Monthly Administration of Long-Acting Injectable Risperidone and Striatal Dopamine D_2 Receptor Occupancy for the Management of Schizophrenia

Hiroyuki Uchida, M.D., Ph.D.; David C. Mamo, M.D., M.Sc., F.R.C.P.C.; Shitij Kapur, M.D., Ph.D., F.R.C.P.C.; Alain Labelle, M.D., F.R.C.P.C.; Chekkera Shammi, M.B.B.S., F.R.C.P.C.; Erik J. L. Mannaert, Ph.D.; Steve W. Mann, B.A.; and Gary Remington, M.D., Ph.D., F.R.C.P.C.

Objective: Long-acting risperidone administered intramuscularly biweekly is approved for the management of schizophrenia. However, dosing of long-acting antipsychotics is frequently extended in clinical practice, and a recent clinical trial has lent support to monthly dosing of long-acting risperidone. The objective of this positron emission tomography (PET) study was to examine the striatal dopamine D_2 binding of long-acting risperidone administered intramuscularly once a month.

Method: Following at least 3 maintenance monthly injections of 50 mg long-acting risperidone, 7 patients with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder underwent PET using [^{11}C]raclopride to measure D_2 binding potential within 4 days of the next scheduled injection. Data were collected from May to October 2003. This PET study was part of a larger 52-week clinical study wherein individuals received long-acting risperidone once monthly over a 1-year interval. One-year follow-up data were obtained from the 52-week parent investigation.

Results: The mean ± SD D_2 receptor occupancy was 56% ± 24% (range, 29%–82%). Of note, there were 4 subjects with less than 60% D_2 occupancy, none of whom relapsed over the course of the 1-year follow-up. The mean ± SD total plasma level of risperidone plus 9-hydroxyrisperidone was 16.6 ± 12.3 ng/mL (range, 5.7–40.8).

Conclusion: As with plasma levels, there was considerable variability in D_2 occupancy levels for individuals receiving long-acting risperidone. This work suggests a possibility that sustained D_2 occupancy at or above the accepted threshold with acute clinical response may not be necessary to maintain response, a hypothesis with important clinical implications as we consider antipsychotic dosing and future antipsychotic development.

Trial Registration: clinicaltrials.gov Identifier: NCT00236353

(J Clin Psychiatry 2008;69:1281–1286)

Received Dec. 11, 2007; accepted Jan. 30, 2008. From the Centre for Addiction and Mental Health, Toronto, Ontario, Canada (Drs. Uchida, Mamo, Kapur, Shammi, and Remington and Mr. Mann); the Department of Psychiatry, University of Toronto, Ontario, Canada (Drs. Uchida, Mamo, Kapur, Shammi, and Remington); the Institute of Psychiatry, De Crespigny Park, London, England (Dr. Kapur); Royal Ottawa Mental Health Center, Ottawa, Ontario, Canada (Dr. Labelle); and Johnson & Johnson Pharmaceutical Research and Development, Beerse, Belgium (Dr. Mannaert).

The study was funded by Johnson & Johnson Pharmaceutical Research and Development, Beerse, Belgium.

The authors gratefully acknowledge Armando Garcia, B.Sc., for his technical assistance and Alan Wilson, Ph.D., for supervising the radiochemical syntheses (both are from the Centre for Addiction and Mental Health, Toronto, Ontario, Canada). They report no financial or other relationships with other organizations, including pharmaceutical companies.

Financial disclosure appears at the end of the article.

Corresponding author and reprints: David C. Mamo, M.D., M.Sc., F.R.C.P.C., Centre for Addiction and Mental Health, Schizophrenia Research Group, PET Centre, 250 College St., Toronto, Ontario, M5T1R8, Canada (e-mail: david_mamo@camh.net).

