**Mental Health Services**
**Prescribing Management Group**

# Combination Antipsychotic & Augmentation Guidance

## Introduction/background

It has been estimated that up to one third of individuals with schizophrenia don't respond to conventional antipsychotics [1,2] and around 40-70% of individuals treated with clozapine fail to obtain an adequate response.[3] Therefore, augmentation of clozapine and other antipsychotics with a second antipsychotic is often encountered in clinical practice.

The evidence-base for combined antipsychotic use however, is poor and its use should be the exception. Antipsychotic combinations should only be given as part of a closely monitored, time-limited treatment plan after more evidence-based approaches have been prescribed.

An augmentation strategy should be guided by available current research, clinical expertise, and the needs and preferences of the patient, with decisions made on a case by case basis. For less well established combinations, consider reviewing the primary references and/or consult with clinical colleagues for advice.

## Optimising monotherapy - before combing antipsychotics, consider;

- ***Time for therapeutic effect***

It is essential that there has been a trial of adequate duration and dose to establish effect, partial response or non-response

- If there is no response to medication after four weeks despite dose optimisation, a change in antipsychotic should be considered.
- Where there is partial response, this should be re-assessed after eight weeks unless there are significant adverse effects. [4]

Some individuals will respond to treatment after a number of months.[5] BAP recommends that for an adequate trial, clozapine monotherapy should be prescribed for 3- 6 months. [6]

- ***Dosing and pharmacodynamics***

All antipsychotics vary in their affinity for $D_2$ receptors and neither the first or second generation antipsychotics are homogenous groups (see Appendix I). To effectively treat the positive symptoms of schizophrenia, antipsychotics need to block at least 60% of $D_2$ receptors (clozapine being the exception).

Effective $D_2$ blockade is achieved at different dose levels and may only be achieved after the concentration is sufficient to block other receptors. When an antipsychotic has stronger affinity for a particular receptor system than for the dopaminergic system, a side effect associated with the blockade of this receptor is likely to occur within the dose range required for antipsychotic efficacy. For example, quetiapine has stronger affinity for histaminergic and alpha-adrenergic receptors than dopaminergic, therefore sedation and postural hypotension are likely to occur within the therapeutic dose range (See Appendix II).

There are subsets of patients who both tolerate and require high levels of $D_2$ antagonism for symptom control and respond to high doses that achieve greater than the traditional degree of $D_2$ receptor occupancy.[7]

- ***Changing antipsychotic monotherapy***

Clozapine should always be considered in treatment resistant schizophrenia where other antipsychotics have failed to elicit an adequate response or caused intolerable adverse effects. Where clozapine is not a viable option, an antipsychotic with a different receptor profile to those previously tried should be



Approved: December 2023
Review date: December 2026 PrescribingManagementGroup.MentalHealth@ggc.scot.nhs.uk

considered prior to combining antipsychotics. For example, switching to a first generation antipsychotic where only second generation antipsychotics have been prescribed previously.

**Antipsychotic augmentation with non-antipsychotic agents should be considered**

Mood stabilisers and/or antidepressants should be considered especially where a mood disturbance is thought to contribute to symptoms. However, where there is not an obvious affective component, a mood stabiliser may also be worth considering in psychosis that has not responded to conventional antipsychotics. Glutamatergic neurotransmission is altered in schizophrenia, therefore lamotrigine with a mechanism of action that inhibits excessive glutamate release may have a potential role as antipsychotic augmentation.[8,9] SIGN recommends lamotrigine augmentation of clozapine for individuals whose symptoms have had an insufficient response to clozapine. [4] There is also some evidence for the effectiveness of lithium as an add-on treatment with antipsychotics for schizophrenia, however a recent Cochrane review indicated that these were low quality studies.[10]

**Principles of combination antipsychotics (**Appendix III antipsychotic treatment flowchart)

The following situations can be considered as appropriate indications for the use of combination antipsychotics;

- Augmentation of clozapine e.g. where clozapine has produced a partial response
- Clozapine is not a viable treatment option e.g. clozapine not tolerated or individual not willing to accept clozapine
- Switching from one antipsychotic to another e.g. temporary cross-titration
- During an acute exacerbation of illness i.e. used as a temporary measure
- Managing adverse effects e.g. hyperprolactinaemia or weight gain

**Consider pharmacodynamics and pharmacokinetics when considering combinations** [11]

- ***Avoid pharmacodynamic redundancy***

Using two drugs with the same or overlapping mechanism of action e.g. two potent $D_2$ blockers, where the addition of one drug to another is unlikely to give additional clinical benefit but will increase the risk of adverse effects.

