Dissociation in Pharmacokinetic Attenuation Between Central Dopamine D_2 Receptor Occupancy and Peripheral Blood Concentration of Antipsychotics: A Systematic Review

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ABSTRACT

Objective: The objective of this study was to examine the extent of possible dissociation in pharmacokinetic decay between central dopamine D_2 receptor occupancy with antipsychotics and their peripheral blood concentrations.

Data Sources: MEDLINE and Embase were searched using the following keywords: (*positron emission tomography* OR *PET* OR *single-photon emission computed tomography* OR *SPECT*) AND (*dopamine* OR *D2*) AND (*receptor** OR *occupanc**) AND *antipsychotic**, with a limitation of English language (last search: December 14, 2019).

Study Selection: The search identified 18 studies that met the following criteria: (1) including patients with schizophrenia spectrum disorders and/or healthy subjects, (2) using positron emission tomography or single-photon emission computed tomography, and (3) examining the time courses of D_2 occupancy with antipsychotics and their blood concentrations.

Data Extraction: The ratios of D_2 occupancy reduction rate (%) from peak to blood concentration reduction rate (%) from peak (relative attenuation ratio) were calculated.

Results: Among the studies, oral risperidone, olanzapine, quetiapine, aripiprazole, ziprasidone, perospirone, haloperidol, sulpiride, and clozapine and long-acting injectable risperidone and haloperidol were included. Relative attenuation ratios were less than 1, indicating a slower central versus peripheral attenuation, across the time points for all antipsychotic types and doses with only a few exceptions. The ratio decreased in a dose-dependent as well as a peak D_2 occupancy–dependent fashion. It contrarily increased in a time-dependent manner.

Conclusions: The findings indicate pharmacokinetic attenuation of antipsychotics was generally slower at the central versus the peripheral level and pose a critical challenge to the current dosing strategy that primarily relies on peripheral pharmacokinetics of antipsychotics.

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All currently available antipsychotics are assumed to exert their effects by attenuating central dopaminergic neural transmission. It has been established that a 65%–80% dopamine D_2 receptor occupancy is associated with antipsychotic therapeutic efficacy while minimizing extrapyramidal side effects in the acute-phase treatment of schizophrenia,[1–3] although recent studies[4] suggest that antipsychotic medications act not only by blocking dopamine D_2 receptors but also by modulating dopamine release, synthesis, and metabolism. On the other hand, it remains unclear as to whether dopamine D_2 receptor blockade with an antipsychotic in the brain changes with time in close parallel with its concentration in peripheral blood. Indeed, some studies[5,6] have indicated that attenuation in dopamine D_2 receptor occupancy is slower than that in plasma pharmacokinetic concentrations of risperidone and olanzapine, whereas this appears not to be the case for ziprasidone.[7]

This issue is of high clinical relevance since central rather than peripheral pharmacokinetics should have more direct implication in deciding appropriate dosing intervals and switching methods of antipsychotics, assuming that relatively constant central antagonism with antipsychotics is required in the treatment of schizophrenia. In our secondary analysis[8] of the Clinical Antipsychotic Trials of Intervention Effectiveness study, in which either a once-daily or twice-daily dosing regimen of perphenazine was randomly assigned, there were no significant differences in any clinical outcomes between the two dosing regimens despite the short peripheral half-life of 8–12 hours for perphenazine. Also, as was noted in our cross-sectional study,[9] clozapine, another antipsychotic with a short half-life in peripheral blood (ie, 12–16 hours), has actually been administrated once a day in approximately 75% of patients in the North America. Furthermore, in our recent meta-analysis of randomized controlled trials comparing immediate versus gradual discontinuation of the

Clinical Points

- Pharmacokinetics of antipsychotics are generally slower centrally than peripherally.
- The relative attenuation ratio of antipsychotics decreased in a dose-dependent as well as a peak D_2 occupancy–dependent fashion. It contrarily increased in a time-dependent manner.
- These findings pose a critical challenge to the current dosing strategy that primarily relies on peripheral pharmacokinetics of antipsychotics in the management of schizophrenia.

previous antipsychotic during switching antipsychotics,[10] no significant differences were shown in any clinical outcomes between the two discontinuation strategies. These findings may collectively point to a possibility of dissociation between decay in central dopamine D_2 receptor occupancy with antipsychotics versus peripheral plasma concentrations. Alternatively, continuous D_2 receptor blockade may not be necessary for the maintenance treatment,[11–14] a notion that had some support in a recent clinical trial.[15]

To date, there have been several studies[7,16–20] examining the time courses of dopamine D_2 receptor occupancy with various types of antipsychotic through a usage of positron emission tomography (PET) or single-photon emission computed tomography (SPECT) in relation to blood antipsychotic concentrations (ie, simultaneous measurements of both occupancy and concentration at multiple time points). Although these studies suggested that attenuation at the central level was slower than peripherally regarding some antipsychotics, eg, haloperidol, quetiapine, and aripiprazole, it is not clear whether this dissociation between central and peripheral attenuation can extend to all antipsychotics and what factors affect the dissociation. To further shed light on this important issue and guide better management for patients with schizophrenia, we conducted a systematic review of these imaging studies.

METHODS

Literature Search

We conducted a systematic literature search in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Statement.[21] MEDLINE and Embase were searched using the following keywords: (*positron emission tomography* OR *PET* OR *single-photon emission computed tomography* OR *SPECT*) AND (*dopamine* OR *D2*) AND (*receptor** OR *occupanc**) AND *antipsychotic**, with a limitation of humans and English language (last search: December 14, 2019).

Study Selection

Two authors (S.K. and Y.M.) independently selected studies that met the following eligibility criteria: (1) including patients with schizophrenia spectrum disorders (ie, schizophrenia, schizoaffective disorder, and schizophreniform disorder) and/or healthy subjects, (2) using PET or SPECT, and (3) examining the time courses of dopamine D_2 receptor occupancy as well as blood concentrations of antipsychotics (ie, simultaneous measurements of both indices at multiple time points). Any disagreements about study selection were resolved by consensus with the corresponding author (H.T.).

Data Extraction

The following data were collected from these studies: (1) study information such as publication year, study design, number of participants, and type and dose of an antipsychotic; (2) dopamine D_2 receptor occupancy with antipsychotics; and (3) blood (plasma or serum) antipsychotic concentrations. Two authors (S.K. and Y.M.) independently extracted the data. Any disagreements about data extraction were resolved by consensus with the corresponding author (H.T.). Data presented in graph form were extracted automatically using an online computer program (Dexter; German Astrophysical Virtual Observatory, University of Heidelberg, Germany; 2008; available at http://dc.zah.uni-heidelberg.de/dexter/ui/ui/custom). If the studies did not provide sufficient data, we contacted the corresponding authors in an attempt to obtain additional information.

Our primary interest was the relationship between the time courses of central dopamine D_2 receptor occupancy in relation to peripheral blood concentrations of antipsychotics. Hence, we calculated the ratio of D_2 occupancy reduction rate (%) from the peak to blood concentration reduction rate (%) from the peak, as a relative attenuation ratio. For example, we calculated the data from the study by Tauscher et al[6] as follows: When D_2 occupancy and blood concentration after taking olanzapine 15–20 mg was 83 ± 2% and 66 ± 4 ng/mL at 6h, 78 ± 4% and 28 ± 4 ng/mL at 24h, and 61 ± 6% and 16 ± 3 ng/mL at 48 h, respectively,

- Reduction rate of D_2 occupancy at 24 h = (83 – 78)/83 = 0.060
- Reduction rate of plasma concentration at 24 h = (66 – 28)/66 = 0.575
- Relative attenuation ratio at 24 h = 0.060/0.575 = 0.10
- Reduction rate of D_2 occupancy at 48 h = (83 – 61)/83 = 0.265
- Reduction rate of plasma concentration at 48 h = (66 – 16)/66 = 0.757
- Relative attenuation ratio at 48 h = 0.265/0.757 = 0.35

If the reduction rate of D_2 occupancy is lower (ie, slower) than that of blood concentrations, the ratio should take a value less than 1 (as the relative attenuation ratio is low, central attenuation is more gradual). For oral antipsychotics, we used the plasma half-life ($T_{1/2}$) of each medication as a unit of time from the peak (Supplementary Table 1). We referred to the article by Hiemke et al[22] for $T_{1/2}$ of antipsychotics. If $T_{1/2}$ was described in a range, we adopted the intermediate value between maximum and minimum values. For $T_{1/2}$ of perospirone, we referred to another

