

## Clozapine Augmentation

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Although clozapine is indicated for the treatment of refractory schizophrenia, there will still be a proportion of patients who will not respond adequately at therapeutic doses. As most patients on clozapine have no viable monotherapy options left, one strategy that is often explored is augmentation of clozapine treatment with another agent.

### **The premise behind certain clozapine augmentation strategies**

Clozapine has a relatively low dopamine D2 receptor occupancy. Augmenting clozapine with antipsychotics that have a higher affinity for D2 receptors attempts to facilitate an additive antipsychotic effect by covering a larger range of receptor profiles. Increasing the D2 receptor occupancy however, increases the likelihood of a patient experiencing extrapyramidal side effects and developing tardive dyskinesia.

Another hypothesis that has been explored in clozapine augmentation is the glutamate hyperfunction hypothesis, which suggests that patients with schizophrenia have dysfunctional glutamatergic neuro-transmission. This has led to trials investigating whether lamotrigine, a glutamate excess release inhibitor, may be effective in the augmentation of clozapine.

Other strategies involve the use of an agent, which may interact with clozapine resulting in

higher clozapine levels, such as risperidone or a selective serotonin reuptake inhibitor (SSRI). How this relates to clinical benefit as opposed to just increasing the dose of clozapine is unclear.

### **Is there any evidence for augmentation?**

In clinical practice, the use of combination antipsychotics, including clozapine, is not uncommon, however, there is limited documentation on efficacy and safety of these practices available in the current academic literature.

There has only been one positive double-blind randomised trial involving clozapine augmentation with an antipsychotic. The antipsychotic involved was sulpiride, which is not available in Australia.

More research is required to establish the efficacy and safety of the often expensive clozapine augmentation strategies.

It is important to note that the addition of another antipsychotic to an existing clozapine regimen will increase the risk of a patient developing agranulocytosis. This risk is further complicated if the drug is given as a depot.

The following tables summarise the available evidence found in various psychotropic texts, journal articles and review articles relating to clozapine augmentation efficacy and safety.

## ANTIPSYCHOTICS

OPTION	EVIDENCE	COMMENTS
<b>RISPERIDONE</b> (1-6mg)	<p>One Single Blind Study<sup>1</sup></p> <ul style="list-style-type: none"> <li>- All patients (N=40) in the study, randomised to either clozapine/risperidone or clozapine /placebo, showed clinical improvement by BPRS (Brief Psychiatric Rating Scale) and CGI(Clinical Global Impression), though patients on risperidone combination had a significantly greater improvement in BPRS.<sup>1</sup></li> </ul> <p>Three Open Trials<sup>2,3,4</sup></p> <ul style="list-style-type: none"> <li>- One 4 week trial (N=12) found no patients responded to this combination<sup>2</sup>.</li> <li>- One 12 week trial (N=13) found improvement in 10 patients on this combination<sup>3</sup>.</li> <li>- One 4 week trial (N=12) found significant reduction in symptoms in 10 patients on this combination<sup>4</sup>.</li> </ul> <p>Twelve Case Reports<sup>5,6,7,8,9,10</sup></p> <ul style="list-style-type: none"> <li>- Ten of the case reports described improvement in patients' positive or positive and negative symptoms on this combination.</li> </ul>	<ul style="list-style-type: none"> <li>• Risperidone may increase plasma concentrations of clozapine due to competitive inhibition of the CYP2D6 enzyme<sup>11,12,13</sup>.</li> <li>• This combination has been shown in one study to result in a moderate elevation of serum prolactin levels and may possibly affect a patient's weight and Body Mass Index (BMI) more than the effect of clozapine alone<sup>14</sup>.</li> <li>• There have been single case reports of arrhythmia<sup>15</sup>, worsening of hoarding behaviour<sup>16</sup>, agranulocytosis<sup>17</sup> and a mild form of neuroleptic malignant syndrome (NMS)<sup>18</sup>, in patients on this combination.</li> </ul>
<b>OLANZAPINE</b> (10-15mg/day)	<p>Three Case reports<sup>19,20</sup></p> <ul style="list-style-type: none"> <li>- Improvement in psychiatric symptoms was seen in all three cases on a clozapine/ olanzapine combination.</li> </ul>	<ul style="list-style-type: none"> <li>• Inadequate evidence available for this combination.</li> <li>• Potential for significant weight gain.</li> <li>• Two reported cases of possible NMS in patients receiving this combination<sup>21,22</sup>.</li> </ul>
<b>AMISULPRIDE</b> (400-800mg)	<p>Three Open Trials<sup>23,24,25</sup></p> <ul style="list-style-type: none"> <li>- In one trial (N=9) 6 patients showed clinical improvement and 1 patient developed agranulocytosis<sup>23</sup>.</li> <li>- One trial (N=9) found all patients showed clinical improvement<sup>24</sup>.</li> <li>- One trial (N=5) found that adding amisulpride to clozapine therapy increased the dopamine D2 receptor occupancy. All patients showed clinical improvement<sup>25</sup>.</li> </ul>	<ul style="list-style-type: none"> <li>• Very limited evidence available at the moment to support the use of this combination.</li> </ul>
<b>QUETIAPINE</b> (200-800mg)	<p>One Retrospective Study<sup>26</sup></p> <ul style="list-style-type: none"> <li>- Quetiapine was added to clozapine therapy in 65 treatment-responsive patients in an attempt to limit the impact of clozapine on weight gain and glycaemic control. It did not study the effect of the combination on the symptoms of schizophrenia.</li> </ul>	<ul style="list-style-type: none"> <li>• No evidence from controlled studies concerning risks and benefits.</li> <li>• There is a case report of granulocytopenia with clozapine and quetiapine<sup>27</sup>.</li> </ul>
<b>SULPIRIDE</b> (400-600mg)	<p>One Double Blind Study (N=28)<sup>28</sup></p> <ul style="list-style-type: none"> <li>- Significant improvements in positive and negative symptoms were seen in the clozapine/sulpiride group after 10 weeks.</li> </ul> <p>One Open Trial<sup>29</sup></p> <ul style="list-style-type: none"> <li>- The 10 week open trial (N=6) found a remarkable reduction in positive and negative symptoms in 4 patients.</li> </ul> <p>One Case Report<sup>30</sup></p> <ul style="list-style-type: none"> <li>- Marked benefit seen in a patient on clozapine and sulpiride.</li> </ul>	<ul style="list-style-type: none"> <li>• The only antipsychotic combination to be supported by a randomised double blind trial.</li> <li>• Sulpiride not available in Australia</li> <li>• The relationship between sulpiride and amisulpride is unclear.</li> </ul>