- ***Consider pharmacodynamic interactions***

Using two drugs with opposing mechanism of action e.g. the use of aripiprazole (a partial $D_2$ agonist) with a potent $D_2$ blocker. Aripiprazole will displace full $D_2$ antagonists and potentially lead to a worsening of positive symptoms.

- ***Consider pharmacokinetic interactions***

Where one drug increases the metabolism of another e.g. carbamazepine induces metabolism of certain antipsychotics and reduces their plasma levels.

**Clozapine and non-clozapine augmentation**

The evidence-base for antipsychotic augmentation is poor. Evidence of effectiveness and side-effect burden of antipsychotic combinations (excluding clozapine) is not robust enough to allow recommendations for combinations to be made. However combinations may be useful in some clinical situations. Choice of augmenting antipsychotic should be based on complementary receptor profiles in terms of optimising therapeutic effect and minimising adverse effects.

There is somewhat better evidence for augmenting clozapine compared to other antipsychotics with some randomised controlled trials of clozapine augmentation; however a recent Cochrane review suggested that the results were limited and evidence is of low or very low quality. [12]

Augmentation strategies with clozapine should only be considered after clozapine treatment has been administered for an adequate period of at least 3 months.[6] It may be appropriate to consider the use of therapeutic drug monitoring of clozapine when optimising the dose and prior to augmentation (Clozapine TDM guide).

When choosing the augmenting antipsychotic, consideration should be given to antipsychotics with a complementary receptor profile to clozapine, and a side effect profile that minimises adverse effects such as sedation, weight gain and metabolic effects. An adequate trial of clozapine augmentation with another antipsychotic should be at least 10 weeks in duration.[4,6]

**The use of more than two antipsychotics should prompt an immediate review of medication.**

**Antipsychotic augmentation for adverse effect management**

Consideration may be given to using a second antipsychotic in order to manage the adverse effects of the original antipsychotic. For example;

- the addition of aripiprazole to individuals treated with clozapine to minimise side effects such as sedation, weight gain and other metabolic parameters [13]
- low dose aripiprazole* to manage symptomatic hyperprolactinaemia. [14,15]

*Aripiprazole (as a partial agonist) at relatively low doses (~10mg) can achieve >80% $D_2$ occupancy and will displace full $D_2$ antagonists and therefore may lead to a worsening of positive symptoms. The optimum dose of aripiprazole for managing symptoms of hyperprolactinaemia is approximately 5mg daily (range 3-6mg). [14,15] There is no rationale for using higher doses as these may have a detrimental impact on mental state.

**Polypharmacy risks**

Combinations of antipsychotics may increase the likelihood of adverse effects. Therefore, being aware of potential adverse effects of both antipsychotics is important when choosing suitable combinations and managing any risks appropriately. Consider the potential for high dose antipsychotic therapy when combining antipsychotics (High Dose Antipsychotic Monitoring Policy).

**Consent and documentation**

Good record-keeping and documentation is fundamental to all prescribing practices. When using antipsychotic augmentation strategies, it is essential to **RECoRD;**

- **R**ationale for treatment
- **E**vidence-base for combination where appropriate
- **Co**nsent - the patient and/or carer's consent (and/or compliance with statutory treatment plans) Include the key elements of the discussion with the patient and/or carer regarding risks/ benefits of treatment and alternative treatments where appropriate
- **R**eview- the process and timescale for ongoing review of treatment with consideration to using symptom and side effect rating scales to objectively assess response and adverse effect burden
- **D**ocument all of the above in the patient's clinical notes

