REVIEW

CNS Neuroscience & Therapeutics

Antipsychotic Occupancy of Dopamine Receptors in Schizophrenia

Magdalena Nord[1] & Lars Farde[1,2]

1 Karolinska Institutet, Department of Clinical Neuroscience, Psychiatry Section, Karolinska University Hospital, Stockholm, Sweden
2 AstraZeneca Pharmaceuticals, Södertälje, Sweden

Keywords
Antipsychotic drugs; Dopamine receptors; Positron emission tomography; Schizophrenia.

Correspondence
Magdalena Nord, Karolinska Institutet, Department of Clinical Neuroscience, Psychiatry Section, R5:00, Karolinska University Hospital, SE-17176 Stockholm, Sweden.
Tel.: +46 8 517 73720;
Fax: +46 8 517 717 53;
E-mail: Magdalena.Nord@ki.se

doi: 10.1111/j.1755-5949.2010.00222.x

SUMMARY

Antipsychotic drugs were introduced in the early 50s on the basis of clinical observations in patients with schizophrenia. Experimental studies later revealed that antagonism at the D_2 dopamine receptor is a common characteristic of all antipsychotic drugs. In the 80s, the advent of brain imaging technologies such as positron emission tomography (PET) allowed for direct noninvasive studies of drug binding in treated patients. The concept receptor occupancy is defined as the fraction (%) of a receptor population that is occupied during treatment with an unlabelled drug. With regard to antipsychotic drugs, the radioligand [^{11}C]-raclopride has been the most widely used for binding to the D_2/D_3-dopamine receptors. The present review discusses the contribution from molecular imaging to the current understanding of mechanism of action (MoA) of antipsychotic drugs. Consistent initial PET-findings of high D2-receptor occupancy in the striatum of patients responding to different antipsychotic drug treatments provided clinical support for the dopamine hypothesis of antipsychotic drug action. It has subsequently been demonstrated that patients with extrapyramidal syndromes (EPS) have higher occupancy (above 80%) than patients with good response but no EPS (65–80%). The PET-defined interval for optimal antipsychotic drug treatment has been implemented in the evolvement of dose recommendations for classical as well as more recently developed drugs. Another consistent finding is lower D_2-occupancy during treatment with the prototype atypical antipsychotic clozapine. The MoA of clozapine remains to be fully understood and may include nondopaminergic mechanisms. A general limitation is that currently available PET-radioligands are not selective for any of the five dopamine receptor subtypes. Current attempts at developing such ligands may provide the tools required to refine further the MoA of antipsychotic drugs.

Prologue

Over the last 50 years, antipsychotic drugs have been widely used to treat psychotic disorders such as schizophrenia. The drugs were discovered empirically, and initially the mechanism of action (MoA) was entirely unknown. In the mid 60s it was suggested that antipsychotic drugs work through blockade of dopamine receptors [1,2]. A few years later, the advent of radioligand binding techniques [3] and the availability of 3H-labeled radioligands allowed for direct studies of antipsychotic drug binding to neuroreceptors. For a series of antipsychotic drugs, a close correlation was subsequently demonstrated between affinity for dopamine receptors *in vitro* and antipsychotic potency in man [4,5]. The results provided strong support for the view that the antipsychotic effect is mediated by blockade of dopamine receptors.

The existence of two distinct dopamine receptors—the D_1 and the D_2 receptors—were later proposed on the basis of pharmacological observations [6]. It was soon demonstrated that antipsychotic drugs bind primarily to the D_2 receptor subtype [7]. In addition, no correlation could be demonstrated between antipsychotic effect and markers for any other neurotransmission system [7].

Brain Imaging Methodology

With brain imaging techniques, such as positron emission tomography (PET) and single photon emission tomography (SPET), it became possible to study receptor binding directly in the living human brain. Wagner and coworkers were pioneers in this field, when they in 1983 demonstrated that D_2 dopamine receptors in the human brain could be visualized with [^{11}C]-N-methylspiperone [8]. Following [^{11}C]-N-methylspiperone, multiple new radioligands were developed for PET imaging of dopamine receptors. Among these, the selective D_2 antagonist [^{11}C]-raclopride, is the hitherto most commonly used [9,10].

The PET systems of the early 1980s had a resolution of 8–12 mm, and allowed for quantitative measurements of D_2 receptor binding only in large brain regions such as the striatum [11]. The

technology has since then been advanced and current high performance PET systems provide a resolution approaching 1.5 mm, which enables a more detailed mapping of the distribution of neuroreceptors in the human brain [12].

The development of iodine 123 ([^{123}I])-labeled radioligands has allowed for detection of D_2 receptors also by using single photon emission computed tomography (SPET). This imaging technique has the advantage of being widely available, and [^{123}I]-labeled radioligands can be produced at one center and transferred across continents. Despite advancements of the technology, the spatial resolution of SPET does not reach the spatial resolution of current PET systems. The requirement to use heavy radionuclides such as [^{123}I] or Technetium 99m ([^{m99}Tc]) also limits the development of suitable radioligands. The following review is thus focused on the use of PET to determine occupancy in relation to antipsychotic drug treatment.

Mechanism of Action of Classical Antipsychotic Drugs

Shortly after the introduction of PET receptor imaging, several laboratories demonstrated high D_2 receptor occupancy in single patients treated with antipsychotic drugs [13–16]. In an early study it was demonstrated that clinical treatment with any of 11 chemically distinct antipsychotic drugs resulted in 65–85% occupancy of D_2 dopamine receptors [17]. This study provided direct *in vivo* evidence for the hypothesis that the antipsychotic effect is mediated by D_2 dopamine receptor antagonism.

