CLINICAL GUIDELINE:

No:	Prescribing Guidance for the Treatment of Schizophrenia in Adults
Agreed by:	The Pharmacological Therapies Committee. April 2019
	Trust Clinical Governance Committee 2019

Aim of guideline

This guideline gives advice on prescribing pharmacological treatments for schizophrenia. It reflects NICE guidance, BAP guidance and more recent evidence. This guideline considers prescribing antipsychotics in Schizophrenia, including initial choice, monitoring and follow up, and an approach to treatment-resistant Schizophrenia.

Although not addressed in this guideline, psychological and social interventions are important in the effective management of schizophrenia and increase the chance of staying well.

Developed by

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Who it applies to

This is prescribing guidance.

Process for review / feedback

Prescribing for schizophrenia may be the subject to audit via the pharmacological therapies committee for adherence to this guidance. This guidance will be updated every two years or in the light of any changes to national or local prescribing practice, NICE guidance or other evidence-based comments from local clinicians.

The next review date will be February 2021.

Abbreviations

LAI Long-acting injection
FGA First-generation antipsychotic
SGA Second-generation antipsychotic
TRS Treatment Resistant Schizophrenia

Newly-Diagnosed Patients

- Patients (and carers) should be involved in decisions about choices of medications [1]. Clinicians should be aware that illness and medication beliefs influence adherence.
- Treatment decisions can be facilitated by providing suitable information e.g. from the *Choice and Medication* website.
- Treat with a **single oral antipsychotic**, consult individual product SPCs for further information.
- Titrate to the lowest effective dose. Consider the likely minimum effective doses for First Episode Schizophrenia. (See Appendix 1).
- Adjust dosage regimen according to therapeutic response and tolerability.
- Antipsychotic response should preferably be assessed by use of recognised rating scales.
- Physical health and side effect monitoring must be carried out as per trust policy *'Physical Health Assessment and Management'* (See Appendix 2).
- The current consensus is that antipsychotics should be prescribed for 1-2 years after a first episode of Schizophrenia [1]

Choosing an Antipsychotic

- All available antipsychotics are superior to placebo [3]
- There is no convincing evidence in relation to efficacy or outcomes to support preference for the first-line use of either FGAs or SGAs. Both classes of antipsychotic can be considered first line choices [4,5].
- SGAs' generally lower propensity to cause EPSEs & tardive dyskinesia is offset by higher propensity for metabolic adverse effects [3].
- When considering choice of antipsychotic, there may be small efficacy advantages for some drugs. The magnitude of differences are small, but potentially clinically important, and must be weighed against the different individual adverse effect profiles of drugs
- Olanzapine, amisulpiride and risperidone may be with superior efficacy over other antipsychotics (not including clozapine) [3].
- When compared to oral antipsychotics, there is evidence that depots / LAIs are associated with reduced risk of relapse and rehospitalisation [6], although the more methodologically robust the study design, the smaller the difference. This benefit of depot / LAI over oral treatment is seen in First Episode patients [7].
- Offer clozapine to people with schizophrenia 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 the drugs should be a non-clozapine second-generation antipsychotic. [1,4,8,9,10] .

List of Approved Medicines (Tier 1)

- **Oral FGAs**
  - Haloperidol, perphenazine, sulpiride, trifluoperazine, zuclopentixol, flupentixol, chlorpromazine, pericyazine

- **Oral SGAs**
  - Risperidone, olanzapine, quetiapine, amisulpride, aripiprazole, clozapine

- **Depot FGAs**
    - Flupentixol decanoate, fluphenazine decanoate, haloperidol decanoate, pipotiazine palmitate, zuclopentixol decanoate.

Medicines with additional requirements for prescribing (Tier 2)

Require consultant documentation of reasons for prescribing, (including why "first tier" drugs are not appropriate and why clozapine is not an option if treatment-resistant) as well as the agreement of the long-term prescriber. Complete restricted medicines form on RiO.

- Quetiapine XL (See PTC guidance), pimozide, penfluridol

Medicines for which prior approval is required (Tier 3)

Follow guidance for each medicine.

- Risperidone LAI, olanzapine LAI, paliperidone monthly LAI, paliperidone threemonthly LAI,aAripiprazole LAI, lurasidone hydrochloride

On-Going Treatment with Antipsychotics

- There is a cumulative 82% risk of relapse after a first episode. Long-term treatment prevents relapses and re-hospitalization [6,11].
- Treatment requirements are usually higher later in treatment as compared to treatment during the first episode (see Appendix 1)
- Check medication adherence, using plasma assays if necessary. If adherence is poor, consider the underlying reasons and an appropriate strategy:
    - *Lack of insight:*
        - Consider depot/LAI.
    - *Poor tolerance:*
        - Consider switch to an antipsychotic with a more favourable adverse-effect profile.
    - *Forgetful/ disorganised:*
        - Consider support of family/ carers;
        - Simplify the drug regimen;
        - Consider depot/LAI;
        - Reduce anticholinergic load.
        - Consider assessment for a compliance aid ○ *Misunderstandings or stigma about treatment:*
        - Consider patient and family/ carer education.