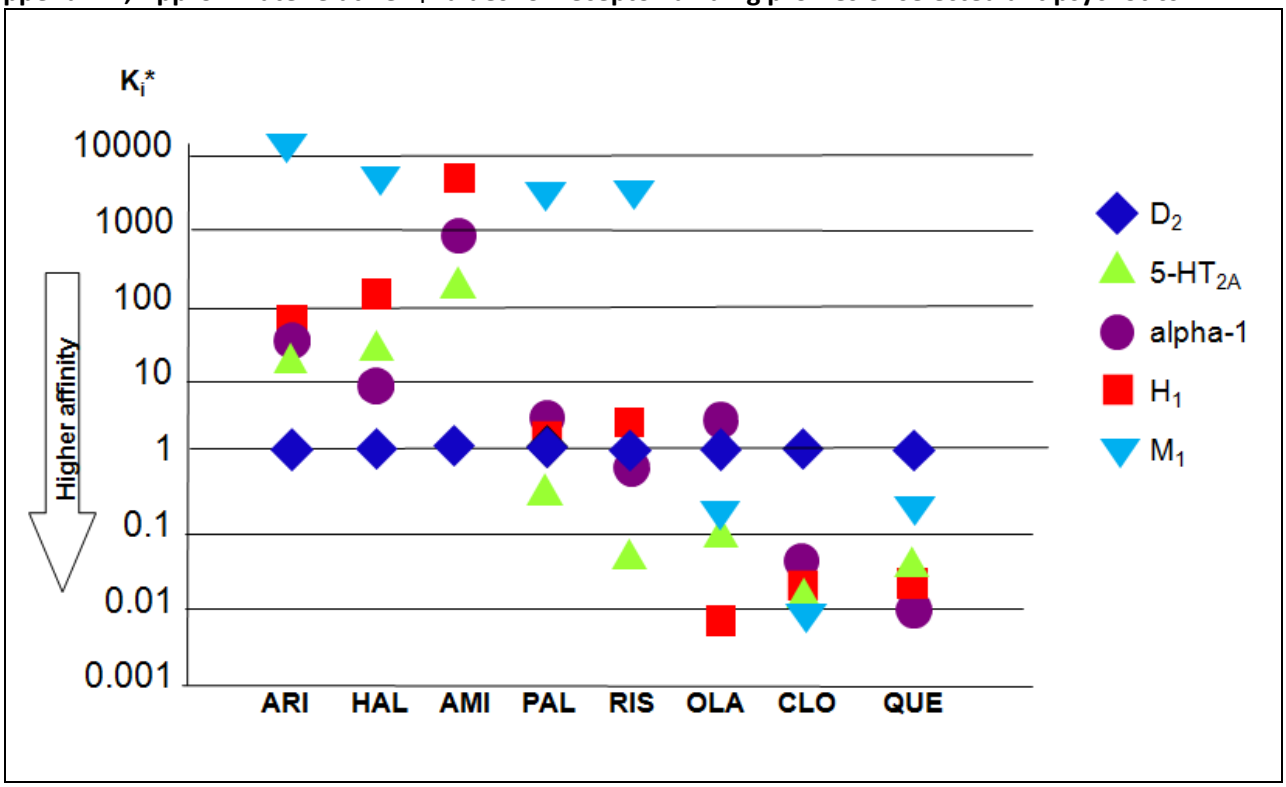
Audit criteria for reviewing current practice is available in Appendix IV.

**Appendix I; Receptor profiles of various antipsychotics** (adapted from Bazire 2018[16])

| | $D_2$ | $5HT_{2a}$ | $M_1$ | $\alpha_1$ | $H_1$ |
|---|---|---|---|---|---|
| **amisulpride** | +++ | Ø | Ø | Ø | Ø |
| **aripiprazole** | PAg | Antag | Ø | Ø | Ø |
| **chlorpromazine** | + | +++ | ++ | +++ | +++ |
| **clozapine** | ++* | +++ | +++ | +++ | +++ |
| **flupentixol** | +++ | ++ | Ø | ? | Ø |
| **haloperidol** | +++ | ++ | + | ++ | + |
| **lurasidone** | +++ | +++ | Ø | ++ | Ø |
| **olanzapine** | ++* | +++ | ++ | ++ | +++ |
| **quetiapine** | ++ | ++ | Ø | ++ | +++ |
| **risperidone** | +++ | +++ | Ø | +++ | ++ |
| **paliperidone** | +++ | ++ | Ø | +++ | +++ |
| **zuclopenthixol** | +++ | +++ | ++ | ++ | + |

+++ - high affinity; ++ - moderate affinity; + - low affinity; Ø - very low affinity;
? - unknown; PAg - partial agonist with very high affinity; Antag – antagonist
*olanzapine & clozapine have $D_2$ limbic selectivity

