59 - Plasma level variations

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56 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 1 network meta-analysis of the dose–response effects of lurasidone in acute schizophrenia suggested that 160mg/day might be the most effective and acceptable dose.9 Several trials have tried to compare high-dose antipsychotic medication with standard dosage. For example, one study10 explored the dose–response relationship of olanzapine in a randomised, double-blind, 8-week, fixed-dose study, comparing doses of 10mg, 20mg and 40mg. While no additional benefit was found with the higher doses (i.e. 40mg was no better than 10mg), there was clear evidence of a greater adverse- effect burden (weight gain and raised plasma prolactin level). Similarly, early studies of risperidone11 compared the usual daily doses of 2mg and 6mg with higher doses, up to 16mg. There was no additional benefit with the higher doses but a clear signal for a greater risk of adverse effects (EPS and raised plasma prolactin). The findings of these studies are in accord with older studies involving fixed doses of haloperidol,12 where 8mg/day is clearly the dose above which no additional benefit is seen.13 Interestingly, the likelihood of inducing EPSEs is not constrained by dose in the same way – the frequency of EPS continues to increase at doses well beyond standard or even high doses.14 Despite the lack of evidence for the benefit of higher doses, it is important to keep in mind that these doses are extracted from group evidence where patients are assigned to different doses, which is a different situation from the clinical one where the prescriber considers increasing the dose only in those patients whose illnesses have failed to respond to the initial dosage regimen. In 1993, Kinon and colleagues15 examined patients who failed to respond to the (then) standard dose of fluphenazine (20mg) and tested three strategies: increasing the dose to 80mg, switching to haloperidol or watchful waiting (on the original dose). All three strategies proved to be equivalent in terms of efficacy. These findings provide little supportive evidence at a group level (as opposed to an individual level) for treatment beyond the recommended dose range. Such RCT evidence is corroborated by the clinical practice norms – Hermes and colleagues examined the CATIE data to identify clinical factors that predicted a prescriber’s decision to increase the dose (within the standard ranges) and found that such decisions were only weakly associated with clinical measures.16 A later trial of lurasidone17 for early, non- responsive schizophrenia showed that after 2 weeks on lurasidone 80mg/day, a dose increase to 160mg/day was associated with significant symptom improvement compared with continuing on lurasidone 80mg/day. However, the clinical implications of these findings are uncertain, given the limitations of the trial: it lasted only 4 weeks, and there was no testing of the intermediate dose of 120mg/day. A 2018 Cochrane systematic review of relevant studies concluded that there was no good-quality evidence that for illness not responding to initial antipsychotic treatment there was any difference between increasing the antipsychotic dose and continuing antipsychotic treatment at the same dose.1 A similar meta-analysis in 20233 concluded that, for early non-responsive schizophrenia,

the evidence for treatment strategies such as dose escalation or switching antipsychotic medication was too limited to allow for any strong clinical recommendations. Plasma level variations There are significant inter-individual variations in plasma drug levels in patients treated with antipsychotic medication. Patients may be encountered who, when receiving medication at the higher end of the dose range (say 6mg of risperidone or 20mg of olanzapine),

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