224 - Alternatives to clozapine

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226 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 1 Alternatives to clozapine Clozapine has the strongest evidence for efficacy for schizophrenia that has proved refractory to adequate trials of standard antipsychotic medication. About three-quarters of these patients are treatment resistant from the onset of illness.1 Where treatment resistance has been established, clozapine treatment should not be delayed or withheld.2,3 The practice of using successive antipsychotic medications (or the latest) instead of clozapine is widespread but not supported by any research. Where clozapine cannot be used because of toxicity or patient refusal or unwillingness to comply with the mandatory monitoring tests, other drugs or drug combinations may be tried (Table 1.53). In practice, outcome is usually disappointing and long-term data on efficacy and safety are generally lacking. Available data do not allow any distinction between treatment regimens to be drawn, particularly choice of antipsychotic medication,4,5 but it seems wise to use single drugs before trying polypharmacy options. Olanzapine is perhaps the most often used antipsychotic monotherapy, usually in doses above the licensed range. If this fails, then the addition of a second antipsychotic (amisulpride, for example) is a possible next step, although the risk–benefit balance of combined antipsychotic medication regimens remains unclear.6 In people who have stopped clozapine, clozapine reintroduction and olanzapine are the only effective treatments.7 Among unconventional agents, minocycline and ondansetron have the advantage of low toxicity and good tolerability. With advances in the understanding of the neurobiology of TRS, non-dopaminergic treatments are an area of active research. Glutamatergic drugs such as evenamide8 (although bitopertin is inactive),9 5HT2A inverse agonists,10 trace amine-associated receptor 1 (TAAR1) agonists and muscarinic receptor agonists such as xanomeline may hold some promise.11 Many of the treatments listed in Table 1.53 are somewhat experimental and some of the compounds difficult to obtain (e.g. glycine, D-serine, sarcosine, etc.). Before using any of the regimens outlined, readers should consult the primary literature cited. Particular care should be taken to inform patients where prescribing is off-label and to ensure that they understand the potential adverse effects of the more experimental treatments. Table 1.53 Alternatives to clozapine (treatments are listed in alphabetical order – no preference is implied by position in table). Treatment Comments Allopurinol 300–600mg/day (+ antipsychotic)12–15 Increases adenosinergic transmission, which may reduce effects of dopamine. Three positive RCTs.12,13,15 Amisulpride16 (up to 1200mg/day) Single, small open study Antipsychotic polypharmacy Various antipsychotics in combination have been used. Data are limited, mainly in the form of case reports, open and

naturalistic studies. RCTs show no advantage for polypharmacy over monotherapy.17 Aripiprazole18,19 (15–30mg/day) Single RCT indicating moderate effect in patients resistant to risperidone or olanzapine (+ others). Higher doses (60mg/day) have been used.20

Schizophrenia and related psychoses CHAPTER 1 Table 1.53 (Continued) Treatment Comments Asenapine (+ antipsychotic)21 A post-hoc analysis of a phase III extension study showed that add-on asenapine may be beneficial in some patients with TRS Blonanserin (+ antipsychotic)22 Atypical antipsychotic licensed in Japan and Korea. A retrospective cohort study involving 69 patients showed improved PANSS scores with add-on blonanserin23 Cariprazine (+ antipsychotic)24–26 Case reports of successful use of cariprazine as monotherapy or as add-on CBT27 Non-drug therapies should always be considered28 Deep brain stimulation Effectiveness of nucleus accumbens and subgenual anterior cingulate cortex targeted deep brain stimulation demonstrated in 4 of 7 patients with TRS29 D–Alanine 100mg/kg/day (+ antipsychotic)30 Glycine (NMDA) agonist. One positive RCT. D–Serine 30mg/kg/day (+ olanzapine)31 Glycine (NMDA) agonist. One positive RCT. D–Serine up to 3g as monotherapy32 Improved negative symptoms in one RCT, but inferior to high-dose olanzapine for treatment of positive symptoms ECT33 Open studies suggest moderate effect, as does a retrospective study.34 Often reserved for last-line treatment in practice but can be successful in the short35 and long36 term. A 2024 RCT was negative.37 Estradiol 100–200mcg transdermal/day (+ antipsychotic)38 Oestrogens may be psychoprotective and/or antipsychotic in women of child- bearing age especially on positive symptoms, at higher doses.39 Contraindications include being post-menopausal, history of VTE, stroke, breast cancer, migraine with aura. Unopposed estradiol increases risk of endometrial hyperplasia and malignancy – consult an endocrinologist. Evidence in men is lacking. Famotidine 100mg bd + antipsychotic40 H2 antagonist. One short (4-week) RCT suggested some benefit in overall PANSS and CGI scale scores. Ginkgo biloba (+ antipsychotic)41 A systematic review of studies published in China showed improvements in total and negative symptoms Lurasidone up to 240mg/day42 (+ vortioxetine) One RCT comparing standard with high-dose lurasidone produced comparable improvements in TRS when given up to 24 weeks.43 Appears to be well tolerated. The addition of vortioxetine to lurasidone was effective in a small case series.44 Memantine 20mg/day (+ antipsychotic)45–47 Memantine is an NMDA antagonist. Two RCTs. The larger of the two (n = 138) was negative. In the smaller (n = 21), memantine improved positive and negative symptoms when added to clozapine. In another study in non-refractory schizophrenia, memantine improved negative symptoms when added to risperidone. Minocycline 200mg/day (+ antipsychotic)48,49 May be anti-inflammatory and neuroprotective. One open study (n = 22) and one RCT (n = 54) suggest good effect on negative and cognitive symptoms. Also, one RCT (n = 52) of augmentation of clozapine showed improvement in some symptoms.50 RCT evidence of neuroprotective effect in early psychosis.51 Mirtazapine 30mg/day (+ antipsychotic)52–54 Two RCTs, one negative,53 one positive.52 Effect seems to be mainly on positive symptoms. N–acetylcysteine 2g/day (+ antipsychotic)40 One RCT suggests small benefits in negative symptoms and rates of akathisia. Another RCT showed benefits in chronic schizophrenia.55 Case study of successful use of 600mg/day.56 A large RCT failed to show any benefit when added to clozapine.57 (Continued)

