A Method to Estimate In Vivo D_2 Receptor Occupancy by Antipsychotic Drugs

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A computational method is presented to estimate in vivo receptor occupancies of frequently used antipsychotic medications, which may provide a way to determine their central nervous system (CNS) effects in humans. The method can be used to estimate occupancies of several receptor types based on the daily dose of antipsychotic medication. Estimates of D_2 receptor occupancy by haloperidol based on this equation were compared with those yielded by positron emission tomography (PET) measures in humans for the same compounds and dosages: the results of this comparison validated the approach.

Key Words: dopamine-2 receptors, receptor occupancy, antipsychotic medication, central nervous system effects

INTRODUCTION

The potentially confounding effects of antipsychotic medications cast a shadow over clinical research into biological substrates of psychiatric disorders. It is increasingly difficult to carry out psychophysiological studies in medication-free patients. Frequently, subjects are treated with different medications or with different doses when treated with the same medication. Typically, psychophysiological studies involving medicated patients have attempted to calculate medication effects by expressing dosages of the different drugs in terms of chlorpromazine equivalent values (Breier and others 1993; McCarley and others 1993). This approach could lead to spurious conclusions if, as is likely, the different antipsychotic medications have differential effects on the CNS. For example, differential effects have been reported by Bartlett and others (1991), Buchsbaum and others (1992), and by Roemer and Shagass (1990). Bartlett and others (1991) reported thiothixene to increase whole brain glucose utilization, while haloperidol reduced such utilization. Buchsbaum and others (1992) reported that clozapine increased and thiothixene decreased metabolic rates in the basal ganglia, with greater effects on the right hemisphere. Roemer and Shagass (1990) noted differential effects of phenothiazine and piperazine versus nonphenothiazine or nonpiperazine medications on evoked potential measures. Thus there is a need to develop a method, in addition to chlorpromazine equivalents, to measure CNS effects of the various neuroleptic medications that may be administered to subjects participating in psychophysiological studies.

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Table 1

D_2 receptor affinity constants[a] of 8 neuroleptics[b]

Neuroleptic	Molecular weight	Vd (L)	Affinity (K_a)
Chlorpromazine hydrochloride	355.3	7520	5.3×10^7
Fluphenazine hydrochloride	510.4	3125	1.3×10^9
Haloperidol	375.9	1942	2.5×10^8
Molindone	312.8	1787	8.3×10^6
Perphenazine	404.0	10 623	7.1×10^8
Thioridazine hydrochloride	406.9	889	3.8×10^7
cis-Thiothixene	443.6	1242	2.2×10^9
Trifluoperazine hydrochloride	407.5	8333	3.8×10^8

[a]$1/K_d$, in which K_d is the equilibrium dissociation constant in molarity. A large number indicates greater affinity and, therefore, greater receptor occupancy at a lower concentration than that of a drug with lower affinity.
[b]From Richelson 1988.
(Volumes of distribution derived from daily doses and plasma levels reviewed in Table 3.)

Typical antipsychotic medications have been shown to reduce neurotransmission in the CNS by blocking neurotransmitter activity at receptors. Using human brain tissue or transfected cells expressing human receptors, Richelson and colleagues (Richelson and Nelson 1984; Richelson 1988; Bolden and others 1991; Kanaba and others 1994) have shown that frequently prescribed antipsychotic medications differ in their affinities for several human receptor types (that is, α_1-adrenergic, α_2-adrenergic, 5-HT_{1A}, 5-HT_{2A}, histamine, muscarinic$_{m1\text{-}m5}$, and dopamine D_1 and D_2). A method to estimate in vivo receptor occupancies of typically used antipsychotic medications in medicated patients may provide a way to equate their CNS effects.

In this paper, we present a mathematical algorithm that can be applied to estimate occupancy of several receptor types simultaneously. We use the algorithm to estimate D_2 occupancy of haloperidol, and we compare estimates to D_2 occupancy measures obtained using PET to provide support for this computational approach. PET studies have been used to document the occupancy of D_2 receptors by several psychotropic drugs in human brain in vivo (Baron and others 1989; Karbe and others 1991; Coppens and others 1991; Farde and others 1992; Wolkin and others 1989). These studies show that haloperidol at conventional doses occupies a high percentage (40% to 97%) of the D_2 receptors in the brain.

