="list-style-type: none"> Length of time taken High level of monitoring of individual required, possibly even in-patient care Risks of relapse Relapse can be misinterpreted as lack of efficacy of second drug
Gradual reduction of drug A followed by starting B	<ul style="list-style-type: none"> Low risk of medication errors Straightforward 	<ul style="list-style-type: none"> Risk of relapse Potential for combined adverse drug reactions Potential for drug interactions
Sudden withdrawal of drug A followed by starting B	<ul style="list-style-type: none"> Appropriate where an acute, severe reaction necessitates abrupt withdrawal e.g. clozapine Low risk of medication errors Straightforward 	<ul style="list-style-type: none"> Risk of relapse especially if discontinuing clozapine Potential for combined adverse drug reactions Potential for drug interactions
Partial overlap	<ul style="list-style-type: none"> Good if there is high risk of relapse Changes are less abrupt Useful for switch from depot to oral as depot plasma levels decline slowly and withdrawal reactions have not been reported Useful for high potency to atypical Useful where there is potential for cholinergic rebound 	<ul style="list-style-type: none"> Tapering too quickly can cause inadequate cover Potential for combined ADRs Potential for drug interactions Potential for medication errors and compliance problems Incomplete switches can result in polypharmacy
Full overlap	<ul style="list-style-type: none"> Useful where relapse prevention is the greatest concern Low risk of discontinuation effects from first drug Low risk strategy when changing from depot to oral as allows opportunity to assess compliance with oral therapy 	<ul style="list-style-type: none"> Possibility of combined ADRs Potential for drug interactions Potential for medication errors and compliance problems Incomplete switches can result in polypharmacy

Equivalent doses

Lack of agreement exists on antipsychotic equivalent doses, due to the different calculation methods used, this is particularly true for high-potency agents. Equivalences quoted are as accurate as the data allows but the following considerations should be remembered:

- ◆ Sedation can cause confusion over equivalence e.g. haloperidol is a potent antipsychotic with relatively low sedative effects
- ◆ Some drugs do not have a linear relationship between dose and antipsychotic effect
- ◆ Dose frequency with depots may be important due to first pass effects
- ◆ For drugs with wide receptor activity conversion tables are inappropriate, as they may result in increased side effects and over-sedation
- ◆ Differences in half-lives may complicate calculation
- ◆ Haloperidol and fluphenazine are particularly problematical and can produce unreliable doses when using conversion calculations
- ◆ Doses for atypical agents are better defined than with conventional agents
- ◆ No equivalent doses are appropriate for atypical antipsychotics
- ◆ Calculations become invalid at the extremes of dose range
- ◆ Always check answers against Summary of Product Characteristics and BNF

High Dose Antipsychotic Therapy

- ◆ Where more than one antipsychotic is prescribed care should be taken not to exceed to cumulative BNF maximum dose¹ unless the patient has a planned and documented regime of high dose antipsychotic therapy
- ◆ For patients detained under the Mental Health Act subject to Section 58 approval for consent to treatment, cumulative BNF maximum can only be exceeded if specifically indicated on forms T2/3 (previously F38/39)
- ◆ More details on high dose antipsychotic therapy are available in the HMHTT *High Dose Antipsychotic Therapy Guideline*

¹ Calculating cumulative BNF max: Someone on oral olanzapine 10mg daily (BNF max 20mg daily) PLUS oral haloperidol 20mg daily (BNF max 30mg daily) is on 50% PLUS 66% = 116% BNF MAX

Table of Antipsychotic Equivalences

Antipsychotic equivalent doses	
Oral	Daily dose (Range, wider range= less certainty)
Chlorpromazine	100mg
Fluphenazine	2mg (1.25 to 5mg)
Levomepromazine	Not established
Pericyazine	24mg
Perphenazine	8mg (7 to 15mg)
Prochlorperazine	15mg (14 to 25mg)
Promazine	100mg (50 to 200mg)
Thioridazine (to be discontinued)	100mg (75 to 104mg)
Benperidol	2mg
Trifluoperazine	5mg (2 to 8mg)
Haloperidol	3mg (1 to 5mg)
Flupentixol	2mg
Zuclopenthixol	25mg (25 to 60mg) up to 150mg
Pimozide	2mg (1 to 3mg) Note: long half life
Amisulpride	100mg (40 to 150mg)
Sulpiride	200mg (200 to 333mg)
Clozapine	100mg (30 to 150mg)
Olanzapine	Not established
Quetiapine	Not established
Zotepine	Not established
Risperidone	1.5mg (0.5 to 3mg)
Aripiprazole	Not established
Depot	Weekly dose (range)
Fluphenazine	5 to 10mg (1 to 12.5mg)
Pipothiazine	10mg (5 to 12.5mg)
Haloperidol	15mg (5 to 25mg)
Flupentixol	10mg (8 to 20mg)
Zuclopenthixol	100mg (40 to 100mg)
Risperidone long acting injection	12.5mg (as 25mg per fortnight)
Injection	Daily dose
Chlorpromazine	25 to 50mg intramuscularly (IM)
Haloperidol	1.5mg intravenously (IV) or intramuscularly (IM)

Ref: Psychotropic Drug Directory 2007 Bazire and information supplied by Drug Company