 Treatment Comments Olanzapine58–63 5–25mg/day Supported by some well-conducted trials but clinical experience disappointing. Some patients show moderate response. Olanzapine 30–60mg/day High-dose olanzapine is more effective than other non-clozapine antipsychotics.64 High-dose olanzapine is not atypical65 and can be poorly tolerated66 with gross metabolic

changes.67 Olanzapine + glycine68 (0.8g/kg/day) Small, double-blind crossover trial suggests clinically relevant improvement in negative symptoms Olanzapine + lamotrigine66,69 (up to 400mg/day) Reports contradictory and rather unconvincing. Reasonable theoretical basis for adding lamotrigine which is usually well tolerated. Ondansetron 8mg/day (+ antipsychotic) A systematic review of RCTs showed improvements in negative symptoms and general psychopathology. Effect on cognition inconclusive.70 Paliperidone LAI Improvement in endocrine and hepatic parameters and lower antipsychotic exposure in a small number of patients switched from clozapine to paliperidone 3-monthly. No data on clinical outcomes.71 Pimavanserin (+ antipsychotics) Clinical improvement with pimavanserin alone or as adjunct to clozapine or other antipsychotics in 10 patients, 6 of whom had failed to respond to clozapine72 Propentofylline + risperidone73 (900mg + 6mg/day) One RCT suggests some activity against positive symptoms Quetiapine74–77 Very limited evidence and clinical experience not encouraging. High doses (>1200mg/day) have been used but are no more effective.78 Raloxifene 60–120mg/day (+ antipsychotic)39 Selective oestrogen receptor modulator. May offer benefits of estradiol without long-term risks, but sexual dysfunction and weight gain may occur.39 Data in non-treatment resistance are rather conflicting, with two overlapping positive trials79,80 and one negative trial.81 One positive RCT in refractory psychosis in women.82 Evidence in men is lacking. Riluzole 100mg/day + risperidone up to 6mg/day83 Glutamate modulating agent. One RCT demonstrated improvement in negative symptoms. Risperidone84–86 4–8mg/day Doubtful efficacy in true TRS but some supporting evidence. May also be tried in combination with glycine68 or lamotrigine60 or indeed with other SGAs.87 Risperidone LAI 50/100mg 2/5288 One RCT showing good response for both doses in refractory schizophrenia. Plasma levels for 100mg dose similar to 6–8mg/day oral risperidone. Ritanserin + risperidone (12mg + 6mg/day) 5HT2A/2C antagonist. One RCT suggests small effect on negative symptoms. Sarcosine (2g/day)89,90 (+ antipsychotic) Enhances glycine action. Supported by two RCTs. Benefits may be in patients with non-TRS.91 Sertindole92 (12–24mg/day) One large RCT (conducted in 1996–68 but published in 2011) suggested good effect and equivalence to risperidone. Around half of subjects responded. Another RCT93 showed no effect at all when added to clozapine. Little experience in practice. Topiramate (300mg/day) (+ antipsychotic)94 Small effect shown in single RCT. Induces weight loss. Cognitive adverse effects likely. Teratogenic. (Continued)

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