To corroborate the view that antipsychotic drugs act by occupying D_2 receptors, the next challenge was to relate the degree of receptor binding to clinical drug effects. In an initial open study, it was observed that occupancy above 80% was associated with an increased risk of extrapyramidal syndromes (EPS) whereas occupancy above 70% was sufficient to obtain antipsychotic effect [18]. Based on these observations, an optimal therapeutic window corresponding to 70–80% occupancy was proposed (Figure 1). The observation of a therapeutic window has later been supported by double-blind studies [19,20].

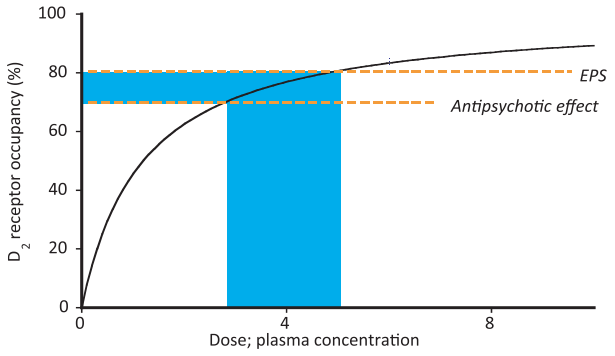

Figure 1 Relationship between plasma concentration (arbitrary values) and D_2 receptor occupancy with suggested thresholds for antipsychotic effect and extrapyramidal side effects (EPS)

Whereas the >80% occupancy level for EPS has been rather consistently confirmed, a defined threshold for antipsychotic effect of classical antipsychotics seems to be more difficult to demonstrate. In a study of Kapur and coworkers, the threshold for antipsychotic effect was suggested to be 65% rather than 70% [19]. An indirect support for a threshold around 65–70% D_2 occupancy is that recommended doses of more recently developed antipsychotic drugs correspond to this occupancy level [17,18,21,22]. However, a few antipsychotic drugs do not seem to fit the therapeutic window, which will be exemplified below.

The "Atypicality" Concept

The antipsychotic drug market was for many years dominated by classical antipsychotics, all known to cause EPS and serum prolactin elevations. Clozapine, introduced in the early 1970s, was the first atypical antipsychotic drug. Clozapine does not induce catalepsy in rodents and has a low propensity of causing EPS and serum prolactin elevations. In addition, clozapine has been shown to have effect also in patients not responding to classical antisychotic drugs [23], (for review see Ref. 24).

It was thus of interest to examine whether clozapine is "atypical" also with regard to the D_2 occupancy induced during clinical treatment. Indeed, initial PET and SPECT studies showed that the D_2 occupancy was below the 65–70% level suggested for classical antipsychotic drugs [18,25–27]. For instance, in a study including 17 patients treated with clozapine 125–600 mg/day, the D_2 occupancy varied between 20% and 67% [25].

Following clozapine, a number of new antipsychotics were introduced on the market—all being discussed as "atypical." Whereas the term "atypical" initially referred to antipsychotic drugs not inducing catalepsy in animals and not causing EPS and hyperprolactinemia, the "atypicality" concept has later been widened. Currently, there is no commonly accepted definition of atypicality, although most people seem to agree that a low risk of EPS and prolactin elevations is a common property of atypical compounds. As there is a lack of consensus regarding the atypicality concept, we will in this review entitle more recently introduced drugs as "second generation" antipsychotics.

Second Generation Antipsychotics

Whereas PET initially was used to understand the MoA of clinically available antipsychotic drugs, the method was subsequently applied to facilitate the development of new antipsychotic drugs [28,29].

The second generation drug risperidone was launched in 1994 [30]. For risperidone it was shown that daily dosing with 2–4 mg correspond to D_2 occupancy between 70% and 80% [31]. For olanzapine, marketed in 1996 [30], the D_2 occupancy of recommended doses (10–20 mg/day) was also within the suggested therapeutic window [32,33].

Ziprasidone was introduced in 2001 [34]. While the recommended dose range initially was 40–200 mg/day, it has later been suggested that a dose between 120 and 160 mg is optimal for clinical treatment [35]. The difference in bioavailability when ziprasidone is administered with a meal or in fasting conditions has been

put forward as a reason for difficulties in defining an optimal dose interval [35]. The few studies made on ziprasidone and D_2 occupancy indicate that also ziprasidone is clinically effective at D_2 occupancy covering the suggested therapeutic interval [36,37].

Quetiapine was approved in 1997 [30]. Interestingly, quetiapine has been shown to induce D_2 occupancy below the therapeutic window when administered in recommended doses [38–40]. As for clozapine, it is possible that the low D_2 occupancy can explain the low risk of EPS during quetiapine treatment [41]. However, quetiapine has a short half life and only transiently high plasma concentration [42]. It can thus not be excluded that maximal D_2 occupancy during quetiapine treatment has been underestimated [43,44].

In contrast, the D_2 occupancy during treatment with aripiprazole in clinical doses exceeds the proposed therapeutic window [45–47]. In control subjects, no EPS were reported or observed despite D_2 occupancy as high as 95% [48]. This finding is supported by the low incidence of EPS reported in clinical trials with aripiprazole [49]. The low risk of EPS despite high D_2 occupancy can be explained by the pharmacological properties of aripirazole. While other clinically used antipsychotics are antagonists at the D_2 receptor, aripiprazole is a partial agonist. Thus, the high D_2 occupancy is at a functional level compensated for by a modest intrinsic activity at the D_2 receptor [48].