Table 1. PET or SPECT Studies Examining Time Courses of Dopamine D_2 Receptor Occupancy and Blood Concentrations of Antipsychotics

Study	PET or SPECT	Radioligand	Study Design	N	Subjects	Subjects for Baseline Binding Potential	Antipsychotic Type and Dose
Mamo et al 2008[29]	PET	[^{11}C]Raclopride	Drug discontinuation	12	SSD	Healthy	Quetiapine IR and XR 300, 600, 800 mg/d
Nord et al 2011[19]	PET	[^{11}C]Raclopride	Drug discontinuation	11	Healthy	Same subjects	Quetiapine IR and XR 300 mg/d
Tauscher-Wisniewski et al 2002[35]	PET	[^{11}C]Raclopride	Drug discontinuation	9	SSD	Different subjects with SSD	Quetiapine IR 400–750 mg/d
Gefvert et al 1998[17]	PET	[^{11}C]Raclopride	Drug discontinuation	4	SSD	Healthy	Quetiapine IR 450 mg/d
Tauscher et al 2002[6] (1)	PET	[^{11}C]Raclopride [^{11}C] FLB457	Single-dose drug administration	8	Healthy	Same subjects	Olanzapine 15 mg/d, Risperidone 3–4 mg/d
Tauscher et al 2002[6] (2)	PET	[^{11}C]Raclopride [^{11}C] FLB457	Drug discontinuation	5	SSD	Different subjects with SSD	Olanzapine 15–20 mg/d, Risperidone 3 mg/d
Catafau et al 2011[25]	SPECT	[^{123}I]Iodobenzamide	Drug discontinuation	3	SSD	Healthy	Risperidone 6 mg/d
Kim et al 2012[28]	PET	[^{11}C]Raclopride	Single-dose drug administration	18	Healthy	Same subjects	Aripiprazole 2, 5, 10, 30 mg/d
Suzuki et al 2013[7]	PET	[^{11}C]Raclopride	Drug discontinuation	12	SSD	Healthy	Ziprasidone 120 mg/d
Arakawa et al 2010[16]	PET	[11C]Raclopride	Single-dose drug administration	4	Healthy	Same subjects	Perospirone 16 mg/d
Nordström et al 1992[20]	PET	[^{11}C]Raclopride	Single-dose drug administration	2	Healthy	Same subjects	Haloperidol 7.5 mg/d
Farde et al 1988[26]	PET	[^{11}C]Raclopride	Drug discontinuation	2	SSD	Different subjects with SSD	Sulpiride 600 mg/d, Haloperidol 6 mg/d
Takano et al 2006[34]	PET	[^{11}C]FLB457	Drug discontinuation	2	SSD	Different subjects with SSD	Clozapine 200, 600 mg/d
Remington et al 2006[33]	PET	[^{11}C]Raclopride	Drug discontinuation	9	SSD	Different subjects with SSD Healthy	Risperidone LAI 25, 50, 75 mg/2w
Nyberg et al 1995[31]	PET	[^{11}C]Raclopride	Drug discontinuation	8	SSD	Healthy	Haloperidol LAI 30–50 mg/4w
Nyberg et al 1997[30]	PET	[^{11}C]Raclopride	Drug discontinuation	3	SSD	Healthy	Haloperidol LAI 30, 50 mg/4w
Regenthal et al 1997[32]	SPECT	[^{123}I]Iodobenzamide	Drug discontinuation	8	SSD	Healthy	Haloperidol LAI 30–70 mg/4w
Kapur et al 2000[27]	PET	[^{11}C]Raclopride	Drug discontinuation	2	SSD	Different subjects with SSD Healthy	Quetiapine IR 400, 450 mg/d

Abbreviations: IR = immediate release, LAI = long-acting injection, PET = positron emission tomography, SPECT = single-photon emission computed tomography, SSD = schizophrenia spectrum disorders, XR = extended release.

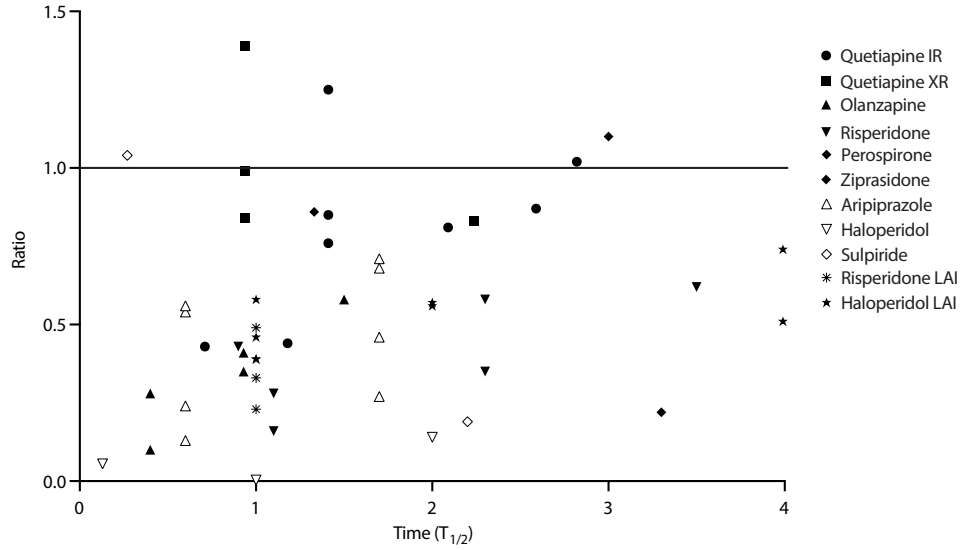
reference,[23] because no data were available in the original reference.[22] We excluded 1 study[24] using intramuscular injection of zuclopenthixol because no data regarding its $T_{1/2}$ were available to our knowledge. It should be noted that for the study by Nordström et al,[20] we excluded some data because necessary data were not available. For long-acting injectable antipsychotics, we used the injection interval of each medication as a unit of time from the peak instead of $T_{1/2}$, because in all the included studies PET was performed at multiple time points based on the injection interval. In addition, we looked at (1) the relationship between relative attenuation ratio and antipsychotic dose, (2) the time course of relative attenuation ratio, and (3) the relationship between the peak D_2 occupancy and relative attenuation ratio. These additional analyses were limited to the data in the striatum because most studies examined D_2 occupancy therein; if both the putamen and caudate were examined separately, we adopted the data in the putamen because there were studies that examined only the putamen but no studies that examined only the caudate. In the study by Gefvert et al,[17] D_2 occupancy was examined in both the putamen and the caudate, but the reported data were unclear regarding the region of interest; thus, we conservatively adopted the D_2 occupancy data that were against our hypothesis, ie, higher ratios.

RESULTS

Included Studies

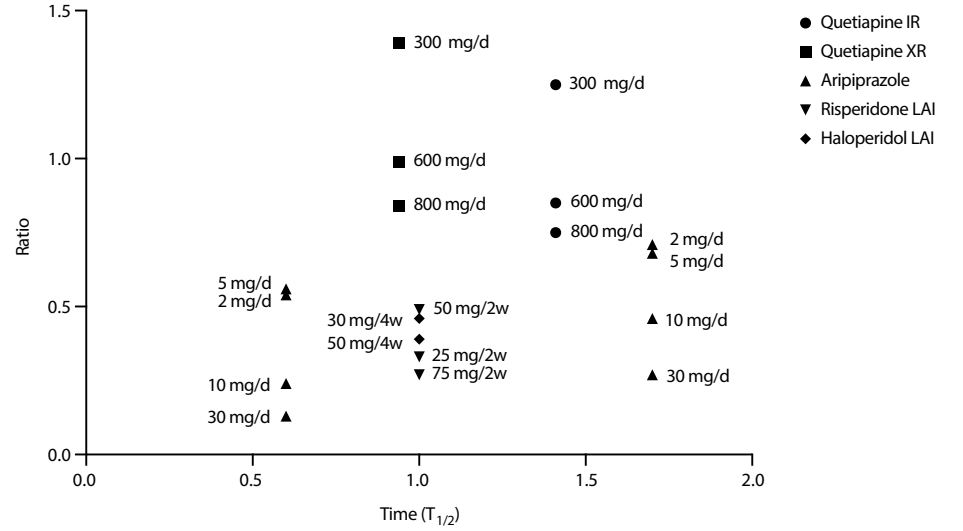
A total of 18 studies from 17 articles[6,7,16,17,19,20,25–35] that met our eligibility criteria were included in the systematic review (Supplementary Figure 1). The characteristics of these studies are summarized in Table 1. Among the included studies, the following antipsychotics were examined: risperidone (3 studies), olanzapine (2 studies), quetiapine immediate release (IR) (5 studies), quetiapine extended release (XR) (2 studies), aripiprazole (1 study), ziprasidone (1 study), perospirone (1 study), haloperidol (2 studies), sulpiride (1 study), clozapine (1 study), risperidone long-acting injection (LAI) (1 study), and haloperidol LAI (3 studies). Thirteen and 5 studies targeted patients with schizophrenia spectrum disorders and healthy subjects, respectively. Fifteen, 3, and 2 studies used [^{11}C] raclopride PET for the striatum, [^{11}C]FLB457 PET for the extrastriatum, and [^{123}I]iodobenzamide SPECT for the striatum, respectively. For the baseline binding potential in a drug-free state, which was used to calculate dopamine D_2 receptor occupancy, 5, 7, 4, and 2 studies utilized the data of the study participants, healthy subjects different from the study participants, patients with schizophrenia spectrum disorders different from the study participants, and both

