65 - Pattern of tapering

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332 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 2 Evidence for long-term treatment Although lithium is accepted as the first-line choice for prophylaxis in bipolar disorder,9 evidence for long-term treatment with lithium and other mood stabilisers is derived from discontinuation studies where patients established on these medications were randomised to either continue or cease treatment.10,11 In these studies, lithium was sometimes stopped abruptly. As mentioned, rapid stopping of lithium is likely to produce withdrawal effects, which can include precipitating mood episodes.2 Indeed, in one study abruptly stopping lithium in patients with depression provoked manic episodes in 13%.12 There is evidence that abrupt cessation of other mood stabilisers can also precipitate mood episodes.3 Patients who are discontinued from these medications often demonstrate relapse rates that are greater than in the untreated disorder, suggesting that withdrawal effects may inflate the apparent rate and extent of relapse.2,13 Few maintenance studies extend beyond a 2-year follow-up period. Observational studies (over longer periods) have found lithium to be more effective than other mood stabilisers but these studies are somewhat limited by confounding effects.14 Duration of tapering With lithium, rapid discontinuation (1–14 days) has been shown to produce a much greater risk of relapse than gradual tapering over 15–30 days.15–17 Time to relapse is decreased and the proportion of patients relapsed at study end is greatly increased in the rapid discontinuation group. These robust and reproducible findings support a recommendation that lithium should not be stopped abruptly unless a serious adverse effect occurs, and that withdrawal should take place over at least a month or preferably longer. There are few studies examining the optimal rate or duration of tapering lithium. However, the finding that 50% of relapses occur in the first 3 months after lithium is stopped but then lessen over time2 suggests that this period of 3 months might be required for underlying adaptations to lithium to resolve. One study that discontinued lithium over 2–5 months found higher relapse rates in these patients than in those who stayed on lithium.18 This might conceivably suggest that tapering should be even slower than the 4-week to 3-month period suggested by NICE in the UK.19 Long withdrawal schedules are not unusual in different areas of medicine. Antiseizure drugs are tapered over between 1 month and 4 years in non-psychiatric conditions, with relapse rates increased in the first 6 months before converging with patients continuing with the antiseizure drugs.8 Pattern of tapering Lithium, like all pharmacological agents, conforms to the law of mass action and therefore demonstrates a hyperbolic pattern between dose and pharmacological effect.12 The mode of action of lithium is unknown, however it is known to affect GSK-3. The relationship between the dose of lithium and effect on this target is hyperbolic.13 As for other psychotropic agents this justifies a hyperbolically reducing dose pattern (in order to produce linearly reducing effects on its target receptors), which may be clinically approximated by a proportionate dose reduction (a reduction by the same proportion each step, so that the size of

the reduction becomes smaller and smaller as the total dose gets lower) (Box 2.3).

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