Occupancy at Other Dopamine Receptor Subtypes

Although many attempts have been made to explain clozapine's superior antipsychotic effect, the MoA is still poorly understood. One hypothesis is that other receptors than the D_2 receptor are important for the antipsychotic effect (for review see Ref. 50).

Though the D_2 dopamine receptor subtype is the most widely examined, also other subtypes have been implicated in the pathophysiology and treatment of schizophrenia. Depending on coupling to second messenger system, the subtypes are divided in two families, with D_1 and D_5 belonging to the D_1 family and D_2, D_3, and D_4 belonging to the D_2 family. A limitation with currently used radioligands is that receptors within the same family cannot be selectively examined. Thus, when measuring D_2 receptors also D_3 receptors are included and when measuring D_1 receptors also D_5 receptors are labeled. Radioligands used for measurements of the same family of dopamine receptors can also differ in their specificity for the subtypes of receptors. For example, [^{11}C]-raclopride binds to D_2 and D_3 receptors whereas [^{11}C]-N-methylspiperone also binds to D_4 receptors [51].

In vitro studies have shown that most antipsychotic drugs bind to both D_2 and D_3 receptors. All antipsychotic drugs developed so far have about the same affinity for the D_2 and D_3 receptor subtype [52,53]. This represents a fundamental challenge to the present understanding of antipsychotic drug action, since it cannot be firmly established whether the antipsychotic effect is mediated by D_2 or D_3 antagonism. The dopamine agonist [^{11}C]-PHNO is the only PET radioligand developed so far that may bind preferentially to the D_3 receptor [54,55]. [^{11}C]-PHNO has together with [11C]raclopride recently been used to estimate the D_3 occupancy of clozapine, risperidone, and olanzapine in patients with schizophrenia. Despite high D_2-occupancy no occupancy at the D_3 receptor could be demonstrated, though these antipsychotics have high D_3-affinity *in vitro* [56]. The validity of using [^{11}C]-PHNO to examine D_3-receptor binding has been corroborated further in a recent study showing a dose-dependent effect of the D_3-antagonist GSK598809 in brain regions known to contain D_3 receptors [57]. However, despite this progress, the field would benefit from new radioligands being highly selective for the D_2 and D_3 receptor, respectively.

The D_4 dopamine receptor has also been suggested as a receptor potentially mediating antipsychotic effect and antagonism at this receptor has been suggested to account for the unique effect of clozapine. Most other antipsychotic drugs have similar or lower affinity for the D_4 receptor when compared to the affinity for D_2/D_3, whereas clozapine has higher affinity for D_4 than for D_2/D_3 [58]. As suitable D_4 receptor radioligands has not yet been developed, drug occupancy at the D_4 receptor has not been examined *in vivo* by PET.

Several radioligands have been developed for the D_1 dopamine receptor family. Even though occupancy at this receptor has not been related to antipsychotic effect, it has been suggested that the comparatively high D_1 occupancy by clozapine could contribute to the atypical properties [18,25,27,59].

Nondopaminergic receptors have also been proposed to have relevance for the therapeutic effect of antipsychotic drugs. Among several receptors nominated, the serotonergic 5-HT_{2A} receptor has been given particular attention (for review see Ref. 60). However, despite extensive research it has not been possible to conclusively demonstrate antipsychotic effect through mechanisms beyond dopaminergic neurotransmission.

Occupancy by Time

The relationship between plasma concentration and D_2 occupancy can be described by a curvilinear (hyperbolic) function (Figure 1). At high occupancy levels, approaching saturation, a substantial decrease in plasma concentration is required to significantly reduce the occupancy. At lower occupancy levels, where the occupancy-plasma concentration curve is steeper, even a smaller change in plasma concentration will translate to a change in occupancy.

The drug plasma concentration required to occupy 50% of available receptors corresponds to the affinity constant, Ki_{plasma} (the apparent inhibition constant). The Ki_{plasma} for a drug can be obtained by definition of the hyperbola, based on a series of PET measurements of dopamine occupancy at different plasma concentrations. Once the Ki_{plasma} is received, it is possible to estimate the time curve for occupancy corresponding to any arbitrary plasma concentration curve of the drug. Ideally, the free (not protein bound) plasma concentration should be used for this purpose. For a freely diffusible drug, the free plasma concentration should correspond to the free concentration in brain, with exception for drugs having affinity for transport proteins such as PGP (for review see Ref. 61).

An important question is if high D_2 occupancy needs to be maintained during a certain time for a drug to mediate antipsychotic effect. In initial studies after oral administration of classical antipsychotics, high D_2 occupancy has been shown to be

maintained throughout the dose interval [17,62,63]. Several second generation drugs have also been shown to maintain D_2 occupancy at a rather stable level throughout the dose interval [64]. However, during maintenance treatment with haloperidol in depot formulation it has been shown that relapse can be prevented even though the D_2 occupancy was moderate (52%, mean $n = 8$) in the end of the 4-week dose interval [65]. Comparable results have been achieved in a study with risperidon in depot formulation, where the dose interval was prolonged to 4 weeks instead of the recommended 2 weeks. Most of the patients had D_2 occupancy lower than the suggested therapeutic level at the end of the dose interval, but did not relapse [66]. However, a fundamental question is if the same time course of occupancy is required to prevent relapse as to treat acute psychosis.

An interesting observation is that the D_2 occupancy obtained at clinical dosing with quetiapine is only transiently high, and reaches low or undetectable levels at the end of the dose interval [38,40,43,44]. The authors proposed that high D_2 occupancy may not need to be maintained throughout the dose interval for the treatment of acute psychosis.