- Assess the impact of side effects systematically, ideally using a recognised rating scale e.g. GASS or LUNSERS. Be aware that adverse effects are a common reason for treatment discontinuation, particularly when efficacy is poor. If problematic adverse effects are reported, options include:
    - reducing the treatment dose;
    - switching antipsychotic treatment;
    - low dose Aripiprazole for iatrogenic hyperprolactinaemia.

- When depot/LAI are prescribed, the preferred method is establishing efficacy and tolerability of oral mediation at a particular dose before converting to equivalent dose of depot/LAI. See Appendix 3 for equivalent doses.
- Be aware that plasma levels usually rise for 6-12 weeks after a depot antipsychotic dose change.
- Where maximum BNF doses are exceeded and/ or combination antipsychotics used, follow Trust guidance on *'The Prescribing of High Dose and Combination Antipsychotic Medication'* (see also below).
- Ensure treatment is consistent with MHA consent to treatment paperwork.
- Patients should be supported to create an advance statement which takes into account their preference for treatment in the short and medium term and in the event of relapse.
- If the patient is stable, there are no significant risks and prescribing is considered suitable for primary care, then consider transfer of prescribing to primary care with the patient's GP**.** A helpful definition of stability is:
    - No significant change in the prescription for a minimum of 1 month.
    - No increases of doses of any treatment and no new treatment starts.
    - No significant acute risks.
    - Any compliance issues are manageable in primary care.
- Send a copy of the Birmingham, Sandwell, Solihull and Environs Area Prescribing Committee ESCA on antipsychotic treatment.
- High dose antipsychotic prescribing should normally be retained within specialist services until doses have reduced to within licensed range.

Treatment Resistance and Clozapine

- See BSMHFT's *Clinical Guidance on Initiation of Clozapine for In-Patients and Patients within Home Treatment Services*
- Offer clozapine to people with schizophrenia whose illness has not responded adequately to treatment despite sequential use of adequate doses of at least two different antipsychotic drugs. At least one of the drugs should be a non-clozapine second generation antipsychotic. (1,4,8,9,10)
- Delay to clozapine, from diagnosis of TRS, predicts much worse response to treatment (12)
- Other benefits of clozapine treatment may include an (group) effect on overall mortality, a beneficial effect on symptoms of hostility and aggression, and reduced risk of suicide.
- Careful monitoring is essential during clozapine treatment, particularly during the first three months.
- The average dose of clozapine in the UK is 450mg/ day. Lower doses are required in the elderly, female and non-smokers, and in those prescribed certain enzyme inhibitors.
- Most studies indicate that the threshold for clozapine response is with pre-dose (trough) serum levels in the range 350-420ng/L.
- Preferably allow at least 3-6 months of optimised clozapine monotherapy(13) .
- The evidence for **Clozapine Combination or Augmentation Treatment** is variable and suggests a small effect size at best. It is recommended that all such treatments are carefully monitored and, if there is no clear benefit, combination/augmenting treatments are withdrawn after 3-6 months. The better evidence for clozapine combination/augmentation is with **amisulpiride, haloperidol, sulpiride** (14) **and lamotrigine** (15).

- If clozapine is not appropriate or not efficacious, and **High Dose Antipsychotic Treatment** is considered, follow BSMHFT's guidance on *'The Prescribing of High Dose and Combination Antipsychotic Medication'* and guidance from the RCPsych [16]
- Evidence that high doses of antipsychotic medication are any more effective than standard doses for Schizophrenia is poor [2,17] .
- There is some evidence of equivalent efficacy (with clozapine) for high dose olanzapine in Treatment Resistant Schizophrenia, but meta-analytic evidence is less favourable Ensure MHA consent to treatment paperwork covers high dose antipsychotics.
- There is little evidence supporting the efficacy of **non Clozapine Combination or Augmentation Treatment** (treatment with a variety of psychotropic agents) [18,19] . There is, however, substantial evidence for potential for harm.
- If clozapine cannot be used (e.g. due to toxicity, intolerance or refusal), consider antipsychotic LAI if not previously used.
- Follow GMC and RCPsych guidance if prescribing medicines 'off-label'.

