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Schizophrenia and related psychoses CHAPTER 1 Pattern of tapering Positron emission tomography demonstrates a hyperbolic relationship between dose of antipsychotic and D2 receptor occupancy.³¹ This hyperbolic relationship applies to other receptor targets of antipsychotics as well (including histaminergic, cholinergic and serotonergic receptors) because it arises from the law of mass action (whereby each additional molecule of a drug has incrementally less effect as receptor targets become saturated).³² The nature of this relationship is often obscured by the habit of plotting dose-response curves on semi-logarithmic axes.³² A hyperbolic relationship between dose of antipsychotic and its therapeutic effects (as measured by symptoms scales) has also been shown,³³ suggesting that clinical response mirrors the neurobiological pattern of effects. This brings into question the rationale for a linear reduction of antipsychotic dose – for example, a reduction from 20 to 15 to 10 to 5 to 0mg of olanzapine. Although this regimen appears logical, the hyperbolic relationship between dose and effect on D2 blockade dictates that these linear dose decreases will produce increasingly larger reductions of D2 blockade (and there may be clinical consequences of this; Figure 1.3a). Indeed, the reduction of dose from 5 to 0mg will produce a reduction in D2 blockade (52.6%) that is larger than that produced by the reduction from 40 to 5mg of olanzapine (37.3%). These increasingly large reductions in D2 blockade are more likely to provoke relapse.^{34,35} Linear or ‘evenly spaced’ reductions in D2 blockade require hyperbolically reducing doses of antipsychotic (Figure 1.3b).³⁶ These hyperbolic reductions are approximated by sequential halving of dose: for example, olanzapine doses of 20mg, 10mg, 5mg, 2.5mg, 1.25mg, 0.6mg, 0.3mg, 0mg produce roughly 15 percentage point reductions in D2 blockade. This pattern of reduction may be less likely to provoke relapse because it avoids large increases in dopaminergic signalling. Example regimens are shown in Table 1.27 and Box 1.1. Preliminary support for this approach comes from a study in which antipsychotics were reduced hyperbolically by on average 40% in people with chronic psychotic disorders, with no difference in relapse rates from the maintenance group but improved clinical outcomes.³⁰

(a) (b) 60 D2 occupancy (%) 0 10
Olanzapine dose (mg) 40 100 60 D2 occupancy (%) 0 10
Olanzapine dose (mg) 40 Figure 1.3 (a)
Linear dose reductions of olanzapine cause increasingly large reductions in D2 dopaminergic receptor blockade. The relationship between dose of olanzapine and D2 blockade is derived from the line of best fit from meta-analysis of positron emission tomography studies.³¹ (b) Linear reductions of D2 dopaminergic occupancy (in this case 20% reductions) correspond to hyperbolically decreasing doses of olanzapine. The doses in this case correspond to 6.9mg (80% D2 occupancy), 2.0mg (60% D2 occupancy), 0.82 mg (40% D2 occupancy) and 0.30mg (20% D2 occupancy). Approximations to this regimen that correspond to available formulations are given in the text.

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