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COMMENTARY

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Non-equipotent doses partly explain differences among antipsychotics – implications of PET studies

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The term "atypical antipsychotic", coined to describe the pharmacology of clozapine, originally implied an *absolute*, qualitative distinction from other antipsychotics. In contrast, Drs. Remington and Kapur subscribe to the view that all new antipsychotics are "atypical" by virtue of their *relative* merits as compared to common clinical treatments. Their main conclusion is that "all the newer antipsychotics are superior on EPS" (extrapyramidal syndromes). We argue that the reported differences among "classical neuroleptics" and "novel" or "atypical" antipsychotics may largely be understood in terms of non-equipotent dosing.

It is widely accepted that the dopamine system is a target for antipsychotic drug action. Indeed, every current antipsychotic has affinity for the D_2 dopamine receptor. Studies with positron emission tomography (PET) have established that schizophrenic patients responding to conventional doses of classical neuroleptics have a uniformly high (70–89%) D_2 receptor occupancy (Farde et al. 1988, 1992). There is an increased risk of EPS at D_2 receptor occupancy above 80%. Based on these findings, we have suggested that 70–80% should be an optimal interval for D_2 receptor occupancy.

In the absolute sense, clozapine remains the only drug that satisfies the criterion of absence of EPS throughout the clinical dose range (Kane et al. 1988; Pickar et al. 1992). In contrast to patients treated with conventional antipsychotics, patients responding to a wide dose range of clozapine had low (20–67%) D_2 receptor occupancy (Farde et al. 1989; Nordström et al. 1995). Thus, the absence of EPS in clozapine-treated patients could be explained solely by the fact that clinical doses of clozapine induce D_2 receptor occupancy far below the 80% required to induce EPS.

Remington and Kapur emphasize that diminished EPS is a "sine qua non" for a drug to be designated "atypical". If atypicality is defined in a relative sense by "diminished" rather than "absent" EPS, the dose-response curve of the reference compound becomes crucial. All new antipsychotics have been compared to haloperidol. The doses of haloperidol in these trials have usually been 10–20 mg/day, probably reflecting current clinical practice in many countries. However, the optimal, minimal effective dose of haloperidol has never been evaluated using the standard approaches of modern clinical trials. Interestingly, evidence from clinical studies over the last decade has suggested that considerably lower doses of haloperidol may be as effective but with a reduced EPS liability. In a large study where patients were titrated to the "neuroleptic threshold", doses around 4 mg/day were as effective as 2–10 times higher doses (McEvoy et al. 1991). A recent phase III trial compared three doses of haloperidol with the new antipsychotic sertindole (Zimbroff et al. 1997). The lowest dose of haloperidol was 4 mg/day, with no or little antipsychotic benefit of higher doses. Based on a limited PET study, Drs. Kapur and Remington have reported that even lower doses were effective, with "no clinically significant EPS" (Kapur et al. 1996). Thus, using the relative definition of atypicality advocated by Remington and Kapur, these observations lend themselves to the surprising conclusion that haloperidol itself, in low doses, might qualify as an atypical antipsychotic.

The first two "novel" antipsychotics risperidone and olanzapine both have compared favorably to haloperidol (Marder and Meilbach 1994; Peuskens 1995; Beasley et al. 1996). However, unlike studies with clozapine, EPS were reported in a significant number of patients treated with higher doses of both drugs. These observations suggest that the proposed difference versus haloperidol may be quantitative and dose-dependent rather than absolute. The high doses of haloperidol (10–20 mg/day) used in these trials have in all probability induced D_2 receptor occupancy well above 80% and put most patients at risk for developing EPS. Importantly, by cautious dosing of the test compound in a comparison with high doses of haloperidol, it is possible to demonstrate that any new D_2 receptor antagonist is clinically advantageous, thus satisfying the relative criteria of atypicality.

Based on large clinical trials in chronic schizophrenic patients, a standard dose of 4–8 mg/day has been pro-

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Table 1 PET-based calculation of equipotency regarding D_2 receptor occupancy. The calculations were based on data from Nordström et al. (1995, 1998) and Nyberg et al. (1995, 1999) and carried out according to Karlsson et al. (1995). K_i is the dose that occupies 50% of central D_2 dopamine receptors. The doses most likely to produce 70–80% occupancy are suggested to be optimal for haloperidol, risperidone and olanzapine, but not for clozapine

Drug (number of measurements)	K_i (mg/day)	Dose (mg/day) required for 70–80% D_2 receptor occupancy	Equipotency
Haloperidol (*n*=31)	1,3	3–5	1
Risperidone (*n*=15)	1,2	3–5	1
Olanzapine (*n*=3)	4,6	10–20	4
Clozapine (*n*=16)	413	(800–1300)	400

posed for risperidone (Marder and Meilbach 1994; Peuskens 1995). The suggested standard dose of olanzapine is 10–15 mg/day (Beasley et al. 1996). At these dose levels, PET studies demonstrate that both compounds induce higher D_2 receptor occupancy than is seen in clozapine-treated patients. Eight patients treated with risperidone 6 mg/day had D_2 receptor occupancy about 80%, and six of them had mild EPS at that time (Nyberg et al. 1999). Three patients receiving olanzapine 10, 15 and 20 mg/day had 74%, 84% and 68% D_2 receptor occupancy, respectively (Nordström et al. 1998). These findings suggest that the proposed standard doses of these new antipsychotics are well targeted to produce D_2 receptor occupancy within the optimal 70–80% range suggested for typical antipsychotics (Table 1). Thus, based on the estimated receptor occupancy it can be predicted that most patients have no or marginal EPS at the proposed standard doses, and in the higher dose ranges EPS are likely to emerge. The salient question remains if these drugs would stand out as advantageous in comparison with haloperidol at the equipotent doses of 2–4 mg/day that produce the same receptor occupancy.

In conclusion, clozapine remains the only antipsychotic with efficacy at low D_2 receptor occupancy. Novel antipsychotics have been suggested to have superior efficacy on the cognitive symptoms of schizophrenia. This efficacy is of particular interest in relation to the high $5\text{-}HT_{2A}$ receptor occupancy induced by such drugs (Nyberg et al. 1993, 1997). However, such benefits may be obscured in drug trials with non-equipotent dosing. To evaluate conclusively the benefit of the new antipsychotics, comparative trials should be conducted with each drug at dose levels likely to produce the same degree of D_2 receptor occupancy.

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