Schizophrenia is a chronic debilitating psychiatric illness requiring long-term antipsychotic treatment.[1] Since antipsychotic drugs not only improve psychotic symptoms but also prevent relapse,[2] regular dosing of antipsychotics is considered critical to any successful maintenance treatment strategy. Long-acting depot antipsychotic medications provide for reliable drug delivery in patients for whom adherence with oral medications is problematic.[3] Long-acting risperidone is the first atypical antipsychotic available in depot formulation, and we have recently shown that the optimal dose in terms of striatal dopamine D_2 receptor occupancy is 50 mg administered every 2 weeks,[4] consistent with results from clinical studies.[5] However, in clinical practice physicians will, on occasion, administer depot antipsychotic drugs at intervals that are longer than those recommended[6] to reduce exposure to the drug and minimize adverse effects, or due to patients' partial adherence with the recommended dosing intervals. For depot formulations of first-generation antipsychotic drugs, the literature has offered some support

for the efficacy of this extended dosing,[7,8] likely due to the pharmacokinetics of oil-based depot antipsychotic drugs.

Given the novel formulation of long-acting risperidone (microspheres), it is not clear whether extending dosing beyond 2 weeks is sufficient to maintain therapeutic effects. In fact, pharmacokinetic modeling based on single-dose (50 mg) studies does not support a once-monthly regimen due to low predicted steady-state levels of active moiety at trough. However, a recent 12-month open-label trial (N = 615) showed that once-monthly dosing of 50 mg long-acting risperidone was well tolerated and associated with a relatively low relapse rate of 17.9%,[9] similar to that reported in a 1-year double-blind study of 25 mg long-acting risperidone administered biweekly (N = 163, relapse rate: 21.6%).[10] Furthermore, this favorable outcome using monthly administration was achieved in spite of low plasma levels of risperidone and its active moiety at trough (mean ± SD = 6.2 ± 3.1 ng/mL), approximately half of that reported for biweekly administration (mean ± SD = 11.3 ± 4.5 ng/mL).[11]

From the standpoint of D_2 occupancy, it has been demonstrated that peripheral pharmacokinetics for antipsychotics does not mirror what occurs in terms of binding at central D_2 receptors.[12] This fact accounts for the relatively poor relationship between peripheral plasma levels, pharmacokinetic modeling, and clinical response; greater success in this regard has been achieved using in vivo neuroimaging techniques such as positron emission tomography (PET). For example, several laboratories employing PET, including our own, have shown that greater than 60% D_2 occupancy is required to maximize chance of therapeutic efficacy for acute response, while risk of extrapyramidal side effects increases markedly beyond 80% occupancy.[13,14] This finding has been successfully used to predict the therapeutic dose of new antipsychotic drugs.[15,16]

However, it is less clear as to whether it is necessary to maintain this threshold of D_2 occupancy in order to sustain response beyond the acute state. The present PET investigation was part of a larger clinical study wherein individuals received long-acting risperidone once monthly over a 1-year interval.[9] Our focus was D_2 occupancy levels at trough (preinjection) and the relationship of occupancy with clinical response. One-year follow-up data were obtained from the 52-week parent study.

METHOD

This PET study was conducted at the Centre for Addiction and Mental Health, Toronto, Ontario, Canada, between May and October of 2003. Subjects were recruited from a multicenter study investigating the use of long-acting risperidone administered once monthly at 50 mg in individuals with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder.[9] The PET investigation was approved by the Research Ethics Board of the Centre for Addiction and Mental Health.

Details of the 52-week parent multicenter clinical trial have been published elsewhere, including design and clinical results.[9] Briefly summarizing, outpatients were candidates for a switch to long-acting risperidone if they met the DSM-IV criteria for schizophrenia or schizoaffective disorder and had been maintained on oral risperidone monotherapy at a stable dose (2–6 mg/day) for 8 weeks. Exclusion criteria included treatment with oral antipsychotic medications other than risperidone within the past 8 weeks or depot antipsychotics within 6 months of enrollment, presence of DSM-IV–defined substance abuse or dependence within the preceding 6 months, a neurologic or medical condition that could adversely influence patient safety or evaluation, or a positive pregnancy test.