The equation presented here employs Richelson's (1984, 1988) data on D_2 receptor binding affinity (K_a, which is the inverse of the equilibrium dissociation constant) of haloperidol. It should be noted that the computational method can be used to estimate receptor occupancies of any of the receptor species for which such affinity constants are available from human brain tissue. Richelson's group has published such values for α_1-adrenergic, α_2-adrenergic, 5-HT_{1A}, 5-HT_{2A}, histamine, muscarinic$_{m1\text{-}m5}$, and dopamine D_1 and D_2 receptors for at least 8 conventional antipsychotic medications. Since species differences in the binding capacities of drugs exist, the use of data from human receptors is essential. The use of these receptor affinity constants, in conjunction with molecular weight and estimates of the steady-state volume of distribution (Vd) of the ligand, makes it possible to compute estimates of receptor occupancy for haloperidol.

METHODS

We computed the percentage of D_2 receptor occupancy for haloperidol for the dosage ranges (1 to 40 mg/d) typically employed in psychiatric treatment. The computations can be performed for the antipsychotic medications presented in Table 1. For any given neuroleptic, a specific daily dose expressed in grams is divided by its molecular weight and divided by the estimated Vd of the neuroleptic. This yields an estimated concentration of the drug. The drug concentration (Cd) is multiplied by the affinity constant of the neuroleptic (K_a) for a given receptor as determined in human tissue. The estimate of receptor occupancy is then computed as $y = (Cd \times K_a)/[1 + (Cd \times K_a)]$.

Table 1 presents the molecular weight, median Vd in liters, and D_2 binding affinities of 8 typical neuroleptics. Steady-state Vd values for an individual can be computed by dividing daily dosage by plasma level obtained after the subject has been on the medication in question for about 5 half-lives (Benet and others 1990). In general, the Vd values of these compounds are not available in the literature or from the pharmaceutical companies manufacturing them.

Table 2

Daily dose of haloperidol, plasma levels, PET estimates of D_2 occupancy[a], our computations of D_2 occupancy, and Vd

Subject	Daily dose (mg)	Plasma level	PET occupancy (%)	Our occupancy (%)	Vd (L)[b]
1[a]	4.0	6.0 nmol/L	75.0	61	1739
2[a]	4.0	11.0 nmol/L	84.0	73	976
3[a]	6.0	9.0 nmol/L	84.0	71	1622
4[a]	6.0	13.0 nmol/L	89.0	76	1224
5[c]	10.0	3.3 μg/L	40.0	69	3030
6[a]	12.0	19.0 nmol/L	84.0	82	1690
7[d]	20.0	21.6 μg/L	97.5	94	926
8[e]	39.0	32.0 ng/mL	88.0	95	1219
9[f]	55.0	50.0 ng/mL	86.0	97	1100
		Patients from Baron and others 1989			
1	0.65	—	4.7	18	—
2	1.1	—	12.3	25	—
3	2.0	—	40.7	40	—
6	35.0	—	73.0	92	—

[a]Data from Farde and others 1992.
[b]Mean Vd for subjects 1 to 9 = 1503 L.
[c]Patient 1 from Karbe and others 1991.
[d]Patient 1 from Coppens and others 1991.
[e]Data from Wolkin and others 1989 (5 responders).
[f]Data from Wolkin and others 1989 (5 nonresponders).
(—) = data unavailable as plasma levels were not published.

Based on the published literature, there is up to a 40-fold interindividual variance in Vd for the same neuroleptic.

To document the robustness of the algorithm and to avoid some of the problems that may derive from such Vd variability, 3 estimates for Vd of haloperidol were used: 1) that of each of 9 data points for which there were PET occupancy data, daily dose, and plasma level (Table 2) for haloperidol, from which individual Vd values were computed; 2) the median Vd of these 9 PET data points (1224 L); and 3) the median Vd values determined from the literature (1942 L).

It should be understood that the issue here is not whether more accurate estimates of Vd can be obtained, but rather whether or not an algorithm that yields receptor occupancy measures of psychotropic medication can be demonstrated. The most direct approach to determining an individual's steady-state Vd is to determine the plasma level of the medication in question. Plasma assays are rarely ordered in clinical settings, however, since in general, plasma levels have not been shown to be associated with therapeutic "windows."

Nonlinear regression (BMDP3R) was used to test the fit of observed data (PET occupancy and/or our estimates) to the derivation of the Michaelis-Menten function of the BMDP statistical software: $f = V \times t/(k + t)$ (Dixon and others 1990), where V is the maximum occupancy, t is the daily dose of medication, and k is the daily dose that gives half of the maximum occupancy. BMDP3R returns nonlinear regression estimates of V and k based on the observed data. Residual values based on these 2 parameters are computed from the difference between the observed values and the predicted values. The mean of the squared residual values is used as an estimate of the goodness of fit for our estimates and the PET estimates of D_2 occupancy. Smaller mean squared residuals of the values derived from the algorithm than mean squared residuals of the PET values are taken as evidence of the accuracy of the approach. Reduced mean squared residuals would indicate that the residual error associated with the computational estimates is lower than such error associated with the PET data.