**Appendix II; Approximate relative $K_i$ values for receptor binding profiles of selected antipsychotics**

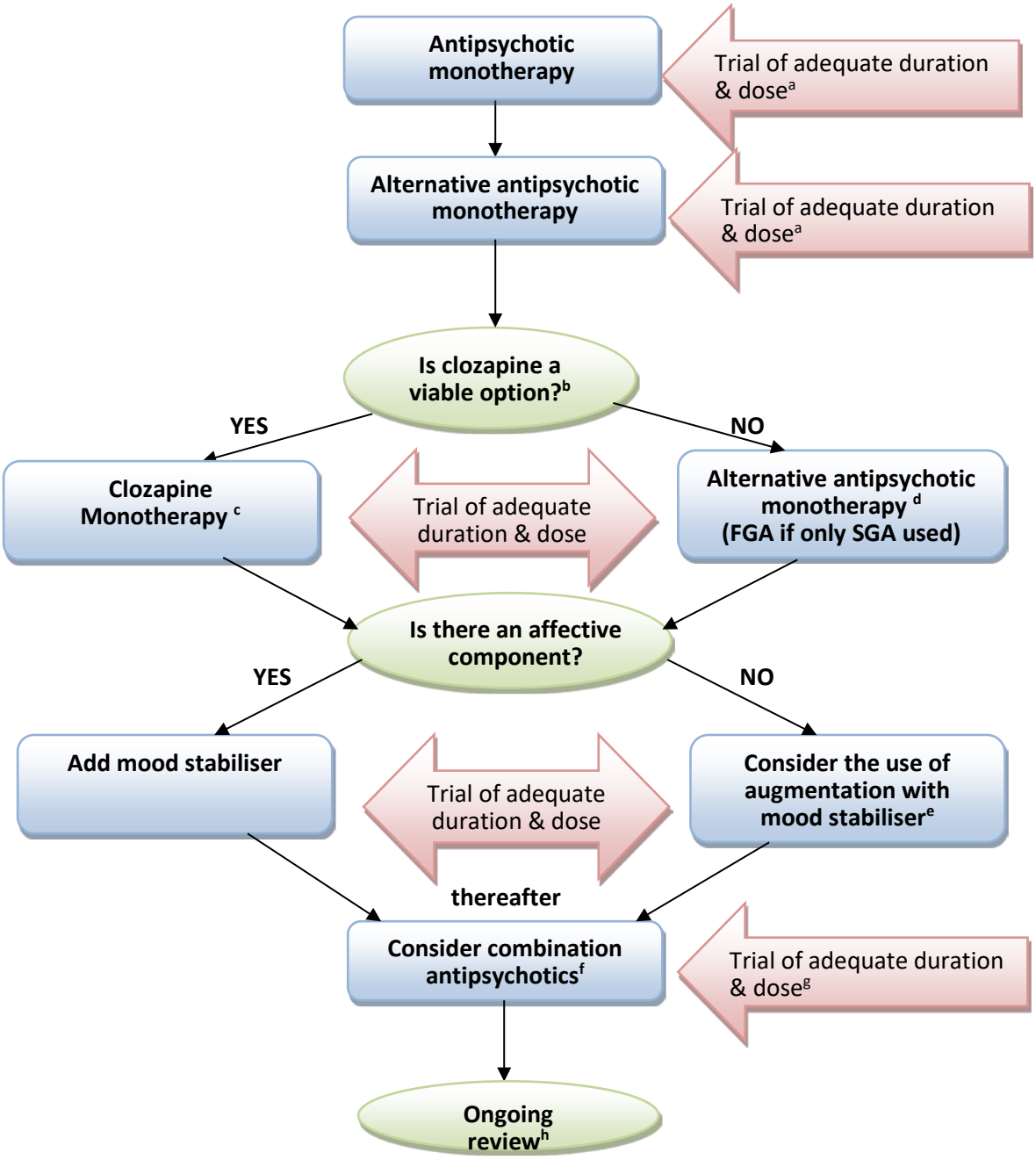



Adapted from Correll Eur Psych 2010[17]

** $K_i$ value for $D_2$ receptor affinity=1 for all antipsychotics.*

*$K_i$ denotes the constant of inhibition- the nanomolar concentration of a given drug required to occupy 50% of the specific receptor type. A low $K_i$ value signifies stronger affinity for the receptor. Where a $K_i$ value is lower than a particular receptor than for dopaminergic receptor i.e. stronger relative affinity, a side effect associated with the blockade of this receptor is likely to occur as part of the antipsychotic treatment.*

**Appendix III; Antipsychotic treatment flowchart**




FGA- first generation antipsychotic; SGA- second generation antipsychotic

a. No response after 4 weeks - consider change in antipsychotic. Partial response- reassess after 8 weeks.
b. Clozapine should always be considered in treatment resistant schizophrenia (ensure trial with at least 2 antipsychotics, one being a SGA).
c. Clozapine monotherapy should be prescribed for 3-6 months before considering augmentation.

d. Switch to an antipsychotic with a different receptor profile.
e. A mood stabiliser may be worth considering in psychosis that has not responded to antipsychotic therapy.
f. Choice of augmenting antipsychotic should be based on complementary receptor profiles in terms of optimising therapeutic effect and minimising adverse effects.
g. An adequate trial of clozapine augmentation should be at least 10 weeks.
h. There should be regular ongoing review (3-6 monthly) of combination antipsychotics and augmentation.