Figure 1. Antipsychotic D_2 Occupancy/Blood Concentration Reduction Ratio



Abbreviations: IR = immediate release, LAI = long-acting injection, $T_{1/2}$ = half-life, XR = extended release.

Figure 2. Antipsychotic D_2 Occupancy/Blood Concentration Reduction Ratio in Studies Comparing Multiple Doses of Antipsychotics



Abbreviations: IR = immediate release, LAI = long-acting injection, $T_{1/2}$ = half-life, XR = extended release.

healthy subjects and patients with schizophrenia spectrum disorders different from the study participants, respectively. For blood antipsychotic concentrations, 14 and 4 studies examined plasma and serum concentrations, respectively.

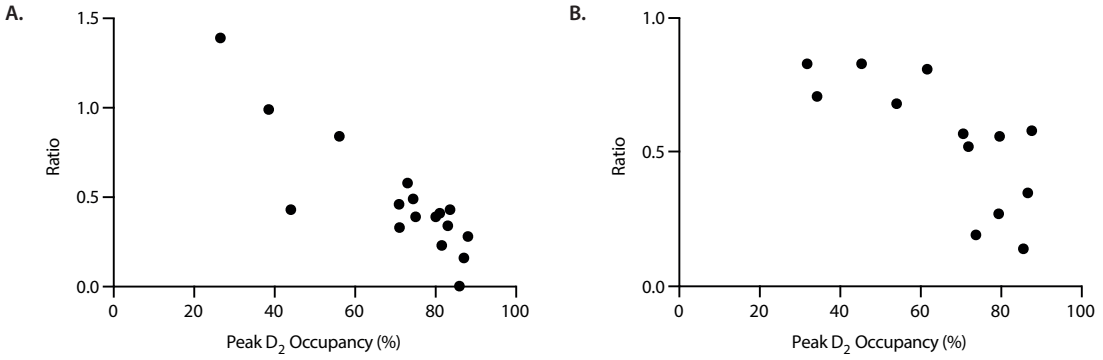
Relative Attenuation Ratio in the Striatum Versus Blood Concentrations From Peak

All of the extracted data of studies examining time courses of dopamine D_2 receptor occupancy in the striatum and blood concentrations of antipsychotics are shown in Supplementary Table 2. Figure 1 summarizes the ratios of D_2 occupancy reduction rate (%) from peak to blood antipsychotic concentration reduction rate (%) from peak and time from peak at up to 4 $T_{1/2}$. Ratios were less than 1 across the time points for all antipsychotic types and doses, except quetiapine IR 300/450 mg/d, quetiapine XR 300 mg/d, sulpiride 600 mg/d, and ziprasidone 120 mg/d. There were no obvious differences in the dissociation between first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs), although the data on only haloperidol and sulpiride were available for FGAs.

Factors Related to Relative Attenuation Ratio

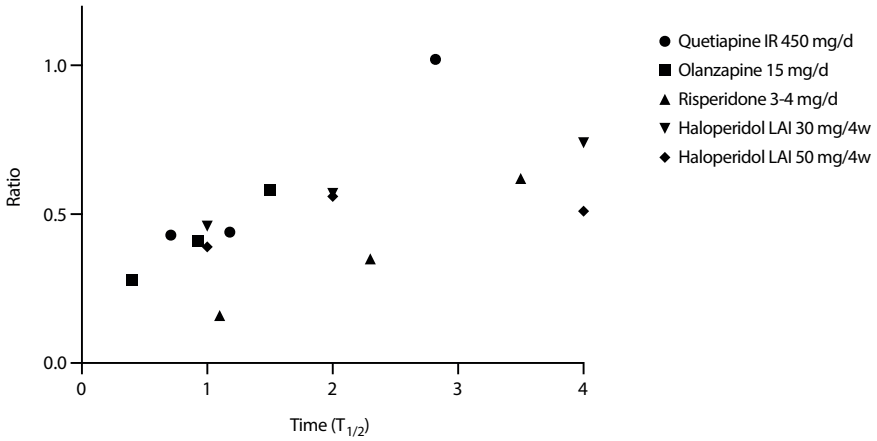
Dose of antipsychotics. Figure 2 summarizes the data from studies comparing multiple doses of antipsychotics. The ratios decreased as dose increased: the ratios for

Figure 3. Peak D_2 Occupancy Versus Ratio[a] at (A) 1.0 ± 0.3 $T_{1/2}$ and (B) 2.0 ± 0.3 $T_{1/2}$



[a]Antipsychotic D_2 occupancy/blood concentration reduction ratio.
Abbreviation: $T_{1/2}$ = half-life.

Figure 4. Ratio[a] in Studies Examining Antipsychotic D_2 Occupancy and Blood Concentrations at ≥ 4 Time Points



[a]Antipsychotic D_2 occupancy/blood concentration reduction ratio.
Abbreviations: IR = immediate release, LAI = long-acting injection, $T_{1/2}$ = half-life.

quetiapine IR at 1.41 $T_{1/2}$ were 1.25 for 300 mg/d, 0.85 for 600 mg/d, and 0.75 for 800 mg/d; the ratios for quetiapine XR at 0.94 $T_{1/2}$ were 1.39 for 300 mg/d, 0.99 for 600 mg/d, and 0.84 for 800 mg/d; the ratios for aripiprazole at 1.70 $T_{1/2}$ were 0.71 for 2 mg/d, 0.68 for 5 mg/d, 0.46 for 10 mg/d, and 0.27 for 30 mg/d; the ratios for haloperidol LAI at 1 $T_{1/2}$ were 0.46 for 30 mg/4 weeks and 0.39 for 50 mg/4 weeks; the ratios for haloperidol LAI at 2 $T_{1/2}$ were 0.57 for 30 mg/4 weeks and 0.56 for 50 mg/4 weeks (see Figure 4); and the ratios for haloperidol LAI at 4 $T_{1/2}$ were 0.74 for 30 mg/4 weeks and 0.51 for 50 mg/4 weeks (see Figure 4).

Peak D_2 occupancy. Figure 3 depicts the relationship between peak D_2 occupancy and the ratio when the time was fixed at 2 points, ie, at 1.0 ± 0.3 $T_{1/2}$ and 2.0 ± 0.3 $T_{1/2}$. The ratios decreased when peak D_2 occupancy increased at both points. Although there were 8 studies in which peak D_2 occupancy was lower than 60%, no notable differences in study characteristics were observed between these and other studies.

Time courses of ratio. Figure 4 summarizes the data from studies examining D_2 occupancy and blood antipsychotic concentrations at 4 or more time points. The ratios increased as time elapsed: the ratios for quetiapine IR 450 mg/d were 0.43 at 0.71 $T_{1/2}$, 0.44 at 1.18 $T_{1/2}$, and 1.02 at 2.82 $T_{1/2}$; the ratios for olanzapine 15 mg/d were 0.28 at 0.40 $T_{1/2}$, 0.41 at 0.93 $T_{1/2}$, and 0.58 at 1.50 $T_{1/2}$; the ratios for risperidone 3–4 mg/d were 0.16 at 1.10 $T_{1/2}$, 0.35 at 2.30 $T_{1/2}$, and 0.62 at 3.50 $T_{1/2}$; and the ratios for haloperidol LAI 30 mg/4 weeks were 0.46 at 1.00 $T_{1/2}$, 0.57 at 2.00 $T_{1/2}$, and 0.74 at 4.00 $T_{1/2}$.