RESULTS

Farde and others (1992) presented data of 5 subjects treated with haloperidol, which included daily dose of medication, plasma level of medication, and D_2 receptor occupancy as determined using PET. Karbe and others

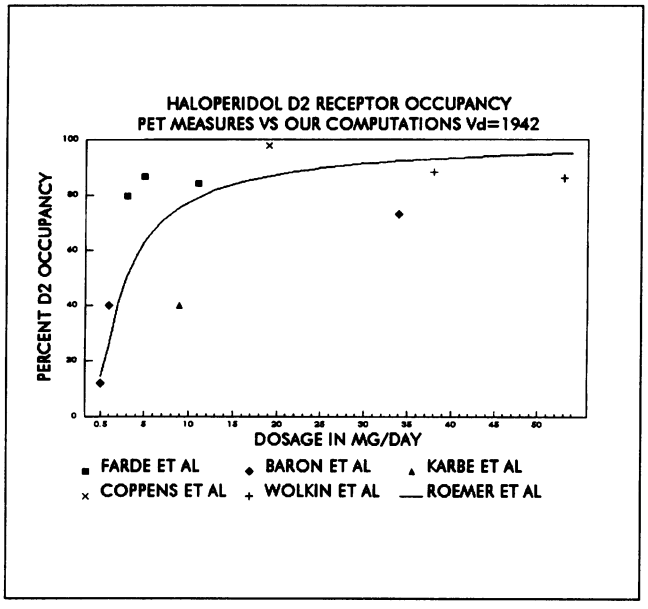

Figure 1. Comparisons between PET and algorithm estimates of D_2 receptor occupancy for several doses of haloperidol.

(1991) and Coppens and others (1991) each presented similar data for 1 patient. Wolkin and others (1989) presented D_2 occupancy, average dose, and plasma levels for 5 haloperidol responders and 5 haloperidol nonresponders. Together, these data provide 9 data points as shown in Table 2. This table lists the daily dose of haloperidol, published plasma level (in noted units), PET estimates of D_2 occupancy, our estimates of D_2 occupancy, individual Vd values, and the mean Vd of these data points. Figure 1 plots these data and the results of our computations using the algorithm in terms of percent of D_2 receptor occupancy and daily dose of haloperidol in milligrams. The correlation between our 13 log-transformed occupancy estimates and the 13 log-transformed PET measures at the respective daily dosages was $r = 0.91$ ($P < 0.001$). This indicates that the curve reflects the variation of the PET data points.

The PET estimates of haloperidol D_2 receptor occupancy ranged from 40% to 97%. With the algorithm, using these 9 doses of haloperidol and the individual Vd values, we computed D_2 receptor occupancy values ranging from 61% to 97%. Nine occupancy and dosage values from PET data and 9 occupancy values for the same dosages from our computations—a total of 18 pairs of numbers—were taken to nonlinear regression. BMDP3R returned nonlinear regression parameter estimates of maximum occupancy equal to 90.93% and a dosage of haloperidol at which 50% occupancy was achieved of 1.15 mg/d. For the 18 residuals, the mean squared residual was 170.62. Based on these 2 parameters, the mean of the squared residuals for the 9 PET data points was 326.9 and the mean of the squared residuals for our 9 computed D_2 occupancy values was 63.1. Nonlinear regression of the 9 PET data points yielded parameters of 84.06% and 0.33 mg/d, with a mean of the squared residuals of 302.33. Application of these parameters to the 9 occupancy values computed by our algorithm resulted in a mean squared residual of 137.0, indicating that our algorithm yields smaller residual values than do the PET values when regression is based on the PET values themselves.

These results provide support for the validity of the algorithm using direct computations of the *individual Vd* based on daily dose of haloperidol and individual plasma levels.

Often, plasma levels of haloperidol (or other neuroleptics of interest) are unavailable. Many studies of psychophysiological relationships to psychiatric disorders do not obtain plasma levels of medications from the subjects involved. Consequently, it would be useful to extend the above validation of our approach to the use of a single estimate for Vd. This we do in 2 steps. The 1st step uses the *median Vd of the 9 PET data points* in the algorithm. The 2nd step uses a measure of central *tendency of Vd based on the published literature* to realize a more generalized application. In both steps, we observe lower mean squared residuals with occupancy estimates based on our computations than those obtained from the PET data.