During a 4-week lead-in phase, patients received 50 mg of long-acting risperidone every 2 weeks. Oral risperidone supplementation (2–6 mg/day) was restricted to the first 2 weeks following the first injection. No concomitant antipsychotics were allowed throughout the rest of the study period. During the subsequent 48 weeks, subjects received 50 mg of long-acting risperidone every 4 weeks, with clinical assessments including the Positive and Negative Syndrome Scale (PANSS).[17]

Men and women already enrolled in the parent study at 1 participating site (the Royal Ottawa Hospital, Ottawa, Ontario, Canada) were candidates for the present PET investigation if they had received at least 3 consecutive monthly injections at the time of study enrollment. Women with positive urine pregnancy test before the scan or currently nursing or those who had medical or psychiatric contraindications to air travel were excluded. Following at least 3 monthly injections of 50 mg long-acting risperidone, subjects who provided written informed consent after receiving detailed information about the protocol of this PET investigation were referred to the Centre for Addiction and Mental Health and underwent a single [^{11}C]raclopride PET scan within 4 days of the next scheduled monthly injection.

The [^{11}C]raclopride PET scans for D_2 receptor occupancy were obtained immediately following injection of 10 mCi of high specific-activity [^{11}C]raclopride (> 300 Ci/mmol) using a bolus plus infusion protocol,[18] with 59% injected as a bolus over 1 minute and the remainder injected via intravenous infusion over 74 minutes. Following a brief transmission scan for attenuation correction of the emission scans, a continuous series of emission scans were obtained every minute for the first 15 minutes and then every 5 minutes until the end of the scan at 75 minutes. PET scanning was conducted using a brain-only GEMS PC2048-Plus PET camera (General Electric Medical Systems, Milwaukee, Wis.) that produced 6.5-mm thick slices with a resolution of about 5 mm in air.

Patients were scanned lying down and with fixation of the head achieved using a thermoplastic facemask (Tru-Scan Imaging, Annapolis, Md.). The regions of interest were drawn directly on averaged PET images and then transferred to the dynamic PET images to obtain a time activity curve.

D_2 receptor binding potential (BP) was estimated by means of previously described methods[19,20] using the mean of the striatum/cerebellum ratio minus 1 obtained between 30 to 75 minutes of scanning as an estimate of the equilibrium BP. Receptor occupancy was then calculated as the percentage reduction of receptor-binding potential with drug treatment compared to baseline ($100 \times [1 - (BP_{drug\ \ scan}/BP_{baseline})]$). Age-corrected measures of BP were obtained from a previously collected data set of 31 antipsychotic-free patients and healthy subjects using the linear regression equation "BP = $(-0.034 \times age) + 3.82$." The absence of the patients' own baseline values introduces a potential error: for D_2 receptor occupancy, this error, as calculated on the basis of variance in the data from antipsychotic-naive patients, is expected to vary from 0% to 9% for patients with 50% occupancy and 0% to 4% for patients with 80% occupancy.

Venous blood was drawn for drug and prolactin concentrations at the time of the PET scan. For risperidone, blood samples were collected in heparinized tubes and centrifuged for 10 minutes at 2500 rpm within 2 hours of collection. Separated plasma was stored at –20°C for transport, and concentration of risperidone plus 9-hydroxyrisperidone was determined using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method.[21] Prolactin levels were measured using a 2-site chemiluminometric immunoassay with a minimal detectable limit of 0.3 ng/mL (ACS, CIBA-Corning Diagnostics, East Walpole, Mass.).

Statistical Analyses

Statistical analyses were carried out using SPSS Version 14.0 (SPSS Inc., Chicago, Ill.) and PRISM Version 4 (GraphPad Software Inc., San Diego, Calif.). Bivariate correlation analysis was used to examine the relationship between the primary variables of interest. Nonlinear regression analysis was used in the estimation of plasma risperidone plus 9-hydroxyrisperidone level associated with 50% D_2 receptor occupancy.

RESULTS

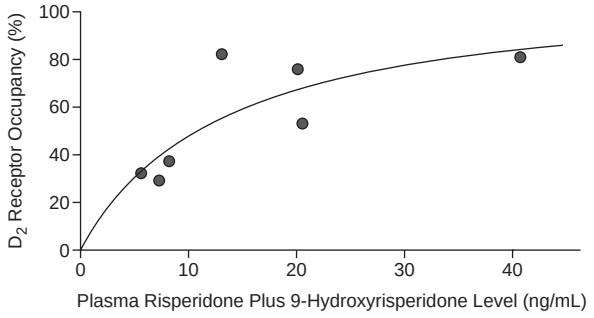
Seven participants (male, N = 6) completed the PET study. The participants' mean (SD) age and duration of illness were 35 ± 14 years (range, 18–59 years) and 11.9 ± 15.0 years (range, 1–41 years), respectively. Data obtained in this study and in the 52-week parent investigation are summarized in Table 1.