Time Courses of Dopamine D_2 Receptor Occupancy in Extrastriatum and Blood Concentrations of Antipsychotics

In the extrastriatum, relative attenuation ratios were less than 1 across the time points for all antipsychotics, although the number of studies was limited (Supplementary Table 3).

DISCUSSION

The major findings summarized in our systematic review are that (1) the reduction rate of dopamine D_2 receptor occupancy is lower than that of blood concentrations

regardless of antipsychotic type in general, meaning that pharmacokinetics of antipsychotics are generally slower centrally than peripherally, replicating the previous results[16–20]; and (2) the dissociation between the reduction rates is dependent on dose, time, and peak D_2 occupancy. The latter finding is a novel suggestion from the current work.

As doses of antipsychotics are closely related to achievable D_2 occupancy, the factors affecting the dissociation between the reduction of D_2 occupancy and blood concentrations are consolidated into two: the peak D_2 occupancy and time from that at peak D_2 occupancy. Further, the dissociation between central D_2 occupancy and peripheral blood concentration became less and more prominent as time elapsed and peak D_2 occupancy increased, respectively. These results are consistent with theoretical findings derived from the equation,[5,36,37] in that (1) the attenuation ratio is determined by time and peak D_2 occupancy; (2) the attenuation ratio increases and decreases as time elapses and peak D_2 occupancy increases, respectively; and (3) peak D_2 occupancy is determined by antipsychotic dose and D_2 binding affinity (regarding the calculation process, see Supplementary Appendix 1).

The finding that the reduction rate of D_2 occupancy is lower than that of blood concentrations regardless of antipsychotic type has serious implications in real-world clinical practice in the context of optimal dosing intervals. Dosing intervals of antipsychotics could be determined based on central pharmacokinetics instead of peripheral pharmacokinetics; the former are slower than the latter in general. Indeed, previous randomized controlled trials demonstrated no significant differences in any clinical outcomes between once-daily and twice-daily dosing regimens of not only risperidone, olanzapine, and asenapine, which have relatively longer plasma half-lives,[38,39] but also perphenazine and quetiapine,[8,40] which have short plasma half-lives and are thus recommended to be taken in divided dosage in the drug information. Besides, our results suggest that relative attenuation rate of D_2 occupancy was lower when peak D_2 occupancy was higher than 50% than when it was lower than 50% (Supplementary Figure 2); dosing intervals might be more prolonged when peak D_2 occupancy is estimated to be high. In fact, although the sample size was small, a previous double-blind randomized controlled trial[41] reported that taking risperidone and olanzapine every other day was not associated with the risks of symptom exacerbation, relapse, and rehospitalization compared with taking these drugs every day. For examples, based on our results, taking risperidone 3–4 mg or olanzapine 15 mg every second day, aripiprazole 30 mg every third day, and haloperidol 6 mg every second day can achieve around 60% D_2 occupancy at trough, which is considered necessary for acute-phase treatment. The findings are relevant in interpreting the so-called dopamine-related withdrawal/discontinuation phenomena including dopamine supersensitivity psychosis. Rebound phenomena may not so commonly occur as has traditionally been suspected from the viewpoint of peripheral pharmacokinetics of antipsychotics, because central D_2 occupancy is more gradually reduced even when antipsychotics are discontinued abruptly. This notion is supported by the findings from meta-analytic studies: (1) there was no difference in relapse rates between abrupt and gradual withdrawal of antipsychotics, (2) symptoms gradually worsened in patients with schizophrenia switching to placebo treatment,[42,43] (3) there were no significant differences in any clinical outcomes between immediate and gradual discontinuation strategies of the current antipsychotic in an antipsychotic switch,[10] and (4) switching to aripiprazole, a dopamine receptor partial agonist, from another antipsychotic did not increase the risk of psychotic worsening compared to switching to another antipsychotic.[44] Important to note, however, is that the risk may vary in accordance with the pharmacologic characteristics of each antipsychotic, as we have found with quetiapine, sulpiride, and ziprasidone, and the withdrawal/discontinuation phenomena at the central or peripheral level related to other neurotransmission systems (eg, anticholinergic rebound, autonomic nerve system) can occur.

Several limitations of this study should be acknowledged. First, we were not able to conduct any statistical analyses to summarize the results because the ratios of reduction rates have no values of standard deviations due to lack of individual data. Second, the available data were limited to some specific antipsychotics. In particular, although clozapine was an important antipsychotic for treatment-resistant schizophrenia, there was no study examining the time course of D_2 occupancy in the striatum for clozapine. Third, we summarized the data from different types of studies: (1) those examining D_2 occupancy and blood concentrations after both single-dose administration and discontinuation of an antipsychotic; (2) those utilizing the data of healthy subjects and patients with schizophrenia for the baseline binding potential in a drug-free state; and (3) those using various radioligands (ie, [^{11}C]raclopride and [^{11}C]FLB457 for PET and [^{123}I]iodobenzamide for SPECT). Fourth, pharmacokinetics, both centrally and peripherally, may not be linear with time, but most of the studies examined herein had only 2 observational timings. Fifth, almost all studies did not take into consideration pharmacokinetic parameters, including age, sex, renal and hepatic functions, and gene polymorphisms. Sixth, our findings do not account for why the dissociation between central and peripheral attenuation occurs. Possible explanations for the dissociation include (1) that the blood-brain barrier maintains the dissociation between central and peripheral attenuation[45] and (2) that tissue concentrations of lipophilic compounds are higher than blood concentrations.[46] Seventh, we were not able to compare the attenuation ratios between patients with schizophrenia and healthy subjects because only 1 study[6] examined the same doses of the same drugs in both patients with schizophrenia and healthy subjects. Moreover, that study showed the opposite results between olanzapine and risperidone: for olanzapine, the attenuation ratios were 0.10 and 0.28 at 0.40 $T_{1/2}$ in patients with schizophrenia and healthy subjects, respectively; for risperidone, the ratios were

0.28 and 0.16 at 1.10 $T_{1/2}$ in patients with schizophrenia and healthy subjects, respectively.[6] Lastly, because all studies included in the current systematic review examined a single antipsychotic, the findings cannot be generalized to other treatment conditions such as antipsychotic polypharmacy. These limitations should be taken into account in interpreting the results. Further studies are warranted to confirm the findings, particularly with respect to clozapine.

In conclusion, the systematic review of 18 studies examining the time courses of dopamine D_2 receptor occupancy and blood antipsychotic concentrations found that attenuation rate of D_2 occupancy was lower than that of blood concentrations regardless of antipsychotic type in general. Further, the relative attenuation ratio decreased and increased in a time-dependent and in a peak D_2 occupancy–dependent fashion, respectively. These findings have two main clinical implications: (1) dosing intervals of antipsychotics can be prolonged based on the central pharmacokinetics, and (2) the concept of the dopamine-related withdrawal/discontinuation phenomena might be at least in part challenged. Further studies are needed to investigate various types of antipsychotics, in particular clozapine, with a larger number of subjects in order to guide better treatment for patients with schizophrenia.