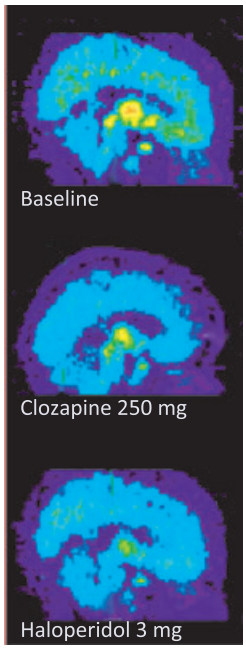

Figure 2 Parasagittal brain sections through the thalamic level showing [^{11}C]FLB457 binding in a control subject (above) a patient treated with clozapine 250 mg/day (middle) and a patient treated with haloperidol 3 mg/day (below) (Talvik et al., 2001) [79]

Striatal/Extrastriatal Regions

An early challenge in schizophrenia research has been to identify specific brain regions or neurocircuits of importance for the pathophysiology. With regard to the MoA of antipsychotic drugs it is of interest to understand if interference with dopaminergic neurotransmission in specific brain regions account for the antipsychotic effect. Besides the striatum, a region receiving dense dopaminergic innervation, limbic and cortical brain regions has attracted particular attention.

A considerable literature on striatal versus extrastriatal antipsychotic drug binding is based on experimental pharmacological findings in the 1970s and 1980s. From behavioral studies in rodents it was suggested that second generation antipsychotics may occupy extrastriatal D_2 receptors to a greater extent than striatal D_2 receptors [67,68]. In addition, the immediate early gene (IEG) c-Fos and its protein product Fos have been used as markers of neuronal activation. Both classical antipsychotics and clozapine increase Fos expression in the shell compartment of nucleus accumbens (part of the limbic system), whereas only classical antipsychotic drugs increase the expression of Fos in the dorsolateral striatum (related to EPS) [69].

Thus, already in the early days of PET research, there was an interest to examine low density receptor populations in extrastriatal brain regions. The commonly used radioligand [^{11}C]-raclopride provides a good signal for D_2 receptors in high density areas such as striatum [70]. However, the affinity is not high enough for imaging of areas with lower densities of D_2 receptors. A series of radioligands having high affinity for the D_2 receptor have therefore been developed. Of such radioligands [^{11}C]-FLB 457 [71] and [^{18}F]-fallypride [72] are the most widely used. In SPET research, the radioligand [^{123}I]-epidepride is used for the same purpose [73,74].

In studies comparing D_2 occupancy in different brain regions with classical antipsychotics (mainly haloperidol), no significant differences between striatal and extrastriatal occupancy have been found [75–79].

For second generation antipsychotic drugs, the results have been discrepant. Most studies on clozapine have shown a higher D_2 occupancy in extrastriatal regions [77,80–82](Figure 2), but the observations have been questioned on methodological grounds, since the measurements may have been made at preequilibrium conditions [83,84].

Studies with other second generation antipsychotics have also produced incongruent results. In studies using individual baseline levels to calculate occupancy, no difference in striatal compared to extrastriatal regions has been reported for risperidone and olanzapine [75,85–87]. As these studies were small, limited to only two antipsychotic drugs and in some cases included healthy controls, further studies with second generation drugs are needed to finally establish if some of them bind preferentially in extrastriatal regions or not.

The D_2 receptor was first cloned in rats [88] and soon thereafter also in humans [89–91]. It was discovered that the human D_2 receptor DNA was coding for two different mRNAs, generated by alternative splicing [90]. The products of these two mRNAs are a short and a long isoform of the D_2 receptor (D_2S and D_2L), differing by a sequence of 29 amino acids [92,93]. D_2S has been suggested to be primarily presynaptic whereas D_2L is primarily postsynaptic [93]. However, pharmacological characterization *in vitro* has shown that antipsychotic drugs have similar affinity for the two isoforms [94]. The two splice variants are thus not expected to provide a condition for regional differences in D_2 occupancy.

Methodological Considerations

The present review includes a large number of PET studies on D_2 occupancy. It may appear tempting to make attempts at a "*meta*-analysis" by pooling data from several studies. Caution must however be exercised before making such attempts. D_2 dopamine receptor density varies several fold between individuals [95]. Some studies have controlled for such interindividual differences by using individual baseline data at untreated conditions, whereas other studies have used a baseline reference value obtained from other subjects. Another variable between studies is the time between last dosing and PET. Here, the availability of plasma concentration values at time of PET is a prerequisite for comparisons. There are also considerable differences at a technical level. The referenced literature originates from studies carried out with several different PET-systems with widely different performance [12] as well as different radioligands though [^{11}C]raclopride has been used in most PET studies. In conclusion, a "*meta*-analysis" approach should ideally be limited to studies with [^{11}C]raclopride, performed with PET-systems of similar performance, and where individual baseline binding data are available as well as drug plasma concentrations at time of PET [22].

Epilogue

The clinically most important contribution from PET-studies on D_2 occupancy in antipsychotic drug treated patients is probably the identification of a 70% (65) to 80% window useful for development of dose recommendations for optimal treatment. This finding has contributed to the use of considerably lower dose-regimes that alleviates patients from unnecessary side effects. A fundamental question in the treatment of acute psychosis is if high D_2 occupancy has to be maintained throughout the dose interval or if intermittently high occupancy is sufficient. For future research on the pathophysiology and treatment of schizophrenia, the field would benefit from radioligands binding selectively to any of the five dopamine receptor subtypes and in particular D_2 and D_3 selective radioligands.