Table 1. D_2 Receptor Occupancy, Risperidone Levels, and Clinical Outcomes Among Patients With Schizophrenia Receiving Monthly Administration of Long-Acting Injectable Risperidone

							Data From the 52-Week Parent Study		
Subject	Gender	Age, y	D_2 Receptor Occupancy (%)	Risperidone Plus 9-Hydroxyrisperidone (ng/mL)	No. of Monthly Injections	Concomitant Psychotropic Medications (mg/d)	PANSS Total Score at Baseline	PANSS Total Score at Endpoint	Prior Oral Risperidone Dose (mg/d)
1	Male	59	29	7.3	5	Trazodone 150, valproate 750, citalopram 40	73	65	4
2	Male	37	32	5.7	5	Citalopram 20, valproate 500	52	46	3
3	Male	23	37	8.3	5	None	37	38	5
4	Male	18	53	20.6	5	None	49	37	2
5[a]	Female	25	76	20.2	5	Citalopram 20, benztropine 2, lorazepam 1	82	53	3
6	Male	38	82	40.8	4	None	42	38	2
7[b]	Male	45	82	13.1	4	Lorazepam 1	80	67	6

[a]Subject 5 withdrew from the study at week 24.
[b]Subject 7 withdrew from the study at week 28.
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

Figure 1. Relationship Between D_2 Receptor Occupancy and Plasma Risperidone Plus 9-Hydroxyrisperidone Level[a]



[a]The regression line was fit to the following saturating hyperbole equation: occupancy = $a \times$ (plasma level/[plasma level + ED_{50}]), where a is the maximal receptor occupancy and ED_{50} is the plasma level of risperidone plus 9-hydroxyrisperidone resulting in 50% maximal receptor occupancy. The maximal occupancy $a \pm$ SE calculated with this regression equation for D_2 receptor occupancy was 111 ± 33, with the estimated ED_{50} of 13.0 ng/mL (95% confidence interval = 0.0 to 36.0). When the maximal occupancy was constrained to 100%, the estimated ED_{50} was 10.3 ng/mL (95% confidence interval = 4.4 to 16.2).

Five of the 7 subjects completed the 52-week parent study without significant clinical deterioration (Table 1). Subject 5 (D_2 occupancy = 76%) withdrew her consent at week 24, which was not related with clinical worsening, and subject 7 (D_2 occupancy = 82%) dropped out at week 28 due to worsened auditory hallucinations and delusions in spite of overall improvement in terms of PANSS score.

The mean ± SD total plasma level of risperidone plus 9-hydroxyrisperidone was 16.6 ± 12.3 ng/mL (range, 5.7–40.8 ng/mL), while the mean ± SD D_2 receptor occupancy was 56% ± 24% (range, 29%–82%). The D_2 occupancy was above the occupancy threshold associated with clinical response (60%)[14] in 3 subjects. As expected, the relationship between plasma levels of risperidone plus 9-hydroxyrisperidone and D_2 receptor occupancy could be fit to the saturating hyperbole equation: occupancy = $a \times$ (plasma level/[plasma level + ED_{50}]), where a is the maximum receptor occupancy and ED_{50} is the estimated plasma risperidone plus 9-hydroxyrisperidone concentration (ng/mL) associated with 50% maximal receptor occupancy (Figure 1). The maximal occupancy (a) ± SE calculated with this regression equation for D_2 receptor occupancy was 111 ± 33, with the estimated ED_{50} 13.0 ng/mL (95% confidence interval = 0.0 to 36.0). When the maximal occupancy was constrained to 100%, the estimated ED_{50} was 10.3 ng/mL (95% confidence interval = 4.4 to 16.2).

The mean ± SD prolactin level at the time of the PET scan was 38.4 ± 37.9 µg/L (range, 7.3–40.8 µg/L). Plasma prolactin level was not correlated with D_2 receptor occupancy ($r = 0.7$, $p = .07$) or plasma risperidone plus 9-hydroxyrisperidone ($r = 0.2$, $p = .7$).