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Supplementary Material

Article Title: Dissociation in Pharmacokinetic Attenuation Between Central Dopamine D_2 Receptor Occupancy and Peripheral Blood Concentration of Antipsychotics: A Systematic Review

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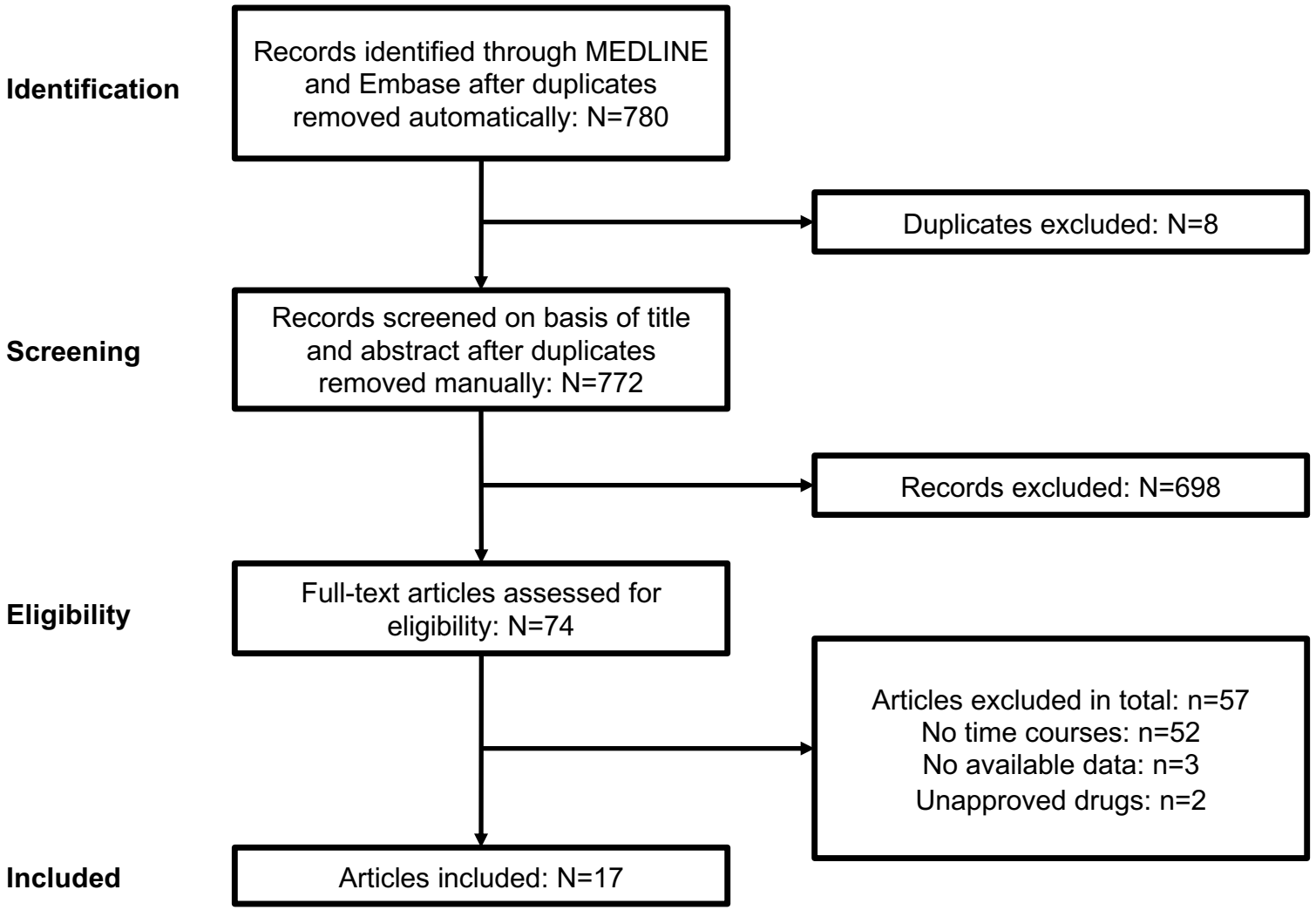
Supplementary Table 1.

Plasma half-life ($T_{1/2}$) of each medication

Antipsychotics	**Plasma half-life**
Risperidone	20 hours
Olanzapine	45 hours
Quetiapine	8.5 hours
Aripiprazole	70 hours
Ziprasidone	6 hours
Perospirone	2 hours
Haloperidol	24 hours
Sulpiride	11 hours
Clozapine	14 hours
Risperidone LAI	2 weeks
Haloperidol LAI	4 weeks

Abbreviation: LAI, long-acting injection



Supplementary Figure 1. PRISMA flow diagram of the literature search

Supplementary Table 2. Time courses of dopamine D_2 receptor occupancy in striatum and blood concentrations of antipsychotics

