

137 - Withdrawal symptoms

Withdrawal symptoms

Depression and anxiety disorders CHAPTER 3 patients with hepatic dysfunction, as diazepam and other longer-acting drugs may accumulate to toxic levels. Pattern of tapering The relationship between dose of benzodiazepines and their effect on their principal target, the GABA-A receptor, is hyperbolic, as dictated by the law of mass action, with the following implications: ■ ■ Reducing dose by fixed amounts (e.g. 12.5mg in Figure 3.5a) will give rise to increasingly large reductions in GABA-A occupancy. ■ ■ This is consistent with clinical observation that withdrawal symptoms are non-linearly related to dose reduction (e.g. a 1mg reduction of diazepam is tolerable from 20mg but intolerable from 5mg).³⁶ ■ ■ Reducing the diazepam dose by 5mg from 50mg will cause a reduction of 2.3 percentage points of GABA-A occupancy, but a 5mg reduction from 5mg will cause a reduction of 18.3 percentage points. In order to reduce the dose of benzodiazepines by equal amounts of effect at their major target, hyperbolically reducing doses are required (Figure 3.5b): ■ ■ This means that the size of dose reductions should be smaller and smaller as the total dose gets smaller. ■ ■ In practice, these reductions can be most easily calculated based on a proportion of the most recent dose (an exponential pattern): for example, reductions of 10% of the most recent dose every month (so that reductions become smaller and smaller as total dose reduces). Final doses before complete cessation may need to be very small (e.g. less than 1mg of diazepam equivalent). (a) (b) GABA-A occupancy (%) 40 0 50 Diazepam dose (mg) 100 GABA-A occupancy (%) 40 0 50 Diazepam dose (mg) Figure 3.5 (a) Linear reductions of dose cause increasingly large reductions in effect on GABA-A receptor occupancy. (b) Reducing effect on GABA-A receptors by even amounts requires hyperbolically reducing doses of diazepam. Note how small the final doses will be required to be to prevent too large a final 'step down'. Source: Adapted from Brouillet et al. (1991).³⁷

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