Conflict of Interest

The authors have no conflict of interest.

References

1. Carlsson A, Lindqvist M. Effect of chlorpromazine or haloperidol on formation of 3-methoxytyramine and normetanephrine in mouse brain. *Acta Pharmacol Toxicol (Copenh)* 1963;**20**:140–144.
2. van Rossum JM. The significance of dopamine-receptor blockade for the mechanism of action of neuroleptic drugs. *Arch Int Pharmacodyn Ther* 1966;**160**:492–494.
3. Snyder SH. Overview of neurotransmitter receptor binding. In: Yamamura HI, editor *Neurotransmitter receptor binding* New York: Raven Press, 1978;1–11.
4. Creese I, Burt DR, Snyder SH. Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. *Science* 1976;**192**:481–483.
5. Seeman P, Lee T, Chau-Wong M, Wong K. Antipsychotic drug doses and neuroleptic/dopamine receptors. *Nature* 1976;**261**:717–719.
6. Kebabian JW, Calne DB. Multiple receptors for dopamine. *Nature* 1979;**277**:93–96.
7. Peroutka SJ, Snyder SH. Relationship of neuroleptic drug effects at brain dopamine, serotonin, alpha-adrenergic, and histamine receptors to clinical potency. *Am J Psychiatry* 1980;**137**:1518–1522.
8. Wagner HN, Jr., Burns HD, Dannals RF, et al. Imaging dopamine receptors in the human brain by positron tomography. *Science* 1983;**221**:1264–1266.
9. Elsinga PH, Hatano K, Ishiwata K. PET tracers for imaging of the dopaminergic system. *Curr Med Chem* 2006;**13**:2139–2153.
10. Farde L, Ehrin E, Eriksson L, et al. Substituted benzamides as ligands for visualization of dopamine receptor binding in the human brain by positron emission tomography. *Proc Natl Acad Sci U S A* 1985;**82**:3863–3867.
11. Litton J, Bergstrom M, Eriksson L, Bohm C, Blomqvist G, Kesselberg M. Performance study of the PC-384 positron camera system for emission tomography of the brain. *J Comput Assist Tomogr* 1984;**8**:74–87.
12. Varrone A, Sjoholm N, Eriksson L, Gulyas B, Halldin C, Farde L. Advancement in PET quantification using 3D-OP-OSEM point spread function reconstruction with the HRRT. *Eur J Nucl Med Mol Imaging* 2009;**36**:1639–1650.
13. Cambon H, Baron JC, Boulenger JP, Loc'h C, Zarifian E, Maziere B. In vivo assay for neuroleptic receptor binding in the striatum. Positron tomography in humans. *Br J Psychiatry* 1987;**151**:824–830.
14. Farde L, Hall H, Ehrin E, Sedvall G. Quantitative analysis of D2 dopamine receptor binding in the living human brain by PET. *Science* 1986;**231**:258–261.
15. Smith M, Wolf AP, Brodie JD, et al. Serial [18F]N-methylspiroperidol PET studies to measure changes in antipsychotic drug D-2 receptor occupancy in schizophrenic patients. *Biol Psychiatry* 1988;**23**:653–663.
16. Maziere B, Loc'h C, Baron JC, Sgouropoulos P, Duquesnoy N, D'Antona R, Cambon H. In vivo quantitative imaging of dopamine receptors in human brain using positron emission tomography and [76Br]bromospiperone. *Eur J Pharmacol* 1985;**114**:267–272.
17. Farde L, Wiesel FA, Halldin C, Sedvall G. Central D2-dopamine receptor occupancy in schizophrenic patients treated with antipsychotic drugs. *Arch Gen Psychiatry* 1988;**45**:71–76.
18. Farde L, Nordstrom AL, Wiesel FA, Pauli S, Halldin C, Sedvall G. 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**:538–544.
19. Kapur S, Zipursky R, Jones C, Remington G, Houle S. 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**:514–520.
20. Nordstrom AL, Farde L, Wiesel FA, Forslund K, Pauli S, Halldin C, Uppfeldt G. Central D2-dopamine receptor occupancy in relation to antipsychotic drug effects: A double-blind PET study of schizophrenic patients. *Biol Psychiatry* 1993;**33**:227–235.
21. Klemm E, Grunwald F, Kasper S, et al. [123I]IBZM SPECT for imaging of striatal D2 dopamine receptors in 56 schizophrenic patients taking various neuroleptics. *Am J Psychiatry* 1996;**153**:183–190.
22. Nyberg S, Farde L. Non-equipotent doses partly explain differences among antipsychotics: Implications of PET studies. *Psychopharmacology (Berl)* 2000;**148**:22–23.
23. Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry* 1988;**45**:789–796.
24. Remington G, Kapur S. Atypical antipsychotics: Are some more atypical than others? *Psychopharmacology (Berl)* 2000;**148**:3–15.
25. Nordstrom AL, Farde L, Nyberg S, Karlsson P, Halldin C, Sedvall G. D1, D2, and 5-HT2 receptor occupancy in relation to clozapine serum concentration: A PET study of schizophrenic patients. *Am J Psychiatry* 1995;**152**:1444–1449.
26. Pilowsky LS, Costa DC, Ell PJ, Murray RM, Verhoeff NP, Kerwin RW. Clozapine, single photon emission tomography, and the D2 dopamine receptor blockade hypothesis of schizophrenia. *Lancet* 1992;**340**:199–202.