For the 1st step, the median of Vd values from subjects 1 through 9 (Table 2) is 1224 L. Using the algorithm and this Vd value, we computed D_2 receptor occupancies for daily doses of haloperidol from 2 to 40 mg ranging from 68% to 97%. PET data included data of 2 patients with 4 mg/d and 2 with 6 mg/d of haloperidol. Thus the 9 occupancy and dosage values from PET data, but only 7 occupancy values from our computations, were taken to nonlinear regression. BMDP3R returned nonlinear regression parameter estimates of maximum occupancy (91.76%) and haloperidol dosage at which 50% occupancy would be achieved (0.98 mg/d). For the 16 residuals, the mean squared residual was 170.85. Based on these 2 parameters, the mean of the squared residuals for the 9 PET data points was 321.93, and the mean of the squared residuals for our 7 computed D_2 occupancy values was 27.68. Nonlinear regression of the 9 PET data points alone yielded a mean squared residual of 303.8. Application of the parameters to the 7 occupancy values computed by our algorithm resulted in a mean squared residual of 102.8. This may be seen to support extension of the algorithm to use of the median Vd instead of individual computations of Vd.

The 2nd step uses a measure of central tendency for Vd of 1942 L. To obtain this estimate of Vd for haloperidol from the literature, we reviewed 11 articles subject to the constraint that published data gave prescribed daily dosages and plasma levels either as group mean values or values for

Table 3

Central tendencies of Vd for 8 antipsychotic medications

Medication	Range of Vd	Reference
Chloropromazine hydrochloride		
2400[a]	—	Vital-Herne and others 1986
2431	2283 to 5607	Smith and others 1984
7520[a]	—	Young and others 1989
7962	1687 to 34 013	Midha and others 1989
12 438[a]	—	Faraone and others 1987
Fluphenazine hydrochloride		
2382[a]	—	Faraone and others 1987
2667[a]	—	Young and others 1989
3125	1471 to 4545	Ereshefsky and others 1985
16 667	12 500 to 18 182	Marder and others 1989
25 000	16 667 to 25 000	Dysken and others 1981
Haloperidol		
1291[a]	—	Jann and others 1989
1368[a]	—	Young and others 1989
1538	476 to 20 000	Janicak and others 1993
1660	129 to 2273	van Putten and others 1992
1717	761 to 3056	Ko and others 1989
1942	1511 to 2500	Smith and others 1988
1977[a]	—	Smith and others 1984
2000	879 to 3250	Biglow and others 1985
2090	785 to 5438	Miller and others 1990
2381	789 to 15 000	Coryell and others 1990
2500	2085 to 3125	Hirschowitz and others 1991
Molindone		
1787	388 to 7091	Pandurangi and others 1989
Perphenazine		
3951[a]	—	Faraone and others 1987
10 623	6186 to 19 768	Bolvig-Hansen and Larson 1985
21 666[a]	—	Mazure and others 1990
Thioridazine hydrochloride		
89[a]	—	de Jonghe and others 1973
90	78 to 101	Cohen and others 1989
564	376 to 753	Cohen and Sommer 1988
641	254 to 1563	Widerlov and others 1982
889[a]	—	Vital-Herne and others 1986
1215[a]	—	Faraone and others 1987
1914[a]	—	Brown and Laughren 1983
1916[a]	—	Young and others 1989
8721[a]	—	Greendyke and Gulya 1988
cis-Thiothixene		
755[a]	—	Faraone and others 1987
816	316 to 16 000	Jacobson and others 1976
1667[a]	—	Yesavage and others 1981
22 917[a]	—	Ereshefsky and others 1991
Trifluoperazine hydrochloride		
5555	1612 to 1000	Hawes and others 1983
8333	1315 to 100 000	Janicak and others 1989
8695[a]	—	Midha and others 1988

[a]Vd was based on published mean values since individual doses and plasma values were not presented.

individuals. In publications where medication doses were presented as mg/kg/d, body weight was assumed to be 65 kg. None of the publications presented data on specific protein binding in the subjects studied. We could therefore not correct for the degree of protein binding, which would, presumably, reduce variation in our estimates. As there was substantial variance in the computed Vd values for a given medication, both between subjects in a given paper and between different papers, we derived a *median Vd based on the measures of central tendency* (means for groups or medians if individual data values were presented) of the publications so reviewed. Table 3 presents the data on which the Vd value of 1942 L for haloperidol used here is based. Also included in Table 3 are Vd values of 7 other antipsychotic medications to which this algorithm can be applied as the human brain tissue receptor affinities of these medications have been published. This table presents the ranges of Vd for individual subjects in each paper (daily dose divided by plasma level for each subject) or the Vd computed from the mean plasma level and the mean daily dosage. It should be noted that several publications used different methods of plasma assay, which is an additional reason for selecting a median value based on the measures of central tendency of the papers reviewed.

