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Treatment options for schizophrenia that is poorly responsive to standard antipsychotic treatment

Schizophrenia and related psychoses CHAPTER 1 have plasma drug levels that are well below the range expected for 2mg risperidone or 10mg olanzapine, and these levels may not reach the threshold required for a therapeutic effect. In such patients, a rational case could be made for increasing the dose, provided the patient is informed and the adverse effects are tolerable, to bring the plasma levels into the optimal range for the particular medication. Genetic analysis is helpful in identifying ultrafast metabolisers of aripiprazole, risperidone18 and clozapine.19 Treatment options for schizophrenia that is poorly responsive to standard antipsychotic treatment So what are the treatment possibilities when a lack of therapeutic response is encountered despite a patient's adherence to their medication regimen, the prescription of a dosage at the top of the recommended range, and apparently sufficient plasma drug levels? There are essentially three options: a trial of clozapine, switching to another antipsychotic medication or adding another (non--clozapine) antipsychotic medication. If the patient meets the criteria for clozapine treatment, this is undoubtedly the preferred option. Yet, in a clinical audit of community (not inpatient) practice in the UK, covering some 5,000 patients in 60 different NHS trusts, it was found that 40% of the patients whose illnesses met the criteria for TRS had not received clozapine. For the vast majority (85%) of those who had started clozapine, this had been delayed after the failure of two serial trials of antipsychotic medication for much longer than is advised in most guidelines.20 Significant delay

in the commencement of clozapine treatment has also been found in early intervention in psychosis services.21 However, when reflecting on the findings suggesting delay or underuse of clozapine, it should be borne in mind that among those patients with a diagnosis of treatment--resistant illness who have not had a trial of clozapine, there will be some who have declined this treatment, some who have yet to be persuaded, and some for whom the prescribing clinician considers, perhaps because of factors such as comorbid physical illness, substance use or adverse social circumstances, that another intervention has a more favourable risk–benefit balance.22 Some patients may be averse to the mandatory regular blood testing, the adverse effects and the regular appointments required as part of the clozapine regimen. In such patients, the options are switching to another antipsychotic medication or adding one. The data on switching are sparse. While almost every clinical trial in patients with established schizophrenia has entailed the patient switching from one antipsychotic medication to another, there are no rigorous studies addressing preferred medication switches (e.g. if risperidone fails – what next? Olanzapine, quetiapine, aripiprazole or ziprasidone?). If one looks at only the switching trials which have been sponsored by the drug companies it leads to a rather confusing picture, with the trial results being very closely linked to the sponsors' interest (see 'Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine: an exploratory analysis of head-to-head comparison studies of second-generation antipsychotics').23 Further, switching can be associated with destabilisation of the illness and the emergence of adverse effects, which may be a consequence of stopping the original antipsychotic medication and/or a response to the subsequent medication and/or differences between the pharmacological profiles of the two medications. The extent to which the management of a switch can minimise such problems is not entirely clear, but a gradual cross- tapering approach is usually recommended.24–26

 CATIE, the major US-based publicly funded comparative trial, examined participants whose illness had failed to respond to a first SGA and were then randomly assigned to a different second one.27 Participants switched to olanzapine and risperidone did better than those switched to quetiapine and ziprasidone. This greater effectiveness is supported by a meta-analysis that compared a number of SGAs with FGAs and concluded that, other than clozapine, only amisulpride, risperidone and olanzapine were superior to FGAs in efficacy.28 Further, the findings of a meta-analysis comparing SGAs among themselves suggested that olanzapine and risperidone (in that order) may be modestly more effective than the others.29 Thus, if olanzapine or risperidone have not yet been tried, it would be a reasonable decision to switch to these medications, provided the risk–benefit balance was considered likely to be favourable for the particular patient. Comparing these two medications, the data are somewhat limited. However, a number of controlled and open-label studies do show an asymmetrical advantage, with a switch to olanzapine being more effective than to risperidone.30,31 Such findings have been reinforced recently: a systematic review32 found high--dose olanzapine to be superior to other commonly used FGAs and SGAs, including risperidone, for TRS, while a network meta-analysis33 confirmed olanzapine as the second most effective antipsychotic, behind clozapine, for such illness. The best medication regimen (aside from clozapine) to choose for a patient whose illness has failed trials of olanzapine and risperidone remains unclear. Should one switch to, say, aripiprazole or ziprasidone or even an older FGA, or should another antipsychotic medication be added? Interestingly, studies that have switched patients to aripiprazole for reasons of tolerability (weight gain, etc.) find either no loss of efficacy34,35 or an improvement in symptom severity.24,36 After switching, adding another antipsychotic is probably the most common clinical strategy chosen. A 2022 clinical audit in the

UK37 found that of 4,156 people on acute adult psychiatric wards, 14% were prescribed more than one antipsychotic medication. By far the most common reason for such a prescription was an insufficient response of symptoms and/or behavioural disturbance with antipsychotic monotherapy at standard dosage. A second antipsychotic may also be added for additional properties (e.g. quetiapine for sedation or aripiprazole to decrease plasma prolactin – these matters are discussed elsewhere) but here we are concerned solely with the use of combined anti psychotic medications to increase efficacy. From a theoretical point of view, since all currently available antipsychotic medications (with xanomeline and pimavanserin as exceptions) block D2 receptors (unlike, say, antihypertensive drugs which use different mechanisms) there is a limited rationale for addition. Studies of add-ons have often chosen combinations on the basis of convenience or clinical lore and perhaps the most systematic evidence is available for the addition of a second antipsychotic to clozapine,38–40 a strategy that may be supported by the rationale that since clozapine has relatively low D2 occupancy, increasing its D2 occupancy may yield additional benefits.41 However, a meta-analysis of RCTs comparing augmentation with a second antipsychotic with continuing monotherapy in schizophrenia42 found a lack of double-blind/high- quality evidence for efficacy, in terms of treatment response and symptom improvement, for a range of antipsychotic combinations. Further, compared with antipsychotic monotherapy, combined antipsychotics seem to be associated with an increased adverse-effect

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Revision #1
Created 2026-01-04 20:13:50 UTC by Omar Ayman
Updated 2026-01-04 20:13:50 UTC by Omar Ayman