OPTIONS	EVIDENCE	COMMENTS
ARIPIPRAZOLE	A new antipsychotic with no published information	<ul style="list-style-type: none"> <li>Clinical trials required to establish its effectiveness in clozapine augmentation.</li> </ul>
CHLORPROMAZINE ( 100-400mg/day)	One Double Blind Study <sup>31</sup> - No significant differences between treatment groups could be demonstrated.	<ul style="list-style-type: none"> <li>No evidence to suggest benefit.</li> <li>Agranulocytosis is listed as a common adverse effect of chlorpromazine. Combined use with clozapine could increase this risk and is best avoided.</li> </ul>
HALOPERIDOL (Doses not clear)	Two Case Studies <sup>32</sup> - Both patients showed significant improvement.	<ul style="list-style-type: none"> <li>No evidence from controlled studies concerning risks and benefits.</li> </ul>
FLUPHENAZINE (Dose not clear)	One Case Study <sup>32</sup> - Patient showed significant improvement.	<ul style="list-style-type: none"> <li>No evidence from controlled studies concerning risks and benefits.</li> </ul>
PIMOZIDE (2-8mg/day)	One Retrospective Study <sup>33</sup> - All patients in study (N=7) had clinical improvement on this combination	<ul style="list-style-type: none"> <li>No evidence from controlled studies concerning risks and benefits.</li> <li>Pimozide can cause prolonged QT interval, arrhythmias and ECG changes. Combined use with clozapine may increase incidence of cardiac side effects.</li> </ul>