The 4 additional PET occupancy data points were available for this 2nd step. They are from Baron and others (1989), who did not publish plasma levels for their patients (see Table 1). Nonlinear regression (BMDP3R) on the D_2 occupancy values derived from our algorithm using a Vd of 1942 L (11 data points) and those values derived from PET data (13 sdata points) yielded parameter estimates of maximum occupancy of 95.66% and dosage of haloperidol at which 50% occupancy was achieved of 2.33 mg/d. For the 24 residuals, the mean squared residual was 179.94. Based on these 2 parameters, the mean of the squared residuals for the 13 PET data points was 353.81; the mean of the squared residuals for our 11 computed D_2 occupancy values was 7.42. Nonlinear regression was performed on the 13 PET data points alone, yielding a residual mean square of 349.81. Residualizing our estimates using the parameters of the 13 PET data points yielded a residual mean square of 134.8. D_2 occupancy estimated by our algorithm resulted in lower error than that obtained from the PET data on which the regression was based. These analyses, using a more general estimate of Vd, may be seen to support extension of the algorithm to the use of a more generalized estimate of Vd.

Twenty-six residual values, based on parameters from the PET data, were computed for both the algorithm and for the PET data (13 each). These 2 sets of residual values were taken to matched t test analysis to test for the significance of differences between the residuals. The difference was not significant ($P = 0.8186$, df 11). Thus we conclude that there

Table 4

Daily dose of 4 other neuroleptics, PET estimates of D_2 occupancy[a], our computations of D_2 occupancy, and Vd

Neuroleptic	Daily dose (mg)	PET occupancy (%)	Our occupancy (%)	Vd (L)
Perphenazine	16	79	87	4000
Trifluoperazine	10	75	57	n/a
Thioridazine	300	73	98	444
Thioridazine	400	80	99	483
Chlorpromazine	200	78	94	2000

[a]Data from Farde and others 1992.

is no significant difference between PET and the algorithm on estimates of D_2 occupancy by haloperidol.

The extent to which this algorithm can be extended to other neuroleptics was tested using additional data from Farde and others (1992). For 4 additional medications, Table 4 lists D_2 occupancy measures, our occupancy computations for the same dosage, and computations of Vd for 5 subjects. The correlation between the 2 sets of D_2 occupancy values was $r = 0.30$. The restricted range of PET occupancy values may have spuriously influenced the correlation coefficients. Thus these 5 pairs of D_2 occupancy values were added to the haloperidol sample to yield a sample of 18 observations for which there were both our computations and PET D_2 occupancy measures. The correlation between log-transformed PET values and our computations was $r = 0.89$ ($P < 0.001$). Subject to the limitations associated with the few PET reports of other typical neuroleptics on D_2 occupancy, this result suggests the algorithm can be extended to other typical neuroleptics.

DISCUSSION

We present a computational method to estimate receptor occupancy of daily dosages of neuroleptics in vivo based on receptor affinity constants determined in human brain tissue. These nonlinear regression analyses may be seen to document the relative accuracy of the approach. Overall, our computational approach to estimating D_2 receptor occupancy of haloperidol yielded residuals that support the validity of the algorithm. The computational method can be used to estimate D_2 occupancy of other neuroleptics in addition to the D_2 receptor for haloperidol (see Table 4).

This initial approach to in vivo estimates of neurotransmitter receptor occupancy in humans has limitations and is based on some untested assumptions. These assumptions are 1) that there is 100% absorption, 2) that in vitro K_d reflects in vivo K_d, and 3) that intrasynaptic concentrations are the same as plasma concentrations. The literature provides no guidance to viable alternatives to assumptions 2 and 3.

The use of plasma levels for each subject avoids the assumption of 100% absorption and permits computation of Vd for individual patients. This was illustrated using the data of Table 2, which presented daily dose, plasma levels, and PET-derived D_2 occupancy values.

In terms of bioavailability, blood to brain ratios of neuroleptics were assumed to be 1:1. Brain to serum ratios of commonly used neuroleptics have been reported to vary by nearly 40-fold in infrahumans (Sunderland and Cohen 1986; Tsuneizumi and others 1992). The literature is not clear on blood to brain ratios of the several neuroleptics in humans. Young and others (1989) used the brain to serum ratios determined in rodents by Sunderland and Cohen (1986) in comparing serum neuroleptic activity of different neuroleptics in their patients. The issue of blood to brain ratios could be resolved by determining the blood to brain ratios of a given neuroleptic at autopsy. When these data become available, the algorithm can be modified to adjust for such ratios.

Volumes of distribution that take into account degree of protein binding should reduce some of the variance in the approach presented here.