DISCUSSION

To our knowledge, this is the first study to assess the central D_2 receptor binding of once-monthly long-acting risperidone in patients with schizophrenia spectrum disorders. We have previously shown that patients receiving long-acting risperidone 50 mg biweekly showed D_2 occupancy levels greater than 60% at expected peak and trough plasma levels.[4]

In contrast, 4 of the 7 subjects in this present study receiving the same dose injected monthly showed D_2 occupancy levels less than 60% (range, 29%–53%) at expected trough plasma levels. We did not measure occupancy at expected peak plasma concentrations in this study, but pharmacokinetic data from the parent study in a subset of subjects (N = 18) showed that the mean ± SD peak plasma concentrations of risperidone plus 9-hydroxyrisperidone were 40.4 ± 15.3 ng/mL for monthly administration of 50 mg of long-acting risperidone,[9] which would be expected to translate into 80% occupancy (calculated from an ED_{50} of 10.3 ng/mL with the maximum receptor occupancy constrained to 100%). Hence, it is likely that D_2 occupancy reached greater than 60% transiently and then declined to the measured less than 60% at trough. In spite of this, these 4 individuals did not relapse over the course of the 1-year follow-up, as reflected in the clinical data gathered in the parent study.[9]

A wide variability in D_2 occupancy was observed, likely related to interindividual pharmacokinetic variation. This notwithstanding, the relationship between the plasma level of risperidone plus its active moiety and D_2 receptor occupancy could be fit to a saturating hyperbole equation, consistent with standard drug-receptor interaction studies.[15,16] Pharmacokinetic data from the parent study in a subset of subjects (N = 18) showed that the mean ± SD trough plasma level of risperidone plus 9-hydroxyrisperidone was 6.2 ± 3.1 ng/mL for monthly administration of 50 mg of long-acting risperidone,[9] much lower than the value reported for our sample (mean ± SD = 16.6 ± 12.3 ng/mL; range, 5.7–40.8 ng/mL). If we applied the regression equation derived from this study to the data derived in the parent study, a mean of 6.2 ng/mL would be expected to translate into 38% occupancy.

Within the context of the results of the parent study, the present PET results suggest a possibility that continuous D_2 blockade greater than 60% may not be necessary to sustain clinical response. One other PET study corroborates this position, demonstrating that clinical response was maintained in 8 stabilized schizophrenic outpatients taking haloperidol decanoate administered every 4 weeks, despite mean D_2 occupancy levels decreasing from 73% (range, 60%–82%) at week 1 to 53% (range, 20%–74%) at week 4.[8] It has been argued that D_2 occupancy is the *sine qua non* of antipsychotic activity, with evidence from several laboratories indicating that optimal clinical

response is achieved with D_2 blockade greater than 60%.[14] The most parsimonious explanation for these PET data seems to be that while D_2 occupancy greater than 60% may be necessary to induce antipsychotic response, sustained D_2 binding at or above the recommended threshold may not be required to maintain clinical response.

Along similar lines, recent work from our group has reported that clinical stability can be maintained with oral antipsychotics where the dosing interval was extended from daily to intervals up to every 3 days.[22] Earlier investigations using intermittent antipsychotic dosing were associated with higher relapse rates.[23–25] However, in these studies the interval was up to months, whereas our "extended" strategy demanded that individuals receive antipsychotic medications within briefer, regular intervals.

There are limitations to be noted in the present study. The small sample size limits extrapolation of results, and the sample studied may not necessarily be representative of the larger parent study population given the higher mean plasma levels observed here, which may have biased the resulting D_2 occupancy results. The social functioning of subjects who consent to participate in a PET study may be different from that of the population of patients with schizophrenia, potentially limiting the generalizability of these data. Further, 1-year follow-up may be insufficient to thoroughly examine the long-term effectiveness of this dosing method. It should also be noted that the parent clinical trial was itself not blind and did not involve a randomized comparator group with biweekly injections.[9] At the same time though, clinical measures were recorded independent of the PET results, mitigating to some extent this potential bias. Finally, the D_2 occupancy needed for the maintenance of clinical response still needs to be discussed with caution given the 2 dropouts paradoxically occurred in individuals who had greater than 60% occupancy in the present study, although one of them was clearly unrelated to clinical worsening. In order to rigorously test the hypothesis discussed in this study, large randomized controlled trials combined with the assessment of D_2 occupancy are warranted.

