16 - Adverse effects

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18 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 1 A small number of RCTs have examined the efficacy of high versus standard dosage in patients with treatment-resistant schizophrenia (TRS).1 Some have demonstrated benefit23 but the majority of these studies are old, the number of patients randomised is small and study design is poor by current standards. Some studies used daily doses equivalent to more than 10g chlorpromazine. One small (n = 12) open study of high- dose quetiapine (up to 1400mg/day) in refractory schizophrenia found modest benefits in a third of patients24 but other, larger studies of quetiapine for such patients have shown no benefit for higher doses.22,23 A further RCT of high-dose olanzapine (up to 45mg/day) versus clozapine for TRS found similar efficacy for the two treatments but concluded that, given the small sample size, it would be premature to conclude that they were equivalent.25 Subsequent systematic reviews of relevant studies addressing high-dose olanzapine for TRS have similarly concluded that while such a regimen may be superior to other, non-clozapine antipsychotic medications, it may be seen as a safe and effective alternative for refractory illness only when clozapine use is not appropriate.26,27 Perhaps the most comprehensive systematic analysis of dose–response28 largely confirmed the observation that the dose–response curve reaches a plateau above a certain dose for nearly all antipsychotic medications, with the possible exceptions of olanzapine and lurasidone. (With these two medications there is some evidence that doses at the upper end of the licensed range are somewhat more effective than lower doses.)14,29 This systematic review also suggested that the doses above which no additional benefit was likely (e.g. risperidone 6.3mg/day; quetiapine 482mg/day) were somewhat higher than the doses of optimal efficacy previously determined (see above). Importantly, however, there was no evidence to support the use of doses of any antipsychotic medication above its licensed dose range. Consensus panel recommendations are broadly in line with clinical trial outcomes. A 2023 international consensus study30 suggested maximum effective doses exceeded licensed doses in only two cases: olanzapine (30mg/day) and quetiapine (800mg/day). A 2023 systematic review of dose–response relationships31 found that the effect of all antipsychotics reached a plateau within the licensed dose range, with the possible exceptions of lumateperone, olanzapine and lurasidone. Adverse effects The majority of adverse effects associated with antipsychotic treatment are doserelated.32 These include EPS,31 weight gain,33 sedation, postural hypotension, anticholinergic effects, QTc prolongation34 and coronary heart disease mortality.35–38 High-dose antipsychotic treatment is clearly associated with a greater adverse-effect burden.16,35,39–41 There is some evidence that antipsychotic dose reduction from a very high (mean 2253mg chlorpromazine equivalents per day) to a high (mean 1315mg chlorpromazine equivalents per day) dose can lead to improvements in cognition and negative symptoms.42

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