27. Farde L, Wiesel FA, Nordstrom AL, Sedvall G. D1- and D2-dopamine receptor occupancy during treatment with conventional and atypical neuroleptics. *Psychopharmacology (Berl)* 1989;**99**(Suppl):S28–31.
28. Lee CM, Farde L. Using positron emission tomography to facilitate CNS drug development. *Trends Pharmacol Sci* 2006;**27**:310–316.
29. Farde L. The advantage of using positron emission tomography in drug research. *Trends Neurosci* 1996;**19**:211–214.
30. Lieberman JA, Golden R, Stroup S, McEvoy J. Drugs of the psychopharmacological revolution in clinical psychiatry. *Psychiatr Serv* 2000;**51**:1254–1258.
31. Nyberg S, Eriksson B, Oxenstierna G, Halldin C, Farde L. Suggested minimal effective dose of risperidone based on PET-measured D2 and 5-HT2A receptor occupancy in schizophrenic patients. *Am J Psychiatry* 1999;**156**:869–875.
32. Nordstrom AL, Nyberg S, Olsson H, Farde L. Positron emission tomography finding of a high striatal D2 receptor occupancy in olanzapine-treated patients. *Arch Gen Psychiatry* 1998;**55**:283–284.
33. Kapur S, Zipursky RB, Remington G, Jones C, DaSilva J, Wilson AA, Houle S. 5-HT2 and D2 receptor occupancy of olanzapine in schizophrenia: A PET investigation. *Am J Psychiatry* 1998;**155**:921–928.
34. Silva RR. Psychopharmacology news. *J Child Adolesc Psychopharmacol* 2001;**11**:111–112.
35. Citrome L. Using oral ziprasidone effectively: The food effect and dose-response. *Adv Ther* 2009;**26**:739–748.
36. Mamo D, Kapur S, Shammi CM, Papatheodorou G, Mann S, Therrien F, Remington G. 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**:818–825.
37. Corripio I, Catafau AM, Perez V, et al. Striatal dopaminergic D2 receptor occupancy and clinical efficacy in psychosis exacerbation: A 123I-IBZM study with ziprasidone and haloperidol. *Prog Neuropsychopharmacol Biol Psychiatry* 2005;**29**:91–96.
38. Gefvert O, Bergstrom M, Langstrom B, Lundberg T, Lindstrom L, Yates R. Time course of central nervous dopamine-D2 and 5-HT2 receptor blockade and plasma drug concentrations after discontinuation of quetiapine (Seroquel) in patients with schizophrenia. *Psychopharmacology (Berl)* 1998;**135**:119–126.
39. Gefvert O, Lundberg T, Wieselgren IM, Bergstrom M, Langstrom B, Wiesel F, Lindstrom L. D(2) and 5HT(2A) receptor occupancy of different doses of quetiapine in schizophrenia: A PET study. *Eur Neuropsychopharmacol* 2001;**11**:105–110.
40. Mamo DC, Uchida H, Vitcu I, Barsoum P, Gendron A, Goldstein J, Kapur S. Quetiapine extended-release versus immediate-release formulation: A positron emission tomography study. *J Clin Psychiatry* 2008;**69**:81–86.
41. Baldwin CM, Scott LJ. Quetiapine extended release: In schizophrenia. *CNS Drugs* 2009;**23**:261–269.
42. DeVane CL, Nemeroff CB. Clinical pharmacokinetics of quetiapine: An atypical antipsychotic. *Clin Pharmacokinet* 2001;**40**:509–522.
43. Tauscher-Wisniewski S, Kapur S, Tauscher J, et al. Quetiapine: An effective antipsychotic in first-episode schizophrenia despite only transiently high dopamine-2 receptor blockade. *J Clin Psychiatry* 2002;**63**:992–997.
44. Kapur S, Zipursky R, Jones C, Shammi CS, Remington G, Seeman P. A positron emission tomography study of quetiapine in schizophrenia: A preliminary finding of an antipsychotic effect with only transiently high dopamine D2 receptor occupancy. *Arch Gen Psychiatry* 2000;**57**:553–559.
45. Kegeles LS, Slifstein M, Frankle WG, et al. Dose-occupancy study of striatal and extrastriatal dopamine D2 receptors by aripiprazole in schizophrenia with PET and [18F]fallypride. *Neuropsychopharmacology* 2008;**33**:3111–3125.
46. Mamo D, Graff A, Mizrahi R, Shammi CM, Romeyer F, Kapur S. Differential effects of aripiprazole on D(2), 5-HT(2), and 5-HT(1A) receptor occupancy in patients with schizophrenia: A triple tracer PET study. *Am J Psychiatry* 2007;**164**:1411–1417.
47. Grunder G, Fellows C, Janouschek H, et al. Brain and plasma pharmacokinetics of aripiprazole in patients with schizophrenia: An [18F]fallypride PET study. *Am J Psychiatry* 2008;**165**:988–995.
48. Yokoi F, Grunder G, Biziere K, et al. Dopamine D2 and D3 receptor occupancy in normal humans treated with the antipsychotic drug aripiprazole (OPC 14597): A study using positron emission tomography and [11C]raclopride. *Neuropsychopharmacology* 2002;**27**:248–259.
49. Swainston Harrison T, Perry CM. Aripiprazole: A review of its use in schizophrenia and schizoaffective disorder. *Drugs* 2004;**64**:1715–1736.