In conclusion, the results of this study suggest a possibility that sustained D_2 binding at or above the currently recommended threshold of 60% may not be required to maintain clinical response in patients who have already been stabilized. This has important clinical implications, both in terms of antipsychotic dosing and future drug development. Numerous lines of investigation have underscored the significant side effects associated with dopamine blockade (e.g., motor,[14] affective,[26] cognitive,[26] and dysphoric adverse events[27]) that may substantially compromise functional outcome. With evidence that sustained D_2 occupancy may not always be necessary to maintain clinical response, we can begin to look at strategies, pharmacologic and otherwise, that incorporate this therapeutic approach. Partial dopamine agonists, drugs with a rapid k_{off}, and extended, but regular, dosing intervals are representative of models in line with such an approach.

Drug names: benztropine (Cogentin and others), citalopram (Celexa and others), haloperidol (Haldol and others), lorazepam (Ativan and others), risperidone (Risperdal).

Financial disclosure: **Dr. Uchida's** fellowship has been supported by the Japanese Society of Clinical Psychopharmacology, Pfizer Health Research Foundation, and Mochida Memorial Foundation. Within the past 5 years, Dr. Uchida has received manuscript fees and speaker's honoraria from Dainippon Sumitomo Pharma and GlaxoSmithKlein. **Dr. Mamo** has received grants, consultant fees, or other financial support from the Canadian Psychiatric Research Foundation, the Schizophrenia Society of Canada, the Stanley Medical Research Institute, and Bristol-Myers Squibb and has received speaker's honoraria from AstraZeneca within the past 5 years. **Dr. Kapur** has received grant/research support from AstraZeneca, Bristol-Meyers Squibb, Eli Lilly, EMD-Darmstadt, GlaxoSmithKlein, Janssen, Neuromolecular Inc., and Pfizer and has served as a consultant to or as a scientific advisor or speaker for AstraZeneca, Bristol-Meyers Squibb, Eli Lilly, GlaxoSmithKlein, Janssen, Otsuka, Organon, Pfizer, Sanofi-Synthelabo, Servier, and Solvay Wyeth within the past 5 years. **Dr. Labelle** has received grant/research support from AstraZeneca, Bristol-Meyers Squibb, Eli Lilly, Janssen-Ortho, and Pfizer and has served as a consultant to or as a scientific advisor or speaker for AstraZeneca, Eli Lilly, Janssen-Ortho, and Pfizer within the past 5 years. **Dr. Shammi** has received grant/research support from Novartis, AstraZeneca, and Bristol-Myers Squibb and has served as a consultant to or as a speaker for AstraZeneca, Novartis, Janssen, and Pfizer within the past 5 years. **Dr. Mannaert** has received financial compensation (salary, stock, and stock options) as an employee of Johnson & Johnson. **Dr. Remington** has received research funding from NARSAD, Stanley Medical Research Institute, Novartis, and Merck (Germany) in the last 5 years. **Mr. Mann** reports no financial or other affiliations relevant to the subject of this article.

REFERENCES

1. Lehman AF, Lieberman JA, Dixon LB, et al. Practice Guideline for the Treatment of Patients With Schizophrenia, second edition. Am J Psychiatry 2004;161(suppl 2):1–56
2. Davis JM. Overview: maintenance therapy in psychiatry, 1: schizophrenia. Am J Psychiatry 1975;132(12):1237–1245
3. McEvoy JP. Risks versus benefits of different types of long-acting injectable antipsychotics. J Clin Psychiatry 2006;67(suppl 5):15–18
4. Remington G, Mamo D, Labelle A, et al. A PET study evaluating dopamine D2 receptor occupancy for long-acting injectable risperidone. Am J Psychiatry 2006;163(3):396–401
5. Kane JM, Eerdekens M, Lindenmayer JP, et al. Long-acting injectable risperidone: efficacy and safety of the first long-acting atypical antipsychotic. Am J Psychiatry 2003;160(6):1125–1132
6. Herriot P, Kheirani K. Survey of depot antipsychotic prescribing in southern Adelaide. Australas Psychiatry 2005;13(3):253–257
7. Carpenter WT Jr, Buchanan RW, Kirkpatrick B, et al. Comparative effectiveness of fluphenazine decanoate injections every 2 weeks versus every 6 weeks. Am J Psychiatry 1999;156(3):412–418
8. Nyberg S, Farde L, Halldin C, et al. D2 dopamine receptor occupancy during low-dose treatment with haloperidol decanoate. Am J Psychiatry 1995;152(2):173–178
9. Gharabawi GM, Gearhart NC, Lasser RA, et al. Maintenance therapy with once-monthly administration of long-acting injectable risperidone in patients with schizophrenia or schizoaffective disorder: a pilot study of an extended dosing interval. Ann Gen Psychiatry 2007 Jan;6:3
10. Simpson GM, Mahmoud RA, Lasser RA, et al. A 1-year double-blind study of 2 doses of long-acting risperidone in stable patients with schizophrenia or schizoaffective disorder. J Clin Psychiatry 2006 Aug;67(8):1194–1203
11. Eerdekens M, Van Hove I, Remmerie B, et al. Pharmacokinetics and