Study name	Antipsychotic type and dose	N	D_2 occ or blood cons of antipsychotics	Brain region	Time 1	Rate* 1 (peak time)	Time 2	Rate* 2	Ratio** 2	Time 3	Rate* 3	Ratio** 3	Time 4	Rate* 4	Ratio** 4	Time 5	Rate* 5	Ratio** 5	Time 6	Rate* 6	Ratio** 6
Mamo 2008	Quetiapine IR 300 mg/d	4	D_2 occ	Putamen/Caudate	37.3 ± 2.4% at 1h	100%	-4.5 ± 8.7% at 13h	-12.1% at 1.41 $T_{1/2}$	1.25 at 1.41 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
			Blood cons		351.3 ± 102.0 ng/mL at 1h	100%	37.0 ± 1.8 ng/mL at 13h	10.5% at 1.41 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Quetiapine IR 600 mg/d	4	D_2 occ	Putamen/Caudate	29.0 ± 14.3% at 1h	100%	8.0 ± 12.2% at 13h	27.6% at 1.41 $T_{1/2}$	0.85 at 1.41 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
			Blood cons		807.8 ± 166.5 ng/mL at 1h	100%	121.0 ± 27.0 ng/mL at 13h	15.0% at 1.41 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Quetiapine IR 800 mg/d	4	D_2 occ	Putamen/Caudate	47.0 ± 14.3% at 1h	100%	24.0 ± 8.8% at 13h	51.1% at 1.41 $T_{1/2}$	0.76 at 1.41 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
			Blood cons		308.8 ± 119.4 ng/mL at 1h	100%	111.0 ± 47.2 ng/mL at 13h	35.9% at 1.41 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Quetiapine XR 300 mg/d	4	D_2 occ	Putamen/Caudate	26.5 ± 8.5% at 5h	100%	-5.5 ± 12.7% at 13h	-20.8% at 0.94 $T_{1/2}$	1.39 at 0.94 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
			Blood cons		427.3 ± 114.8 ng/mL at 5h	100%	55.5 ± 9.3 ng/mL at 13h	13.0% at 0.94 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Quetiapine XR 600 mg/d	4	D_2 occ	Putamen/Caudate	38.5 ± 2.6% at 5h	100%	12.4 ± 6.8% at 13h	32.2% at 0.94 $T_{1/2}$	0.99 at 0.94 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
			Blood cons		543.8 ± 53.3 ng/mL at 5h	100%	172.5 ± 21.0 ng/mL at 13h	31.7% at 0.94 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Quetiapine XR 800 mg/d	4	D_2 occ	Putamen/Caudate	56.1 ± 6.7% at 5h	100%	17.9 ± 15.2% at 13h	31.9% at 0.94 $T_{1/2}$	0.84 at 0.94 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
			Blood cons		641.3 ± 191.6 ng/mL at 5h	100%	120.8 ± 93.3 ng/mL at 13h	18.8% at 0.94 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Nord 2011	Quetiapine IR 300 mg/d	9	D_2 occ	Putamen/Caudate	50 ± 4% at 2h	100%	7 ± 7% at 24h	14% at 2.59 $T_{1/2}$	0.87 at 2.59 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
			Blood cons		1,460 ± 510 nmol/L at 2h	100%	20.3 ± 7.8 nmol/L at 24h	1.39% at 2.59 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Quetiapine XR 300 mg/d	10	D_2 occ	Putamen/Caudate	32 ± 11% at 5h	100%	8 ± 6% at 24h	25% at 2.24 $T_{1/2}$	0.83 at 2.24 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
			Blood cons		719 ± 310 nmol/L at 5h	100%	69.9 ± 40 nmol/L at 24h	9.72% at 2.24 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Tauscher-Wisniewski 2002	Quetiapine 400-750 mg/d	9	D_2 occ	Striatum	62.0 ± 9.8% at 1-2.5h	100%	14.3 ± 7.9% at 19-20h	23.0% at 1.94-2.24 $T_{1/2}$	0.81 at 1.94-2.24 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
			Blood cons		589 ± 530 ng/mL at 1h	100%	29 ± 15 ng/mL at 20h	4.92% at 2.24 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Gefvert 1998	Quetiapine 450 mg/d	8	D_2 occ	Putamen/Caudate	44 ± 21% at 2h	100%	30 ± 22% at 8h	68.2% at 0.71 $T_{1/2}$	0.43 at 0.71 $T_{1/2}$	27 ± 21% at 12h	61.4% at 1.18 $T_{1/2}$	0.44 at 1.18 $T_{1/2}$	0 ± 27% at 26h	0% at 2.82 $T_{1/2}$	1.02 at 2.82 $T_{1/2}$	NA	NA	NA	NA	NA	NA
			Caudate/Putamen		40% at 2h	100%	27% at 8h	68% at 0.71 $T_{1/2}$	0.43 at 0.71 $T_{1/2}$	26% at 12h	65% at 1.18 $T_{1/2}$	0.40 at 1.18 $T_{1/2}$	0% at 26h	0% at 2.82 $T_{1/2}$	1.02 at 2.82 $T_{1/2}$	NA	NA	NA	NA	NA	NA
			Blood cons		402.8 ng/mL at 2h	100%	102.2 ng/mL at 8h	25.4% at 0.71 $T_{1/2}$	NA	47.0 ng/mL at 12h	11.7% at 1.18 $T_{1/2}$	NA	7.2 ng/mL at 26h	1.79% at 2.82 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA
Tauscher 2002 (1)	Olanzapine 15 mg/d	4	D_2 occ	Striatum	81 ± 1% at 6h	100%	72 ± 4% at 24h	88.9% at 0.40 $T_{1/2}$	0.28 at 0.40 $T_{1/2}$	58 ± 3% at 48h	71.6% at 0.93 $T_{1/2}$	0.41 at 0.93 $T_{1/2}$	42% at 72h	51.9% at 1.5 $T_{1/2}$	0.58 at 1.5 $T_{1/2}$	NA	NA	NA	NA	NA	NA
			Blood cons		23 ng/mL ± 4 at 6h	100%	14 ± 4 ng/mL at 24h	60.9% at 0.40 $T_{1/2}$	NA	7 ± 1 ng/mL at 48h	30.4% at 0.93 $T_{1/2}$	NA	4 ± 0 ng/mL at 72h	17.4% at 1.5 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA
	Risperidone 3-4 mg/d	4	D_2 occ	Striatum	87 ± 1% at 2h	100%	77 ± 0% at 24h	88.5% at 1.10 $T_{1/2}$	0.16 at 1.10 $T_{1/2}$	59% at 48h	67.8% at 2.30 $T_{1/2}$	0.35 at 2.30 $T_{1/2}$	36% at 72h	41.4% at 3.5 $T_{1/2}$	0.62 at 3.5 $T_{1/2}$	NA	NA	NA	NA	NA	NA
			Blood cons		37 ± 14 ng/mL at 2h	100%	10 ± 7 ng/mL at 24h	27.0% at 1.10 $T_{1/2}$	NA	3 ng/mL at 48h	8.11% at 1.9 $T_{1/2}$	NA	2 ± 1 ng/mL at 72h	5.41% at 3.5 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA
Tauscher 2002 (2)	Olanzapine 15-20 mg/d	3	D_2 occ	Striatum	83 ± 2% at 6h	100%	78 ± 4% at 24h	94.0% at 0.40 $T_{1/2}$	0.10 at 0.40 $T_{1/2}$	61 ± 6% at 48h	73.5% at 0.93 $T_{1/2}$	0.35 at 0.93 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA
			Blood cons		66 ± 4 ng/mL at 6h	100%	28 ± 4 ng/mL at 24h	42.4% at 0.40 $T_{1/2}$	NA	16 ± 3 ng/mL at 48h	24.2% at 0.93 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Risperidone 3 mg/d	2	D_2 occ	Striatum	88 ± 1% at 2h	100%	72 ± 9% at 24h	81.8% at 1.10 $T_{1/2}$	0.28 at 1.10 $T_{1/2}$	47 ± 16% at 48h	53.4% at 2.30 $T_{1/2}$	0.58 at 2.30 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA
			Blood cons		31 ± 12 ng/mL at 2h	100%	11 ± 8 ng/mL at 24h	35.5% at 1.10 $T_{1/2}$	NA	6 ± 5 ng/mL at 48h	19.4% at 2.30 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Catafau 2011	Risperidone 6 mg/d	3	D_2 occ	Striatum	83.6 ± 3.4% at 6 ± 2h	100%	64.4 ± 3.6% at 24 ± 4h	77.03% at 0.90 $T_{1/2}$	0.43 at 0.90 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
			Blood cons		55.5 ± 31.9 ng/mL at 6 ± 2h	100%	26.1 ± 20.0 ng/mL at 24 ± 4h	47.03% at 0.90 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Kim 2012	Aripiprazole 2 mg/d	4	D_2 occ	Striatum	34.52 ± 9.16% at 3h	100%	21.78 ± 13.11% at 45h	63.1% at 0.6 $T_{1/2}$	0.54 at 0.6 $T_{1/2}$	14.39 ± 9.26% at 120h	41.7% at 1.7 $T_{1/2}$	0.71 at 1.7 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA
			Blood cons		8.48 ± 2.16 ng/mL at 3h	100%	2.65 ± 0.65 ng/mL at 45h	31.3% at 0.6 $T_{1/2}$	NA	1.53 ± 0.73 ng/mL at 120h	18.0% at 1.7 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Aripiprazole 5 mg/d	4	D_2 occ	Striatum	54.43 ± 9.14% at 3h	100%	35.54 ± 3.58% at 45h	65.3% at 0.6 $T_{1/2}$	0.56 at 0.6 $T_{1/2}$	23.27 ± 12.50% at 120h	42.8% at 1.7 $T_{1/2}$	0.68 at 1.7 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA
			Blood cons		15.53 ± 5.28 ng/mL at 3h	100%	5.94 ± 1.46 ng/mL at 45h	38.2% at 0.6 $T_{1/2}$	NA	2.39 ± 0.10 ng/mL at 120h	15.4% at 1.7 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Aripiprazole 10 mg/d	5	D_2 occ	Striatum	72.30 ± 6.10% at 3h	100%	63.21 ± 9.94% at 45h	87.4% at 0.6 $T_{1/2}$	0.24 at 0.6 $T_{1/2}$	45.50% at 120h	62.9% at 1.7 $T_{1/2}$	0.46 at 1.7 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA
			Blood cons		29.76 ± 7.19 ng/mL at 3h	100%	14.22 ± 4.86 ng/mL at 45h	47.8% at 0.6 $T_{1/2}$	NA	5.87 ng/mL at 120h	19.7% at 1.7 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Aripiprazole 30 mg/d	5	D_2 occ	Striatum	79.71 ± 4.88% at 3h	100%	74.82 ± 4.37% at 45h	93.9% at 0.6 $T_{1/2}$	0.13 at 0.6 $T_{1/2}$	62.92% at 120h	78.9% at 1.7 $T_{1/2}$	0.27 at 1.7 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA
			Blood cons		83.33 ± 32.96 ng/mL at 3h	100%	43.77 ± 11.43 ng/mL at 45h	52.5% at 0.6 $T_{1/2}$	NA	17.08% at 120h	20.5% at 1.7 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Suzuki 2013	Ziprasidone 120 mg/d	12	D_2 occ	Putamen	65.6 ± 9.9% at 5h	100%	38.5 ± 25.8% at 13h	58.7% at 1.33 $T_{1/2}$	0.86 at 1.33 $T_{1/2}$	1.99 ± 30.2% at 23h	3.0% at 3.0 $T_{1/2}$	1.1 at 3.0 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA
			Caudate		62.4 ± 10.0% at 5h	100%	34.9 ± 24.6% at 13h	55.9% at 1.33 $T_{1/2}$	0.92 at 1.33 $T_{1/2}$	-5.72 ± 31.3% at 23h	-9.2% at 3.0 $T_{1/2}$	1.2 at 3.0 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA
			Ventral striatum		68.1 ± 7.7% at 5h	100%	46.8 ± 20.9% at 13h	68.7% at 1.33 $T_{1/2}$	0.65 at 1.33 $T_{1/2}$	11.2 ± 29.8% at 23h	16.4% at 3.0 $T_{1/2}$	0.93 at 3.0 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA
			Blood cons		288.12 ± 73.60 nmol/L at 5h	100%	150.45 ± 98.10 nmol/L at 13h	52.2% at 1.33 $T_{1/2}$	NA	30.20 ± 19.22 nmol/L at 23h	10.5% at 3.0 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Arakawa 2010	Perospirone 16 mg/d	4	D_2 occ	Striatum	74.8 ± 8.0% at 1.5h	100%	60.1 ± 5.6% at 8h	80.3% at 3.3 $T_{1/2}$	0.22 at 3.3 $T_{1/2}$	31.9 ± 6.4% at 25.5h	42.6% at 12 $T_{1/2}$	0.57 at 12 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA
			Blood cons		3.80 ng/mL at 1.5h	100%	0.46 ng/mL at 8h	12.1% at 3.3 $T_{1/2}$	NA	0 ng/mL at 25.5h	0% at 12 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Nordström 1991	Haloperidol 7.5 mg/d	2	D_2 occ	Putamen	87.5 ± 4.5% at 3h	100%	86.5 ± 2.5% at 6h	98.9% at 0.13 $T_{1/2}$	0.055 at 0.13 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
			Blood cons		9.78 ± 2.67 nmol/L at 3h	100%	7.83 ± 0.36 nmol/L at 6h	80.1% at 0.13 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Farde 1988	Haloperidol 6 mg/d	1	D_2 occ	Putamen	85.9% at 6h	100%	85.7% at 30h	99.8% at 1.0 $T_{1/2}$	0.0036 at 1.0 $T_{1/2}$	77.6% at 53h	90.3% at 2.0 $T_{1/2}$	0.14 at 2.0 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA
			Blood cons		24.7 nmol/L at 6h	100%	10.9 nmol/L at 30h	44.1% at 1.0 $T_{1/2}$	NA	7.56 nmol/L at 53h	30.6% at 2.0 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Sulpiride 600 mg/d	1	D_2 occ	Putamen	74.1% at 3h	100%	70.0% at 6h	94.5% at 0.27 $T_{1/2}$	1.04 at 0.27 $T_{1/2}$	63.2% at 27h	85.3% at 2.2 $T_{1/2}$	0.19 at 2.2 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA
			Blood cons		4.90 µmol/L at 3h	100%	4.64 µmol/L at 6h	94.7% at 0.27 $T_{1/2}$	NA	1.17 µmol/L at 27h	23.9% at 2.2 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Remington 2006	Risperidone LAI 25 mg/2w	2	D_2 occ	Putamen/Caudate	71.0 ± 5.7% at peak	100%	54.0 ± 1.4% at trough	76.05% at 1.0 $T_{1/2}$	0.33 at 1.0 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
			Blood cons		33.35 ng/mL at peak	100%	9.3 ng/mL at trough	27.88% at 1.0 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Risperidone LAI 50 mg/2w	5	D_2 occ	Putamen/Caudate	74.4 ± 10.7% at peak	100%	65.4 ± 2.1% at trough	87.90% at 1.0 $T_{1/2}$	0.49 at 1.0 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
			Blood cons		34.18 ng/mL at peak	100%	25.8 ng/mL at trough	75.48% at 1.0 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Risperidone LAI 75 mg/2w	2	D_2 occ	Putamen/Caudate	81.5 ± 5.0% at peak	100%	75.0 ± 5.7% at trough	92.02% at 1.0 $T_{1/2}$	0.23 at 1.0 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
			Blood cons		67.9 ng/mL at peak	100%	44.5 ng/mL at trough	65.53% at 1.0 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Nyberg 1995	Haloperidol LAI 30-50 mg/4w	8	D_2 occ	Putamen	73% at 1w	100%	52% at 4 weeks	71.23% at 1.0 $T_{1/2}$	0.58 at 1.0 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
			Blood cons		4.6 nmol/L at 1w	100%	2.3 nmoL at 4w	50.00% at 1.0 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Nyberg 1997	Haloperidol LAI 30 mg/4w	2	D_2 occ	Putamen	70.91 ± 7.71% at 1w	100%	58.51 ± 0.91% at 4w	82.5% at 1.0 $T_{1/2}$	0.46 at 1.0 $T_{1/2}$	47.62% at 8w	67.2% at 2.0 $T_{1/2}$	0.57 at 2.0 $T_{1/2}$	18.57% at 16w	26.2% at 4.0 $T_{1/2}$	0.74 at 4.0 $T_{1/2}$	24.08% at 28w	33.96% at 7.0 $T_{1/2}$	0.66 at 7.0 $T_{1/2}$	NA	NA	NA
			Blood cons		3.70 ± 0.40 nmol/L at 1w	100%	2.29 ± 1.33 nmol/L at 4w	61.9% at 1.0 $T_{1/2}$	NA	1.554 nmol/L at 8w	42.0% at 2.0 $T_{1/2}$	NA	0 nmol/L at 16w	0% at 4.0 $T_{1/2}$	NA	0 nmol/L at 28w	0% at 7.0 $T_{1/2}$	NA	NA	NA	NA
	Haloperidol LAI 50 mg/4w	2	D_2 occ	Putamen	80.03 ± 2.29% at 1w	100%	63.1 ± 10.3 at 4w	78.8% at 1.0 $T_{1/2}$	0.39 at 1.0 $T_{1/2}$	49.6 ± 11.4% at 8w	62.0% at 2.0 $T_{1/2}$	0.56 at 2.0 $T_{1/2}$	45.7 ± 2.1% at 16w	57.1% at 4.0 $T_{1/2}$	0.51 at 4.0 $T_{1/2}$	32.9 ± 1.1% at 28w	41.1% at 7.0 $T_{1/2}$	0.71 at 7.0 $T_{1/2}$	18.7 ± 4.5% at 56w	23.4% at 14 $T_{1/2}$	0.77 at 14 $T_{1/2}$
			Blood cons		7.91 ± 1.73 nmol/L at 1w	100%	3.66 ± 0.75 nmol/L at 4w	46.3% at 1.0 $T_{1/2}$	NA	2.58 ± 1.26 nmol/L at 8w	32.6% at 2.0 $T_{1/2}$	NA	1.31 ± 1.31 nmol/L at 16w	16.6% at 4.0 $T_{1/2}$	NA	1.31 ± 1.31 nmol/L at 28w	16.6% at 7.0 $T_{1/2}$	NA	0 nmol/L at 56w	0% at 14 $T_{1/2}$	NA
Regenthal 1997	Haloperidol LAI 30-70 mg/4w	8	D_2 occ	Striatum	75% at 1w	100%	53% at 4w	70.7% at 1.0 $T_{1/2}$	0.39 at 1.0 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
			Blood cons		7.3 nmol/L at 1w	100%	1.8 nmol/L at 4w	24.7% at 1.0 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Kapur 2000	Quetiapine IR 400 mg/d	1	D_2 occ	Striatum	58% at 3h	100%	20% at 12h	34.5% at 1.1 $T_{1/2}$	0.74 at 1.1 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
			Blood cons		770 ng/L at 3h	100%	92 ng/L at 12h	11.9% at 1.1 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Quetiapine IR 450 mg/d	1	D_2 occ	Striatum	64% at 2h	100%	0% at 26h	0% at 2.8 $T_{1/2}$	1.06 at 2.8 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
			Blood cons		1,584 ng/L at 2h	100%	92 ng/L at 26h	5.8% at 2.8 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