Violence and Aggression

For guidance on the treatment of violence and aggression with medication refer to BSMHFT's *'Rapid Tranquilisation Policy'*.

References

(1) NICE CG178 Psychosis and schizophrenia in adults: treatment and management, February 2014. (Checked & not updated by NICE, surveillance report, November 2017).

(2) Kinon BJ et al., Schiz Res. 2010.doi.10.1016/j.schres.2008.02.021

(3) Leucht S et al., Lancet 2013;382:951-62

(4) Lieberman JA et al.,NEJM 2005;353:1209-23

(5) Tihonen J et al., Am J Psych 2001 doi 10.1176/apt.ajp.2001.10081224

(6) Leucht et al., Lancet 2012;379:2063-2071

(7) Subotnik KL et al., JAMA 2015;72(8):822-9

(8) Wahlbeck et al., Cochrane Database Systematic Reviews 2000;(2):CD000059

(9) Tuuainen et al., Cochrane Database Systematic Reviews 2000;(2):CD000966

(10) Agid 0 et al., J Clin Psychiatry 2011; 72(11):1439

(11) Robinson D et al., Arch Gen psych 1999;56:2063-71

(12) Yoshimura et al., Psychiatry Research 2017;250:65-70

(13) Kerwin and Bolonna Advances in Psych Treatment 2005;11:101-6

(14) Barber et al., Cochrane Systematic Review 2017,CD006324

(15) Tihonen J et al., Schizophrenia Res 2009; 109:10-14

(16)Consensus Statement on High Dose Antipsychotic Medication. RCPsych CR190, 2014

(17) Davis and Chen, J Clin Psychopharmacol 2004

(18) Galling et al., World Psychiatry 2017;16:77-89

(19) Correll et al., JAMA Psychiatry 2017;74;675

Appendix 1: Minimum Effective Doses for Oral Antipsychotics

Drug	First episode	Multi-episode
FGAs		
Chlorpromazine	200mg	300mg
Haloperidol	2mg	4mg
Sulpiride	400mg	800mg
Trifluoperazine	10mg	15mg
SGAs		
Amisulpride	300mg	400mg
Aripiprazole	10mg	10mg
Lurasidone	40mg HCL / 37mg base	40mg HCL / 37mg base
Olanzapine	5mg	7.5mg
Quetiapine	150mg (but higher doses often used)	300mg
Risperidone	2mg	4mg

Appendix 2: Monitoring of Antipsychotic Drugs

Monitoring stage	**Baseline**	**During Initiation**	**At three months**	**At Annual Review**
Monitoring setting	**Secondary care**	**Secondary care**	**GP/outpatients clinic**	**GP/outpatients clinic**
Who undertakes the monitoring	Undertaken by specialist initiating medication	Undertaken by specialist initiating medication	Undertaken by specialist initiating medication or by GP with prior agreement	Undertaken by GP unless prescribing is retained by the specialist
Weight/BMI				
Pulse				
Blood Pressure				
Blood Glucose/HbA1c				
Blood lipids				
U&Es				
Renal Function				
Full Blood Count				
Liver Function tests				
Prolactin				
ECG (if indicated in the SPC)				

Appendix 3: Approximate Equivalent Doses for FGAs and SGAs

The values should be used as a rough guide, alongside clinical judgement

Drug	**Equivalent dose (consensus)**	**Range of values in literature**
Chlorpromazine	100mg/day	Reference
Flupenthixol	3mg/day	2-3mg/day
Flupentixol depot	10mg/week	10-20mg/week
Fluphenazine depot	5mg/week	1-12.5mg/week
Haloperidol	2mg/day	1.5-5mg/day
Haloperidol depot	15mg/week	5-25mg/week
Pericyazine	10mg/day	10mg/day
Perphenazine	10mg/day	5-10mg/day
Pimozide	2mg/day	1.33-2mg/day
Pipothiazine depot	10mg/week	10-12.5mg/week
Sulpiride	200mg/day	133-300mg/day
Trifluoperazine	5mg/day	2.5-5mg/day
Zuclopenthixol	25mg/day	25-60mg/day
Zuclopenthixol depot	100mg/week	40-100mg/week

Comparing potency of FGAs with SGAs introduces more uncertainty: very approximately 100mg Chlorpromazine is equivalent to 1.5mg Risperidone

Drug	**Approximate equivalent dose**
Amisulpride	400mg
Aripiprazole	15mg
Lurasidone	80mg (74mg)
Olanzapine	10mg
Paliperidone LAI	75mg/month
Quetiapine	300mg
Risperidone	3mg
Risperdone LAI	37.5mg/2 weeks