## MOOD-STABILISERS

OPTION	EVIDENCE	COMMENTS
LAMOTRIGINE (25-250mg/day)	One Double Blind Study <sup>34</sup> - Lamotrigine with clozapine was more effective in reducing positive symptoms than placebo with clozapine. No effect on negative symptoms. (N=16) Two Open Trials <sup>35,36</sup> - Both trials (N=6 and N=17) found significant improvement in all patients on combination <sup>35,36</sup> . Four Case Studies <sup>37,38</sup> - 3 cases showed significant decrease in BPRS in patients on this combination <sup>37</sup> , while another case saw improvement in a bipolar patient <sup>38</sup> .	<ul style="list-style-type: none"> <li>Promising evidence that this combination may be useful in partial or non-responders to clozapine.</li> <li>There is one case report of lamotrigine causing elevated clozapine levels, with no clinical improvement in patient<sup>39</sup>.</li> </ul>
VALPROATE (Doses not clarified)	One Retrospective Study <sup>40</sup> - The combination was efficacious and well tolerated in the majority of patients (N=55)	<ul style="list-style-type: none"> <li>No evidence from controlled studies to suggest benefit.</li> <li>Potential for significant weight gain.</li> <li>Case reports of oversedation<sup>41</sup>, increased risk of neutropenia and agranulocytosis<sup>42</sup>, hepatic encephalopathy<sup>43</sup> and small increases in plasma concentrations of clozapine<sup>44</sup>, in patients on this combination.</li> </ul>
CARBAMAZEPINE	No information found	<ul style="list-style-type: none"> <li>No evidence at all to suggest a benefit.</li> <li>Carbamazepine can decrease clozapine levels<sup>45,46</sup>.</li> <li>Combination is best avoided as increases risk of serious haematological adverse effects.</li> </ul>

OPTION	EVIDENCE	COMMENTS
LITHIUM (Commenced on 600mg/day, adjusted according to lithium levels)	One Randomised Controlled Trial(N=20) <sup>47</sup> - Improvement in 10 patients with schizoaffective disorder, though no improvement in 10 patients with schizophrenia on this combination.	<ul style="list-style-type: none"> <li>Limited evidence available to suggest benefit.</li> <li>Case reports of reversible neurotoxicity<sup>48</sup>, diabetic ketoacidosis<sup>49,50</sup>, seizures<sup>51</sup> and apparent NMS<sup>52</sup> with this combination.</li> </ul>
TOPIRAMATE (200-300mg/day)	Two Open Trials <sup>36,53</sup> - No significant improvement seen in any patients on this combination (N=9) in one trial <sup>36</sup> , while deterioration was seen in all patients in the other trial (N=4) <sup>53</sup> . One Case Study <sup>54</sup> - Worsening of psychosis on this combination.	<ul style="list-style-type: none"> <li>Although it has been suggested that topiramate may induce weight loss in clozapine patients, it appears that it may actually worsen psychosis and should be used with caution.</li> </ul>
GABAPENTIN	No information found	<ul style="list-style-type: none"> <li>No evidence at all to suggest a benefit.</li> </ul>

## OTHERS

OPTION	EVIDENCE AND COMMENTS
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)	<ul style="list-style-type: none"> <li>Only one double-blind controlled trial with an SSRI (fluoxetine) was found. It found this combination had no significant improvement in psychotic symptoms<sup>55</sup>.</li> <li>There are case reports regarding fluoxetine, fluvoxamine, sertraline and paroxetine with some citing clinical improvement, some no improvement and others reported adverse effects<sup>56,57,58,59,60</sup>.</li> <li>SSRIs can interact with clozapine to increase clozapine levels. Citalopram appears the least likely to do so, and fluvoxamine the most likely to do so. This interaction is sometimes utilised to increase clozapine levels to give a greater therapeutic response. How this equates to clinical benefit as opposed to just increasing the dose of clozapine needs to be clarified.</li> <li>Although rare, SSRIs can also cause blood dyscrasias.</li> <li>There is limited evidence to support using SSRIs for augmentation of clozapine and care should be taken due to their potential to increase clozapine levels.</li> </ul>
ELECTROCONVULSIVE THERAPY (ECT)	<ul style="list-style-type: none"> <li>The use of ECT with clozapine is not contraindicated, however caution must be taken as clozapine lowers the seizure threshold in a dose-dependent manner.</li> <li>No controlled studies concerning risks and benefits have been carried out.</li> <li>One retrospective study found 67% of patients reviewed (N=36) benefited from combined clozapine and ECT treatment<sup>61</sup>. Another retrospective study (N=7) found a 27% improvement in total BPRS<sup>62</sup>.</li> <li>There have also been a few case reports of clinical improvement in patients receiving both clozapine and ECT<sup>63,64,65</sup>, although improvement may not necessarily be sustained<sup>65</sup>.</li> </ul>
FISH OIL (1-4g Eicosapentaenoic Acid [EPA]. Each 1g fish oil capsule contains approx 180mg EPA depending on brand)	<ul style="list-style-type: none"> <li>Case reports and prospective trials suggest possible benefit in schizophrenia, including patients on clozapine, a summary of which can be found in Maudsley prescribing guidelines<sup>66</sup>.</li> </ul>

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