* Rate: rate from peak
** Ratio: ratio of % D2 occupancy reduction rate to % blood concentration reduction rate
$T_{1/2}$ represents plasma half-life for oral formulation and injection interval for long-acting injectable formulation
Abbreviations: cons, concentrations; occ, occupancy; LAI, long-acting injection

Supplementary Table 3. Time courses of dopamine D_2 receptor occupancy in extra-striatum and blood concentrations of antipsychotics

Study name	Antipsychotic type and dose	N	D_2 occ or blood cons of antipsychotics	Brain region	Time 1	Rate* 1 (peak time)	Time 2	Rate* 2	Ratio** 2	Time 3	Rate* 3	Ratio** 3	Time 4	Rate* 4	Ratio** 4	Time 5	Rate* 5	Ratio** 5	Time 6	Rate* 6	Ratio** 6
Tauscher 2002 (1)	Olanzapine 15 mg/d	4	D2 occ	Extra-striatum	79 ± 4% at 6h	100%	63 ± 9% at 24h	79.7% at 0.40 $T_{1/2}$	0.52 at 0.40 $T_{1/2}$	NA	NA	NA	32 ± 7% at 72h	40.5% at 1.5 $T_{1/2}$	0.72 at 1.5 $T_{1/2}$	NA	NA	NA	NA	NA	NA
			Blood cons		23 ng/mL ± 4 at 6h	100%	14 ± 4 ng/mL at 24h	60.9% at 0.40 $T_{1/2}$	NA	7 ± 1 ng/mL at 48h	30.4% at 0.93 $T_{1/2}$	NA	4 ± 0 ng/ml at 72h	17.4% at 1.5 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA
	Risperidone 3-4 mg/d	4	D2 occ	Extra-striatum	74 ± 3% at 2h	100%	51% at 24h	68.9% at 1.10 $T_{1/2}$	0.43 at 1.10 $T_{1/2}$	NA	NA	NA	29% at 72h	39.2% at 3.5 $T_{1/2}$	0.64 at 3.5 $T_{1/2}$	NA	NA	NA	NA	NA	NA
			Blood cons		37 ± 14 ng/mL at 2h	100%	10 ± 7 ng/mL at 24h	27.0% at 1.10 $T_{1/2}$	NA	3 ng/mL at 48h	8.11% at 1.9 $T_{1/2}$	NA	2 ± 1 ng/mL at 72h	5.41% at 3.5 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA
Takano 2006	Clozapine 200 mg/d	1	D2 occ	Prefrontal cortex, temporal cortex and thalamus	45.6 ± 3.3% at 1h	100%	43.4 ± 2.3% at 6h	95.18% at 0.36 $T_{1/2}$	0.18 at 0.36 $T_{1/2}$	16.8 ± 6.2% at 25h	36.84% at 1.7 $T_{1/2}$	0.83 at 1.7 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA
			Blood cons		541.3 ng/mL at 1h	100%	395.8 ng/mL at 6h	73.12% at 0.36 $T_{1/2}$	NA	130.3 ng/mL at 25h	24.07% at 1.7 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Clozapine 600 mg/d	1	D2 occ	Prefrontal cortex, temporal cortex and thalamus	73.7 ± 8.7% at 2h	NA	75.5 ± 4.3% at 7h	100%	NA	59.5 ± 10.2% at 26h	78.8% at 1.4 $T_{1/2}$	0.43 at 1.4 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA
			Blood cons		992.6 ng/mL at 2h	NA	1004 ng/mL at 7h	100%	NA	513.7 ng/mL at 26h	51.2% at 1.4 $T_{1/2}$	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

* Rate: rate from peak
** Ratio: ratio of % D2 occupancy reduction rate to % blood concentration reduction rate
$T_{1/2}$ represents plasma half-life for oral formulation and injection interval for long-acting injectable formulation
Abbreviations: cons, concentrations; occ, occupancy

Appendix 1.

Plasma concentration and D_2 occupancy were expressed by the following equation:

$C = me^{-bt}$, (a)
$D_2, occ = 100 \times me^{-bt}/(ED_{50} + me^{-bt})$, (b)

where *C* is plasma concentration, *D_2, occ* is D_2 occupancy, *m* is the estimated maximal plasma concentration at peak time, *b* is a constant, and *t* is the time after the peak time. Substituting 0 for t in (b), peak D_2 occupancy was expressed by the following equation:

$O_0 = 100 \times m \,/\, ED_{50} + m$, (c)

where *O_0* is peak D_2 occupancy. Combining equations (b) and (c),

$D_2, occ = 100 \times O_0 e^{-bt} \,/\, (100 - O_0 + O_0 e^{-bt})$, (d)

Using equations (a), (c) and (d), we calculated the reduction rate of D_2 occupancy and plasma concentration, respectively, as following equations:

$$reduction\ rate\ of\ D_2, occ = \{(c) - (d)\} \,/\, (c)$$
$$= (100 - O_0)(1 - e^{-bt}) \,/\, \{100 - O_0(1 - e^{-bt})\}, \text{(e)}$$
$$reduction\ rate\ of\ plasma\ concentrations$$
$$= (m - me^{-bt}) \,/\, m = 1 - e^{-bt}, \text{(f)}$$

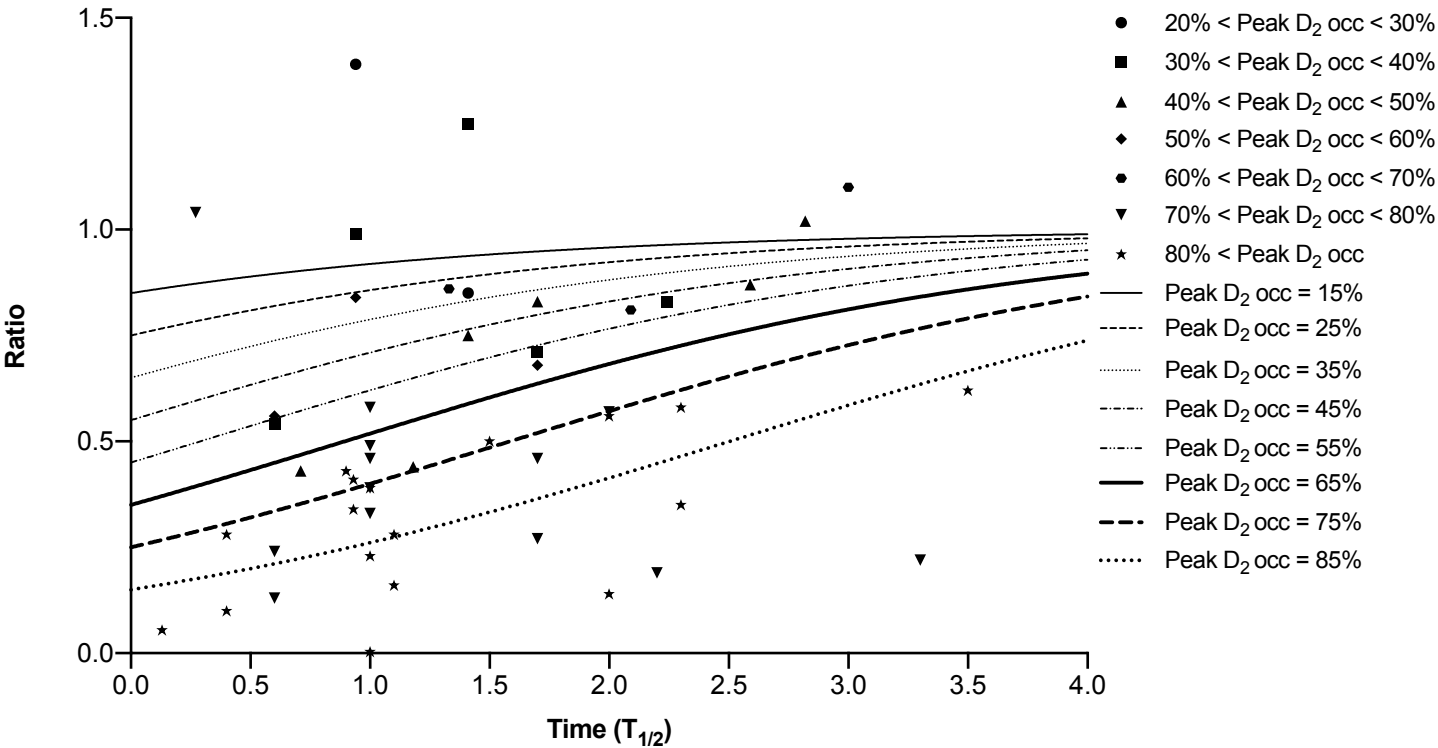
The ratio of D_2 occupancy reduction rate (%) from peak to blood concentration reduction rate (%) from peak was expressed by the following equations:

$ratio = (e) \,/\, (f) = (100 - O_0) \,/\, \{100 - O_0(1 - e^{-bt})\}$, (g)

This equation indicates that the ratio is determined by time and peak D_2 occupancy. Further, by differentiating ratio for time and peak D_2 occupancy, respectively, we calculated how ratio changed as time and peak D_2 occupancy changed, as following equations:

$dratio \,/\, dt = (100 - O_0) b O_0 e^{-bt} \,/\, (O_0 e^{-bt} + 100 - O_0)^2 > 0$, (h)
$dratio/dO_0 = -100e^{-bt} \,/\, \{100 - O_0(1 - e^{-bt})\}^2 < 0$, (i)

The ratio increases and decreases when a differential value of ratio is positive and negative, respectively. Thus, these results show that the ratio increases and decreases as time elapses by and peak D_2 occupancy increases, respectively, which is consistent with our findings.



Supplementary Figure 2. Ratio* sorted by peak D_2 occupancy

The dots and the solid lines represent extracted data and theoretical data, respectively.

* Antipsychotic D_2 occupancy/blood concentration reduction ratio