This presentation illustrates a method for estimating D_2 receptor occupancy by haloperidol. In addition to the 8 neuroleptics presented by Richelson, Seeman (1992) has reviewed dissociation constants of D_2 receptors, in molarity, of 22 neuroleptics (the reciprocal is the affinity constant). These values are not derived from human brain tissue, so caution in generalizing to humans is required. Such data can be derived for other receptor types, which would provide the basis for a more general application of this algorithm to neuroleptics in addition to those whose molecular weights, estimated volumes of distribution, and affinities are presented in Table 1.

This algorithm may be extended to other receptor types and can be applied to any psychotropic medication when the Vd, molecular weight of the medication, and equilibrium

dissociation constants for the human receptor types are known. Currently, there seems to be no method available to estimate or determine the neuroleptic receptor occupancy of several neurotransmitter species simultaneously. One application of this algorithm is to express effects of different neuroleptics by their occupancy of several receptor types (Richelson and Nelson 1984; Richelson 1988; Bolden and others 1991; Kanba and others 1994). Consider a typical clinical study where different patients may have been administered any 1 of several drugs (for example, thiothixene, haloperidol, or chlorpromazine) at 1 of several dosages. Conventionally, one would express drug treatment in terms of chlorpromazine equivalent dosages. In addition to the conventional approach, one could now apply this equation to each of several receptors of interest, for example, D_2, muscarinic, and 5-HT_{2A}. The Vd for an individual subject could be determined by plasma assay of the neuroleptic (say, thiothixene in 1 group of patients, haloperidol in another group of patients, and chlorpromazine in a 3rd group) in relation to the daily administered dose (at steady state), or it could be determined using the "central tendency Vd" values as shown in Table 1. Using the algorithm presented here, one could then compute the occupancies of dopaminergic, cholinergic, and serotonergic receptors by thiothixene, haloperidol, and chlorpromazine. Such a set of occupancy values, across the different neuroleptics and doses, could be used to control for CNS effects by regression or covariance methods.

The algorithm presented here may be seen as an alternate method to estimate receptor occupancy in the absence of PET scanning capabilities. The method requires further development and testing with a larger number of antipsychotic medications.

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REFERENCES

Baron JC, Martinot JL, Cambon H, Boulenger JP, Poirier MF, Caillard V, Blin J, Huret JD, Loc'h C, Maziere B. 1989. Striatal dopamine receptor occupancy during and following withdrawal from neuroleptic treatment: correlative evaluation by positron emission tomography and plasma prolactin levels. Psychopharmacology 99:463–72.

Bartlett EJ, Wolkin A, Brodie JD, Laska EM, Wolf AP, Sanfilipo M. 1991. Importance of pharmacologic control in PET studies: effects of thiothixene and haloperidol on cerebral glucose utilization in chronic schizophrenia. Psychiatry Res 40:115–24.

Benet LZ, Mitchell JR, Sheiner LB. 1990. Pharmacokinetics: the dynamics of drug absorptions, distribution, and elimination. In: Gilman AG, Rall TW, Nies AS, Taylor P, editors. Goodman and Gilman's the pharmacological basis of therapeutics. 8th edition. New York: McGraw-Hill. p 3–33.

Biglow LB, Kirch DG, Braun T, Korpi ER, Wagner RL, Zalcman S, Wyatt RJ. 1985. Absence of relationship of serum haloperidol concentration and clinical response in chronic schizophrenia: a fixed-dose study. Psychopharmacol Bull 21:66–8.

Bolden C, Cusack B, Richelson E. 1991. Antagonism by antimuscarinic and neuroleptic compounds at the five cloned human muscarinic cholinergic receptors expressed in chinese hamster ovary cells. J Pharmacol Exp Ther 260:576–80.

Bolvig-Hansen L, Larsen NE. 1985. Therapeutic advantages of monitoring plasma concentrations of perphenazine in clinical practice. Psychopharmacology 87:16–9.

Breier A, Davis OR, Buchanan RW, Moricle LA, Munson RC. 1993. Effects of metabolic perturbation on plasma homovanillic acid in schizophrenia: relationship to prefrontal cortex volume. Arch Gen Psychiatry 50:541–50.

Brown WA, Laughren T. 1983. Serum neuroleptic levels in the maintenance treatment of schizophrenia. Psychopharmacol Bull 19:76–8.

Buchsbaum MS, Potkin SG, Marshall JF, Lottenberg S, Teng C, Heh CW, Tafalla R, Reynolds C, Abel L, Plon L, and others. 1992. Effects of clozapine and thiothixene on glucose metabolic rate in schizophrenia. Neuropsychopharmacology 6:155–63.

Cohen BM, Sommer BR. 1988. Metabolism of thioridazine in the elderly. J Clin Psychopharmacol 8:336–9.

Cohen BM, Lipinski JF, Waternaux C. 1989. A fixed dose study of the plasma concentration and clinical effects of thioridazine and its major metabolites. Psychopharmacology 97:481–8.

