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Schizophrenia and related psychoses CHAPTER 1 Antipsychotic response – to increase the dose, to switch, to add or just wait – what is the right move? For any clinician actively involved in the care of people with schizophrenia, perhaps the single most common clinical dilemma is what to do when treatment with the current antipsychotic medication seems to be suboptimal (symptoms are well controlled but adverse effects are problematic or the therapeutic response is inadequate). Fortunately, with regard to poor tolerability, the diversity of the available antipsychotic medications means that it is usually possible to find one that has an adverse-effect profile that is more appropriate and more tolerable. With regard to inadequate symptom response, what to do next is a more difficult question. If the illness has not shown sufficient improvement despite serial adequate trials, in terms of dosage, duration and adherence, of at least two antipsychotic medications, then a trial of clozapine should be considered. However, should the person be reluctant to try clozapine, the clinician has four main options: to increase the dose of the current medication, to switch to another anti psychotic medication, to add an adjunctive medication, or just to monitor the illness in the hope that changing external factors will allow recovery. Unfortunately, the evidence base supporting these management options is limited.^{1–3}

Optimal dosage While the optimal doses for FGAs were always a matter of debate, the recommended doses of the SGAs are generally based on careful and extensive (fixed-dose) clinical trials. Despite this, the consensus on optimal SGA dosages has changed over time. For example, when risperidone was first introduced it was suggested that the optimal dose was 6mg or more for all patients. However, subsequently clinical practice moved towards the use of lower doses.⁴ On the other hand, when quetiapine was introduced, 300mg was considered the optimal dose. The overall consensus now is towards higher doses,⁵ although RCT and other evidence does not consistently support this shift.^{5,6} Nonetheless, most clinicians feel comfortable in navigating within the recommended clinical dose ranges for the SGAs. The more critical question is what should be done if the upper limit of the dose range has been reached and, while the individual is tolerating the medication well, there is only limited benefit.

High dosage For antipsychotic medications, the dose-response relationships for the treatment of schizophrenia are not that well defined. Davis and Chen⁷ performed the first comprehensive systematic meta-analysis of relevant dose-response data available up to 2004 and concluded that the average dose that produces maximal benefit was 4mg for risperidone, 16mg olanzapine, 120mg ziprasidone and 10–15mg aripiprazole (they could not determine such a dose for quetiapine using their method). In 2020, Leucht and colleagues⁸ carried out a similar meta-analysis of dose-response in acute schizophrenia and concluded that doses higher than standard doses were not more efficacious. However, they did suggest that for a few medications (such as olanzapine, lurasidone, ziprasidone) with clearly increasing dose curves (i.e. did not plateau), it might be worth testing higher-than-licensed doses in clinical trials. For example, the findings of a

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