50. Miyamoto S, Duncan GE, Marx CE, Lieberman JA. Treatments for schizophrenia: A critical review of pharmacology and mechanisms of action of antipsychotic drugs. *Mol Psychiatry* 2005;**10**:79–104.
51. Seeman P, Guan HC, Van Tol HH. Dopamine D4 receptors elevated in schizophrenia. *Nature* 1993;**365**:441–445.
52. Sokoloff P, Giros B, Martres MP, Bouthenet ML, Schwartz JC. Molecular cloning and characterization of a novel dopamine receptor (D3) as a target for neuroleptics. *Nature* 1990;**347**:146–51.
53. Schwartz JC, Levesque D, Martres MP, Sokoloff P. Dopamine D3 receptor: Basic and clinical aspects. *Clin Neuropharmacol* 1993;**16**:295–314.
54. Graff-Guerrero A, Willeit M, Ginovart N, et al. Brain region binding of the D2/3 agonist [11C]-(+)-PHNO and the D2/3 antagonist [11C]raclopride in healthy humans. *Hum Brain Mapp* 2008;**29**:400–410.
55. Narendran R, Slifstein M, Guillin O, et al. Dopamine (D2/3) receptor agonist positron emission tomography radiotracer [11C]-(+)-PHNO is a D3 receptor preferring agonist in vivo. *Synapse* 2006;**60**:485–495.
56. Graff-Guerrero A, Mamo D, Shammi CM, et al. The effect of antipsychotics on the high-affinity state of D2 and D3 receptors: A positron emission tomography study With [11C]-(+)-PHNO. *Arch Gen Psychiatry* 2009;**66**:606–615.
57. Searle G, Beaver JD, Comley RA, et al. Imaging dopamine D3 receptors in the human brain with positron emission tomography, [11C]PHNO, and a selective D3 receptor antagonist. *Biol Psychiatry* 2010;**68**:392–399.
58. Van Tol HH, Bunzow JR, Guan HC, Sunahara RK, Seeman P, Niznik HB, Civelli O. Cloning of the gene for a human dopamine D4 receptor with high affinity for the antipsychotic clozapine. *Nature* 1991;**350**:610–614.
59. Tauscher J, Hussain T, Agid O, et al. Equivalent occupancy of dopamine D1 and D2 receptors with clozapine: Differentiation from other atypical antipsychotics. *Am J Psychiatry* 2004;**161**:1620–1625.
60. Richelson E. Receptor pharmacology of neuroleptics: Relation to clinical effects. *J Clin Psychiatry* 1999;**60**(Suppl 10):5–14.
61. Innis RB, Cunningham VJ, Delforge J, et al. Consensus nomenclature for in vivo imaging of reversibly binding radioligands. *J Cereb Blood Flow Metab* 2007;**27**:1533–1539.
62. Nyberg S, Nordstrom AL, Halldin C, Farde L. Positron emission tomography studies on D2 dopamine receptor occupancy and plasma antipsychotic drug levels in man. *Int Clin Psychopharmacol* 1995;**10**(Suppl 3):81–85.
63. Baron JC, Martinot JL, Cambon H, et al. Striatal dopamine receptor occupancy during and following withdrawal from neuroleptic treatment: Correlative evaluation by positron emission tomography and plasma prolactin levels. *Psychopharmacology (Berl)* 1989;**99**:463–472.
64. Catafau AM, Penengo MM, Nucci G, et al. Pharmacokinetics and time-course of D(2) receptor occupancy induced by atypical antipsychotics in stabilized schizophrenic patients. *J Psychopharmacol* 2008;**22**:882–894.
65. Nyberg S, Farde L, Halldin C, Dahl ML, Bertilsson L. D2 dopamine receptor occupancy during low-dose treatment with haloperidol decanoate. *Am J Psychiatry* 1995;**152**:173–178.
66. Uchida H, Mamo DC, Kapur S, et al. Monthly administration of long-acting injectable risperidone and striatal dopamine D2 receptor occupancy for the management of schizophrenia. *J Clin Psychiatry* 2008;**69**:1281–1286.
67. Ogren SO, Hall H, Kohler C, Magnusson O, Lindbom LO, Angeby K, Florvall L. Remoxipride, a new potential antipsychotic compound with selective antidopaminergic actions in the rat brain. *Eur J Pharmacol* 1984;**102**:459–474.
68. Arnt J, Skarsfeldt T, Hyttel J. Differentiation of classical and novel antipsychotics using animal models. *Int Clin Psychopharmacol* 1997;**12**(Suppl 1):S9–17.
69. Deutch AY. Identification of the neural systems subserving the actions of clozapine: Clues from immediate-early gene expression. *J Clin Psychiatry* 1994;**55**(Suppl B):37–42.
70. Hall H, Kohler C, Gawell L, Farde L, Sedvall G. Raclopride, a new selective ligand for the dopamine-D2 receptors. *Prog Neuropsychopharmacol Biol Psychiatry* 1988;**12**:559–568.
71. Olsson H, Halldin C, Swahn CG, Farde L. Quantification of [11C]FLB 457 binding to extrastriatal dopamine receptors in the human brain. *J Cereb Blood Flow Metab* 1999;**19**:1164–1173.
72. Mukherjee J, Christian BT, Dunigan KA, Shi B, Narayanan TK, Satter M, Mantil J. Brain imaging of 18F-fallypride in normal volunteers: Blood analysis, distribution, test-retest studies, and preliminary assessment of sensitivity to aging effects on dopamine D-2/D-3 receptors. *Synapse* 2002;**46**:170–188.