Colquhoun D. 1971. Lectures on biostatistics: an introduction to statistics with applications in biology and medicine. London: Clarendon Press.

Coppens HJ, Slooff CJ, Panns AMJ, Wiegman T, Vaalburg W, Korf JW. 1991. High central D_2-dopamine receptor occupancy as assessed with positron emission tomography in medicated but therapy-resistant schizophrenic patients. Biol Psychiatry 29:629–34.

Coryell W, Kelly M, Perry PJ, Miller DD. 1990. Haloperidol plasma levels and acute clinical change in schizophrenia. J Clin Psychopharmacol 10:397–402.

de Jonghe FERER, van der Helm HJ, Shalken HFA, Theil JH. 1973. Therapeutic effect and plasma level of thioridazine. Acta Psychiatr Scand 49:535–45.

Dixon WJ, Brown MB, Engelman L, Jennrich RI. 1990. BMDP statistical software manual. Berkeley: University of California Press. 1500 p.

Dysken MW, Javiad JI, Chang SS, Schaffer C, Shahid A, Davis JJ. 1981. Fluphenazine pharmacokinetics and therapeutic response. Psychopharmacology 73:205–10.

Ereshefsky L, Jann MW, Saklad SR, Davis CM, Richards AL, Burch NR. 1985. Effects of smoking on fluphenazine clearance in psychiatric inpatients. Biol Psychiatry 20:329–32.

Ereshefsky L, Saklad SR, Watanabe MD, Davis CM, Jann MW. 1991. Thiothixene pharmacokinetic interactions: a study of hepatic enzyme inducers, clearance inhibitors, and demographic variables. J Clin Psychopharmacol 11:296–301.

Faraone SV, Brown WA, Laughren TP. 1987. Serum neuroleptic levels, prolactin levels, and relapse: a two-year study of schizophrenic outpatients. J Clin Psychiatry 48:151–4.

Farde L, Nordstrom AL, Wiesel FA, Pauli S, Halldin C, Sedvall G. 1992. Positron emission tomographic analysis of central D_1 and D_2 receptor occupancy in patients treated with classical neuroleptics and clozapine. Arch Gen Psychiatry 49:538–44.

Greendyke RM, Gulya A. 1988. Effect of pindolol administration on serum levels of thioridazine, haloperidol, phenytoin, and phenobarbital. J Clin Psychiatry 49:105–7.

Hawes EM, Aravagiri M, Dulos RA, Rauw GA, Stonkus MD. 1983. Radioimmunoassays for phenothiazine drugs and their major metabolites in plasma. Progr Neuropsychopharmacol Biol Psychiatry 7:709–14.

Hirschowitz J, Hitzemann R, Burr G, Schwartz A. 1991. A new approach to dose reduction in chronic schizophrenia. Neuropsychopharmacology 5:103–11.

Jacobson L, von Knorring L, Mattson B, Mjomdal T, Oreland L, Perris C, Rapp W, Edenius B, Kettner B, Magnusson KE, and others. 1976. Penfluridol and thiothixene: dosage, plasma levels and changes in psychopathology. Int Pharmacopsychiatry 11:206–14.

Janicak PG, Javiad JI, Davis JM. 1993. Neuroleptic plasma levels: methodological issues, study design and clinical applicability. In: Marder SR, Davis JM, Janicak PG, editors. Clinical use of neuroleptic plasma levels. Washington (DC): American Psychiatric Press. p 17–44.

Janicak PG, Javaid JI, Sharma RP, Comaty JE, Peterson J, Davis JM. 1989. Trifluoperazine plasma levels and clinical response. J Clin Psychopharmacol 9:340–6.

Jann MW, Chang W-H, Davis CM, Chen T-Y, Deng H-C, Lung F-W, Ereshefsky L, Saklad SR, Richards AL. 1989. Haloperidol and reduced haloperidol plasma levels in Chinese and non-Chinese psychiatric patients. Psychiatry Res 30:45–52.

Kanba S, Suzuki E, Nomura T, Yagi G, Asai M, Richelson E. 1994. Affinity of neuroleptics for D_1 receptor of human brain striatum. J Psychiatry Neurosci 19:265–9.

Karbe H, Wienhard K, Hamacher K, Huber M, Herholz K, Coenen HH, Stocklin G, Lovenich A, Heis WD. 1991. Positron emission tomography with (^{18}F) methylspiperone demonstrates D_2 dopamine receptor binding differences of clozapine and haloperidol. J Neural Transm Gen Sect 86:163–73.

Ko GN, Korpi ER, Kirch DG. 1989. Haloperidol and reduced haloperidol concentrations in plasma and red blood cells from chronic schizophrenic patients. J Clin Psychopharmacol 9:186–90.

