222 - Clozapine augmentation

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220 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 1 Optimising clozapine treatment Using clozapine alone Target dose (dose is best adjusted according to patient tolerability and plasma level) ■ ■Average dose in UK is around 450mg/day1 ■ ■Response usually seen in the range 150–900mg/day2 ■ ■Lower doses required in the elderly, females, people of Asian or Native American heritage, non-smokers, and those prescribed certain enzyme inhibitors3,4 ■ ■Genetic testing of CYP enzymes accurately predicts therapeutic dose5 Plasma levels ■ ■Most studies indicate that threshold for response is in the range 350–420mcg/L.6,7 Threshold in some may be as high as 500mcg/L.8 One study suggests a minority of patients only respond at levels between 500 and 1000mcg/L.9 ■ ■In male smokers who cannot achieve therapeutic plasma levels, metabolic inhibitors (fluvoxamine10,11 or cimetidine,12 for example) can be co-prescribed, but extreme caution is required13 ■ ■Importance of norclozapine levels not established. Clozapine/norclozapine ratio is not a reliable indicator of partial adherence nor of clozapine metabolism.14 Clozapine augmentation Clozapine augmentation has become common practice because inadequate response to clozapine on its own is a frequent clinical event. The evidence base supporting augmentation strategies is fairly large but, despite more than 50 reviews and meta-analyses on the subject, it remains insufficient to allow the development of any algorithm or schedule of treatment options.15 In practice, the result of clozapine augmentation is often disappointing and substantial changes in symptom severity are rarely observed. This clinical impression is supported by the equivocal results of many studies, which suggest a small effect size at best. Network meta-analyses examining pharmacological augmentation options often draw conclusions based on only a few studies of dubious merit and may come to different conclusions.16–19 That mirtazapine augmentation has the largest effect size (and the addition of memantine, the second largest) is something most recent systematic reviews agree on17–19 although, with both strategies, the supporting evidence was, at best, weak. Meta-analyses of antipsychotic augmentation of clozapine suggest either no effect,20 a small effect in long-term studies,21 a very small effect overall22 or small effects in specific symptom domains.23 Few high--quality studies in this area exist – when only large, high- quality studies are included, most meta--analyses report no benefit to pharmacological augmentation.24 This is consistent with imaging studies – investigations into dopaminergic activity in refractory schizophrenia suggest there is no overproduction of dopamine.25,26 Dopamine antagonists are thus unlikely to be effective. All augmentation attempts should be carefully monitored and, if no clear benefit is forthcoming,

abandoned after 3–6 months. The addition of another drug to clozapine treatment might be expected to worsen overall adverse effect burden, so continuing ineffective treatment is only likely to be detrimental. In some cases, however, the addition of an augmenting agent may reduce the severity of some adverse effects (e.g. weight gain, dyslipidaemia – see below) or allow a reduction in clozapine dose. The addition of aripiprazole to clozapine may be particularly effective in reversing metabolic effects.27,28 International consensus guidelines recommend (after optimising plasma levels) tailoring augmentation agent choice to residual symptoms, and adding amisulpride or aripiprazole

Schizophrenia and related psychoses CHAPTER 1 for positive symptoms, antidepressants for negative symptoms, and mood stabilisers for suicidal ideation or aggression.24 Recent data on cariprazine suggest particular benefit on negative symptoms unresponsive to clozapine.29–32 Table 1.52 shows suggested treatment options (in alphabetical order) where 3–6 months of optimised clozapine alone at maximum tolerated dose has provided unsatisfactory benefit.
Table 1.52 Suggested options for augmenting clozapine. Option Comment Add amisulpride33–40 (400–800mg/day) Some evidence and experience suggest that amisulpride augmentation may be worthwhile. Five small RCTs (not all positive), the largest of which showed some benefit to positive symptoms and cognition, two of which found an increased adverse-effect burden, including cardiac adverse effects.41,42 May allow clozapine dose reduction.43 Add antipsychotic long-acting injection15,44–48 Case series and observational studies suggest benefits to residual symptoms as well as number and length of hospitalisations. Appears to be well tolerated. Does not protect against relapse if clozapine is not taken. Add aripiprazole27,49–52 (15–30mg/day) Very limited evidence of therapeutic benefit, although a meta-analysis suggests some effect.53 Reduces weight and LDL cholesterol.53 LAI has been used.54,55 Add cariprazine56 Three small case series and one pilot study suggest benefit, particularly for negative symptoms.29–32 Two case reports of worsening psychosis.57 Add haloperidol51,58,59 (2–3mg/day) Modest evidence of benefit Add lamotrigine60–62 (25–300mg/day) May be useful in partial or non-responders. May reduce alcohol consumption.63 Several equivocal reports.64–66 Some meta-analyses suggest moderate effect size67 but this is largely influenced by two outlying studies.68 Add lurasidone32,69 One case series, one retrospective chart review and a case report. Appears to be well tolerated. Add omega-3 triglycerides70,71 (2–3g EPA daily) Modest, and somewhat contested, evidence to support efficacy in non- or partial responders to antipsychotics, including clozapine Add risperidone72,73 (2–6mg/day) Supported by an RCT but there are also two negative RCTs, each with minuscule response rates.74,75 Small number of reports of increases in clozapine plasma levels. LAI also an option.55,76 Paliperidone LAI has also been used.48,55 Add sodium valproate68,77 (400–800mg/day) Pooled effects from five Chinese RCTs68 suggest improvement in positive symptoms, although studies are mostly of poor quality. Cochrane suggests benefit of adding valproate to antipsychotics in general, especially for excitement and aggression.78 Add sulpiride79 (400mg/day) May be useful in partial or non-responders. Supported by a single randomised trial in English and three in Chinese.80 Overall effect modest. Add topiramate81–85 (50–300mg/day) Two positive RCTs, two negative. Can worsen psychosis in some.61,86 Two meta- analyses including hitherto unknown Chinese data68,87 suggested robust effect on positive and negative symptoms, substantial weight loss but often with psychomotor slowing and attention difficulties. Add ziprasidone88–91 (80–160mg/day) Supported by three RCTs.91,92 Associated with QTc prolongation. Rarely used. Note: consider the use of mood stabilisers and/or antidepressants especially where mood disturbance is thought to contribute to symptoms.93–95 EPA, eicosapentaenoic acid; LAI, long-acting injection; LDL, low-density lipoprotein.

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