73. Kornhuber J, Brucke T, Angelberger P, Asenbaum S, Podreka I. SPECT imaging of dopamine receptors with [123I]epidepride: Characterization of uptake in the human brain. *J Neural Transm Gen Sect* 1995;**101**:95–103.
74. Kuikka JT, Akerman KK, Hiltunen J, et al. Striatal and extrastriatal imaging of dopamine D2 receptors in the living human brain with [123I]epidepride single-photon emission tomography. *Eur J Nucl Med.* 1997;**24**:483–487.
75. Kessler RM, Ansari MS, Riccardi P, Li R, Jayathilake K, Dawant B, Meltzer HY. Occupancy of striatal and extrastriatal dopamine D2/D3 receptors by olanzapine and haloperidol. *Neuropsychopharmacology* 2005;**30**:2283–2289.
76. Farde L, Suhara T, Nyberg S, Karlsson P, Nakashima Y, Hietala J, Halldin C. A PET-study of [11C]FLB 457 binding to extrastriatal D2-dopamine receptors in healthy subjects and antipsychotic drug-treated patients. *Psychopharmacology (Berl)* 1997;**133**:396–404.
77. Xiberas X, Martinot JL, Mallet L, Artiges E, Loc HC, Maziere B, Paillere-Martinot ML. Extrastriatal and striatal D(2) dopamine receptor blockade with haloperidol or new antipsychotic drugs in patients with schizophrenia. *Br J Psychiatry* 2001;**179**:503–508.
78. Bigliani V, Mulligan RS, Acton PD, et al. In vivo occupancy of striatal and temporal cortical D2/D3 dopamine receptors by typical antipsychotic drugs. [123I]epidepride single photon emission tomography (SPET) study. *Br J Psychiatry* 1999;**175**:231–238.
79. Talvik M, Nordstrom AL, Nyberg S, Olsson H, Halldin C, Farde L. No support for regional selectivity in clozapine-treated patients: A PET study with [(11)C]raclopride and [(11)C]FLB 457. *Am J Psychiatry* 2001;**158**:926–930.
80. Grunder G, Landvogt C, Vernaleken I, et al. The striatal and extrastriatal D2/D3 receptor-binding profile of clozapine in patients with schizophrenia. *Neuropsychopharmacology* 2006;**31**:1027–1035.
81. Kessler RM, Ansari MS, Riccardi P, Li R, Jayathilake K, Dawant B, Meltzer HY. Occupancy of striatal and extrastriatal dopamine D2 receptors by clozapine and quetiapine. *Neuropsychopharmacology* 2006;**31**:1991–2001.
82. Pilowsky LS, Mulligan RS, Acton PD, Ell PJ, Costa DC, Kerwin RW. Limbic selectivity of clozapine. *Lancet* 1997;**350**:490–491.
83. Erlandsson K, Bressan RA, Mulligan RS, Ell PJ, Cunningham VJ, Pilowsky LS. Analysis of D2 dopamine receptor occupancy with quantitative SPET using the high-affinity ligand [123I]epidepride: Resolving conflicting findings. *Neuroimage* 2003;**19**:1205–1214.
84. Olsson H, Farde L. Potentials and pitfalls using high affinity radioligands in PET and SPET determinations on regional drug induced D2 receptor occupancy–a simulation study based on experimental data. *Neuroimage* 2001;**14**:936–945.
85. Ito H, Arakawa R, Takahashi H, et al. No regional difference in dopamine D2 receptor occupancy by the second-generation antipsychotic drug risperidone in humans: A positron emission tomography study. *Int J Neuropsychopharmacol* 2009;**12**:667–675.
86. Tauscher J, Jones C, Remington G, Zipursky RB, Kapur S. Significant dissociation of brain and plasma kinetics with antipsychotics. *Mol Psychiatry* 2002;**7**:317–321.
87. Yasuno F, Suhara T, Okubo Y, Sudo Y, Inoue M, Ichimiya T, Tanada S. Dose relationship of limbic-cortical D2-dopamine receptor occupancy with risperidone. *Psychopharmacology (Berl)* 2001;**154**:112–114.
88. Bunzow JR, Van Tol HH, Grandy DK, et al. Cloning and expression of a rat D2 dopamine receptor cDNA. *Nature* 1988;**336**:783–787.
89. Grandy DK, Marchionni MA, Makam H, et al. Cloning of the cDNA and gene for a human D2 dopamine receptor. *Proc Natl Acad Sci U S A* 1989;**86**:9762–9766.
90. Dal Toso R, Sommer B, Ewert M, et al. The dopamine D2 receptor: Two molecular forms generated by alternative splicing. *EMBO J.* 1989;**8**:4025–4034.
91. Selbie LA, Hayes G, Shine J. The major dopamine D2

receptor: Molecular analysis of the human D2A subtype. *DNA* 1989;**8**:683–689.
92. Picetti R, Saiardi A, Abdel Samad T, Bozzi Y, Baik JH, Borrelli E. Dopamine D2 receptors in signal transduction and behavior. *Crit Rev Neurobiol* 1997;**11**:121–142.
93. Usiello A, Baik JH, Rouge-Pont F, et al. Distinct functions of the two isoforms of dopamine D2 receptors. *Nature* 2000;**408**:199–203.
94. Malmberg A, Jackson DM, Eriksson A, Mohell N. Unique binding characteristics of antipsychotic agents interacting with human dopamine D2A, D2B, and D3 receptors. *Mol Pharmacol* 1993;**43**:749–754.
95. Farde L, Hall H, Pauli S, Halldin C. Variability in D2-dopamine receptor density and affinity: A PET study with [11C]raclopride in man. *Synapse* 1995;**20**:200–208.