Marder SR, van Putten T, Aravagiri M, Hubbard JW, Hawes EM, McKay G, Midha KK. 1989. Plasma levels of parent drug and metabolites in patients receiving oral and depot fluphenazine. Psychopharmacol Bull 25:479–82.

Mazure CM, Nelson JC, Jatlow PI, Kincare P, Bowers MB Jr. 1990. The relationship between blood perphenazine levels, early resolution of psychotic symptoms, and side effects. J Clin Psychiatry 51:330–4.

McCarley RW, Shenton ME, O'Donnell BF, Faux SF, Kikinis R, Nestor PG, Jolesz FA. 1993. Auditory P300 abnormalities and left posterior superior temporal gyrus volume reduction in schizophrenia. Arch Gen Psychiatry 50:190–7.

Midha KK, Hawes EM, Hubbard JW, Korchinski ED, McKay G. 1988. A pharmacokinetic study of trifluoperazine in two ethnic populations. Psychopharmacology 95:333–8.

Midha KK, Hawes EM, Hubbard JW, Korchinski ED, McKay G. 1989. Intersubject variation in the pharmacokinetics of chlorpromazine in healthy men. J Clin Psychopharmacol 9:4–8.

Miller DD, Perry PJ, Kelly MW, Coryell WH. 1990. Pharmacokinetic protocol predicting plasma haloperidol concentration. J Clin Psychopharmacol 10:207–12.

Pandurangi AK, Narasimhachari N, Blackard WG, Landa BS. 1989. Relation of serum molindone levels to serum prolactin levels and antipsychotic response. J Clin Psychiatry 50:379–81.

Richelson E, Nelson A. 1984. Antagonism by neuroleptics of neurotransmitter receptors of normal human brain in vitro. Eur J Pharmacol 103:197–204.

Richelson E. 1988. Neuroleptic binding to human brain receptors: relation to clinical effects. Ann N Y Acad Sci 537:435–42.

Roemer RA, Shagass C. 1990. Replication of an evoked potential study of lateralized hemispheric dysfunction in schizophrenics. Biol Psychiatry 28:275–91.

Seeman P. 1992. Dopamine receptor sequences: therapeutic levels of neuroleptics occupy D_2 receptors, clozapine occupies D_4. Neuropsychopharmacology 2:261–84.

Smith RC, Baumgartner R, Misra CH, Mauldin M, Shvartsburd A, Ho BT, DeJohn C. 1984. Haloperidol; plasma levels and prolactin response as predictors of clinical improvement in schizophrenia: chemical vs radioreceptor plasma level assays. Arch Gen Psychiatry 41:1044–8.

Smith M, Wolf AP, Brodie J, Arnett CD, Barouche F, Shiue C-Y, Fowler JS, Russell JAG, MacGregor RR, Wolkin A, and others. 1988. Serial [^{18}F] N-methylspiroperidol PET studies to measure changes in antipsychotic drug D-2

receptor occupancy in schizophrenic patients. Biol Psychiatry 23:653–63.

Sunderland T, Cohen BM. 1986. Blood to brain distribution of neuroleptics. Psychiatry Res 20:299–305.

Tsuneizumi T, Babb SM, Cohen BM. 1992. Drug distribution between blood and brain as a determinant of antipsychotic drug effects. Biol Psychiatry 32:817–24.

van Putten T, Marder SR, Mintz J, Poland RE. 1992. Haloperidol plasma levels and clinical response: a therapeutic window relationship. Am J Psychiatry 149:500–5.

Vital-Herne J, Gerbino L, Kay SR, Katz IR, Opler LA. 1986. Mesoridazine and thioridazine: clinical effects and blood levels in refractory schizophrenics. J Clin Psychiatry 47:375–9.

Widerlov E, Haggstrom JE, Kilts CD, Andersson U, Breese GR, Mailman RB. 1982. Serum concentrations of thioridazine, its major metabolites and serum neuroleptic-like activities in schizophrenics with and without tardive dyskinesia. Acta Psychiatr Scand 66:294–305.

Wolkin A, Barouche F, Wolf AP, Rotrosen J, Fowler JS, Shiue CY, Cooper TB, Brodie JD. 1989. Dopamine blockade and clinical response: evidence for two biological subgroups of schizophrenia. Am J Psychiatry 146:905–8.

Yesavage JA, Holman CA, Cohn R. 1981. Correlation of thiothixene serum levels and age. Psychopharmacology 74:170–2.

Young AS, Faraone SV, Brown WA. 1989. Correction of serum neuroleptic activity for blood-to-brain distribution: a method that may render radioreceptor assay results comparable between neuroleptics. J Clin Psychopharmacol 9:361–3.