Specific Recommendations on Antipsychotic Medication Switches

Switch	Issues/problems	Recommendation
Oral typical antipsychotic to typical depot	Anecdotal evidence shows the change can usually be made uneventfully, though there are no formal studies.	Converting to the same drug as depot should present few problems by choosing the equivalent dose carefully from the conversion table Give test dose and start titration of depot to maintenance, withdraw oral medication gradually as depot dose escalates.
Oral haloperidol to depot haloperidol	Accumulation occurs	Multiply the total daily dose by 15 to 20 (to a maximum of 300mg) and administer every 4 weeks. Decrease the dose by 25% each month until the minimum effective dose is achieved. Elderly or those on < 10mg per day orally should have a dose 10 to 15 times the oral dose, every 4 weeks
Oral fluphenazine to depot fluphenazine	Accumulation occurs after approximately 3 weeks of depot therapy.	Multiply the total daily dose by 1.2 and give as fluphenazine decanoate IM every one to two weeks. Increase the dose interval to 3 weeks or so after 4 to 6 weeks of therapy
From depot to oral		Cross titration is not necessary when switching from depot to oral. Commence oral medication on the day the next depot would be due.
From depot to clozapine	Increased risk of agranulocytosis. As clozapine is sedative & hypotensive, care is needed. Pharmacokinetic interactions are unlikely	Start clozapine on day that depot would have been due. Monitor white cell count, for signs suggestive of infection, blood pressure and level of sedation closely

Switch	Issues/problems	Recommendation
Typical depot to another typical depot	No significant problems are usually experienced	Direct conversion can be made by choosing the equivalent dose carefully from the conversion table. Administer the new depot on the date the previous depot was due
Combined oral plus depot to depot alone	Unexpectedly problematical, relapses occurring more frequently with this compared to other changes	Increase the dose of depot before reduction of the oral dose to provide adequate antipsychotic cover.
To clozapine	Increased risk of agranulocytosis. As clozapine is sedative & hypotensive, care is needed. Pharmacokinetic interactions are unlikely	Withdraw previous drug and allow washout period wherever possible. <ul style="list-style-type: none"> • Monitor white cell count, • For signs suggestive of infection • Blood pressure • Level of sedation.
From clozapine	Problematical-high incidence of rapid relapse with severe withdrawal symptoms	Gradually withdraw clozapine and simultaneously introduce and escalate dose of replacement drug. Monitor white cell count, for signs suggestive of infection and mental state closely
From clozapine to olanzapine	Reports of severe withdrawal in 2 cases	Slow clozapine weaning over 3 or more weeks with anticholinergic cover
From clozapine to quetiapine	Have been used together to reduce potential for clozapine induced weight gain	May be safely switched in any way depending on the reason for switch, problem would be risks associated with relapse due to discontinuation of clozapine
To oral olanzapine	Additive EPS, hypotension and drug interactions unlikely. Consider potential for pregnancy if switching from a typical agent	Introduce olanzapine and increase dose while at the same time gradually reduce the dose of the first antipsychotic.
From olanzapine		Any method is acceptable, there are no reported problems with stopping olanzapine suddenly

Switch	Issues/problems	Recommendation
To aripiprazole from oral olanzapine, risperidone, thioridazine or haloperidol		<p>In the case of olanzapine, risperidone, thioridazine and haloperidol there were no reported problems when using either following method.</p> <ul style="list-style-type: none"> • Immediate start at 15mg per day and sudden withdrawal of existing agent • Immediate start at 15mg per day followed by withdrawal of existing agent over 2 weeks • Starting at 10mg per day and titrating up to 30mg while withdrawing existing antipsychotic over 2 weeks
To oral risperidone	Hypotensive- may result in additive hypotension with low potency drugs.	<p>Gradually increase dose over ≥ 3 days to 4 -6mg per day. A sudden switch may be successful in 60% of individuals. However one review recommended avoiding a sudden switch</p>
From risperidone		<p>Few problems but there is potential for NMS, increased prolactin and additive EPS if switching to phenothiazines or D2 blockers</p>
From risperidone to olanzapine	For elderly/frail patients gradually discontinue and then gradually introduce	<p>Of three methods the most successful method was starting 10mg daily of olanzapine and then gradually reducing and stopping risperidone</p>

Switch	Issues/problems	Recommendation
Haloperidol to risperidone	Neuroleptic Malignant Syndrome (NMS)	Caution- monitor closely for signs of NMS
From quetiapine		Few problems, any method may be considered
To risperidone long acting injection (RLA)	Therapeutic levels are not reached until week 4 and do not become optimal until 5 to 6 weeks after starting. Oral cover is essential- there is potential for polypharmacy	Assess response to oral risperidone before initiation, as recommended by SPC. Oral therapy should continue for 3 to 4 weeks before being gradually reduced. Doses of RLA above 25mg per 2 weeks are rarely necessary and associated with a high incidence of ADR without antipsychotic gain.
Typical depot to RLA	As 'To risperidone long acting injection (RLA)'	Assess response to oral risperidone before initiation, as recommended by SPC. Manufacturer recommends starting RLA one week before the last the last fortnightly injection with oral therapy if relapse risk high. Alternative strategy- switch on date depot due and supplement with oral risperidone for 3 to 4 weeks.
From RLA to typical depot		The manufacturer recommends 8 weeks after the last risperidone long acting injection before commencing an alternative depot. Plasma levels remain at steady state for 5 weeks after the last injection

Where specific recommendations are found in the literature they are often based on single case reports or data derived from a limited number of cases. The potential for inter-individual variation should always be considered. The table is a summary of information from the Psychotropic Drug Directory 2003/04 and information provided by manufacturers.

Key: **Less Hazardous**  **Problematical** 

Ref: Psychotropic Drug Directory 2007 Bazire and information supplied by Drug Company