## Appendix IV; Combination Antipsychotic & Augmentation Audit Criteria

| | Criteria | Standard | Exception |
|---|---|---|---|
| 1 | Individuals should have had at least 2 adequate trials of antipsychotic monotherapy prior to considering combination antipsychotics. | 90% | |
| 2 | Clozapine should have been considered prior to a trial of combination antipsychotics. | 80% | Where clozapine is not tolerated, contraindicated or the individual will not consent to its use. |
| 3 | Where there is evidence of an affective component, the use of mood stabiliser/ antidepressant is considered. | 90% | |
| 4 | Where combination antipsychotics are used, the clinical rationale is documented. | 100% | |
| 5 | There is documented evidence of informed consent from patient/carer regarding decision to use combination antipsychotics. | 100% | Unless subject to compulsory treatment under a T3 |
| 6 | There is evidence of regular review (3-6 monthly) of combination antipsychotics. | 90% | |
| 7 | If the combined doses of antipsychotics are greater than 100% BNF maximum, the high dose antipsychotic monitoring policy is implemented | 100% | |

## References;

1. Conley RR, Kelly DJ. Management of Treatment Resistance in Schizophrenia. Biol Psychiatry. 2001;50: 898-911
2. Hellewell JSE. Treatment-Resistant Schizophrenia: Reviewing the options and identifying the way forward. J Clin Psychiatry. 1999; 60(s23):14-19
3. Porcelli S, Balzarro B, Serretti A. Clozapine resistance: Augmentation strategies. Eur Neuropsychopharmacol. 2012; 22: 165–182
4. Scottish Intercollegiate Guidelines Network (SIGN). Management of schizophrenia. Edinburgh: SIGN; 2013. (SIGN publication no. 131). Available from URL: http://www.sign.ac.uk
5. Melzer HY. Treatment of the neuroleptic-nonresponsive schizophrenic patient. Schiz Bull. 1992; 18(3):515-542
6. Barnes TRE et al. Evidence-based guidelines for the pharmacological treatment of schizophrenia: recommendations from the British Association for Psychopharmacology. J Psychopharmacol. 2011; 0(0):1-54
7. Moore BA, Morrissette DA, Meyer JM, Stahl SM, Drug information update. Unconventional treatment strategies for schizophrenias: polypharmacy and heroic doing. BJPsych Bull. 2017; 41:164-168
8. Tiihonen J, Wahlbeck K, Kiviniemi. The efficacy of lamotrigine in clozapine-resistant schizophrenia: A systematic review and meta-analysis. Schiz Res. 2009; 109:10-14
9. Kremer I, Vass A, Gorelik I, Bar G, Blanaru M, Javitt DC, Heresco-Levy U. Placebo-controlled trial of lamotrigine added to conventional and atypical antipsychotics in schizophrenia. Biol Psych. 2004; 56:441-446
10. Leucht S, Helfer B, Dold M, Kissling W, McGrath JJ. Lithium for schizophrenia. Cochrane Database Syst Rev. 2015, Issue 10. Art. No: CD003834
11. Zigman D, Blier P. A framework to avoid irrational polypharmacy in psychiatry. J Psychopharm. 2012 ; 0(0): 1-5
12. Barber S, Olotu U, Corsi M, Cipriani A. Clozapine combined with different antipsychotic drugs for treatment-resistant schizophrenia. Cochrane Database Syst Rev. 2017, Issue 3. Art. No: CD006324
13. Srisurapanont M, Suttajit S, Maneeton N, Maneeton B. Efficacy and safety of aripiprazole augmentation of clozapine in schizophrenia: A systematic review and meta-analysis of randomized-controlled trials. J Psych Res. 2015; 62:38-47 62

14. Yasui-Furukori N, Furukori H, Sugawara N, Fujii A, Kaneko S. Dose-dependent effects of adjunctive treatment with aripiprazole on hyperprolactinemia induced by risperidone in female patients with schizophrenia. J Clin Psychopharmacol. 2010;30: 596-599
15. Gupta S, Lakshmanan DEM, Khastgir U, Nair R Management of antipsychotic-induced hyperprolactinaemia. BJPsych Advances. 2017; 23:278–286
16. Bazire S. Psychotropic Drug Directory 2018. Lloyd-Reinhold Publications
17. Correll CU. From receptor pharmacology to improved outcomes: individualising the selection, dosing, and switching of antipsychotics. Eur Psych. 2010; 25: S12-S21