tolerability of long-acting risperidone in schizophrenia. Schizophr Res 2004;70(1):91–100
12. Tauscher J, Jones C, Remington G, et al. Significant dissociation of brain and plasma kinetics with antipsychotics. Mol Psychiatry 2002; 7(3):317–321
13. Farde L, Nordstrom AL, Wiesel FA, et al. Positron emission tomographic analysis of central D1 and D2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine: relation to extrapyramidal side effects. Arch Gen Psychiatry 1992;49(7):538–544
14. Kapur S, Zipursky R, Jones C, et al. Relationship between dopamine D(2) occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. Am J Psychiatry 2000;157(4): 514–520
15. Mamo D, Kapur S, Shammi CM, et al. A PET study of dopamine D2 and serotonin 5-HT2 receptor occupancy in patients with schizophrenia treated with therapeutic doses of ziprasidone. Am J Psychiatry 2004; 161(5):818–825
16. Kapur S, Zipursky RB, Remington G, et al. 5-HT2 and D2 receptor occupancy of olanzapine in schizophrenia: a PET investigation. Am J Psychiatry 1998;155(7):921–928
17. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 1987;13(2):261–276
18. Carson RE, Breier A, de Bartolomeis A, et al. Quantification of amphetamine-induced changes in [11C]raclopride binding with continuous infusion. J Cereb Blood Flow Metab 1997;17(4):437–447
19. Mintun MA, Raichle ME, Kilbourn MR, et al. A quantitative model for the in vivo assessment of drug binding sites with positron emission tomography. Ann Neurol 1984;15(3):217–227
20. Remington G, Kapur S, Zipursky R. The relationship between risperidone plasma levels and dopamine D2 occupancy: a positron emission tomographic study. J Clin Psychopharmacol 1998;18(1):82–83
21. Remmerie BM, Sips LL, de Vries R, et al. Validated method for the determination of risperidone and 9-hydroxyrisperidone in human plasma by liquid chromatography-tandem mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci 2003 Jan; 783(2):461–472
22. Remington G, Seeman P, Shammi C, et al. "Extended" antipsychotic dosing: rationale and pilot data. J Clin Psychopharmacol 2005;25(6): 611–613
23. Jolley AG, Hirsch SR, Morrison E, et al. Trial of brief intermittent neuroleptic prophylaxis for selected schizophrenic outpatients: clinical and social outcome at two years. BMJ 1990;301(6756):837–842
24. Gaebel W, Janner M, Frommann N, et al. First vs multiple episode schizophrenia: two-year outcome of intermittent and maintenance medication strategies. Schizophr Res 2002 Jan;53(1–2):145–159
25. Gaebel W. Intermittent medication: an alternative? Acta Psychiatr Scand Suppl 1994;382:33–38
26. Saeedi H, Remington G, Christensen BK. Impact of haloperidol, a dopamine D2 antagonist, on cognition and mood. Schizophr Res 2006 Jul;85(1–3):222–231
27. Mizrahi R, Rusjan P, Agid O, et al. Adverse subjective experience with antipsychotics and its relationship to striatal and extrastriatal D2 receptors: a PET study in schizophrenia. Am J Psychiatry 2007;164(4): 630–637

