The Slow and Long-Lasting Blockade of Dopamine Transporters in Human Brain Induced by the New Antidepressant Drug Radafaxine Predict Poor Reinforcing Effects

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Background: (2S,3S)-2-(3-Chlorophenyl)-3,5,5-trimethyl-2-morpholinol hydrochloride (radafaxine) is a new antidepressant that blocks dopamine transporters (DAT). A concern with drugs that block (DAT) is their potential reinforcing effects and abuse liability. Using positron emission tomography (PET) we have shown that for DAT-blocking drugs to produce reinforcing effects they must induce >50% DAT blockade and the blockade has to be fast (within 15 minutes). This study measures the potency and kinetics for DAT blockade by radafaxine in human brain.

Methods: PET and [11C]cocaine were used to estimate DAT blockade at 1, 4, 8, and 24 hours after radafaxine (40 mg p.o) in 8 controls. Plasma pharmacokinetics and behavioral and cardiovascular effects were measured in parallel.

Results: DAT blockade by radafaxine was slow, and at 1 hour, it was 11%. Peak blockade occurred at about 4 hours and was 22%. Blockade was long lasting: at 8 hours 17%, and at 24 hours 15%. Peak plasma concentration occurred about 4 to 8 hours. No behavioral or cardiovascular effects were observed.

Conclusions: The relatively low potency of radafaxine in blocking DAT and its slow blockade suggests that it is unlikely to have reinforcing effects. This is consistent with preclinical studies showing no self-administration. This is the first utilization of PET to predict abuse liability of a new antidepressant in humans based on DAT occupancy and pharmacokinetics.

Key Words: PET, kinetics, abuse, reinforcement, striatum

Depression is one of the most prevalent psychiatric disorders of adulthood (Kessler et al 1994). The lifetime prevalence for major depression in the United States in persons 15–54 years of age has been estimated to be 17.1% (Blazer et al 1994). Although there are a wide variety of antidepressant medications, there is still need for newer medications. There are still a significant number of depressed patients who do not respond or have inadequate responses; the overall mean response rate for antidepressants was recently estimated to be 62% (Lam et al 2002). It would also be desirable to develop new antidepressant drugs with a better safety margin and fewer side effects than those currently available.

In the study reported here, we evaluated a new antidepressant drug (23S)-2-(3-Chlorophenyl)-3,5,5-trimethyl-2-morpholinol hydrochloride (radafaxine; GlaxoSmithKline, Research Triangle Park, North Carolina). The efficacy of radafaxine in depression is attributed to its activity at both the dopamine transporters (DAT) and the norepinephrine transporters (NERT) (Sanchez and Hyttel 1999). It is thought that radafaxine might have advantages over other antidepressants in terms of reduced side effects, such as diarrhea and nausea, which very often prevent people from taking medication regularly. Radafaxine is the (+) isomer of hydroxybupropion (Sanchez and Hyttel 1999). Hydroxybupropion is chiral, and the ability to block the DAT and NERT resides in the (+) isomer, radafaxine (Sanchez and Hyttel 1999). The (+) isomer of hydroxybupropion also seems to underlie the efficacy of hydroxybupropion in a mouse model of depression (forced swimming) (Damaj et al 2004). In addition, this isomer is also an antagonist of the α4β2 nicotine receptor and has been shown to interfere with the acute effects of nicotine in mice (Damaj et al 2004).

A concern regarding drugs that block DAT is that they might be reinforcing (Ritz et al 1987). Indeed, human imaging studies have shown a linear relationship between the degree of DAT blockade by drugs such as cocaine and methylphenidate (MP) and their reinforcing effects when they are injected intravenously (IV), as assessed by self-reports of drug effects such as “high” and “rush” (Volkow et al 1997, 1999b). Using positron emission tomography (PET), we have assessed the properties of DAT-blocking drugs that are associated with their reinforcing effects. We have shown that for these drugs to be reinforcing, they have to block more than 50% of the DAT within a relatively short period (<15 min from administration) and clear the brain rapidly to enable fast repeated administration (Volkow et al 1995a, 1997, 1998).

In this study, we used PET to evaluate the effects of radafaxine at the DAT in the human brain (potency and pharmacokinetics) as a means to predict its reinforcing effects and hence its abuse liability. Dopamine transporter blockade was measured with the DAT radioligand [11C]cocaine in eight healthy control subjects. To assess the pharmacokinetics of DAT blockade, we measured DAT blockade at different times after radafaxine administration (1, 4, 8, and 24 hours) in each individual, in addition to a baseline [11C]cocaine scan before drug administration. To assess the level of DAT occupancy by radafaxine, we
selected a dose of 40 mg, which is the targeted dose for the treatment of depression. The behavioral and cardiovascular responses to radafaxine were monitored during the PET studies.

**Methods and Materials**

**Subjects**

Eight healthy male subjects, 31 ± 6 years of age (mean ± SD), were studied. Written informed consent was obtained from all subjects after a complete description of the study and following the guidelines set by the institutional review board at Brookhaven National Laboratory (Upton, New York).

**PET Scan**

The PET studies were carried out with an HR+ tomograph (resolution 4.5 × 4.5 × 4.5 mm full width half-maximum, 65 slices), with \(^{11}\text{C}\) cocaine used as a DAT ligand (Fowler et al 1989). Methods for positioning of subjects, catheterizations, transmission scans, and blood sampling and analysis have been published (Fowler et al 1989). Briefly, emission scans were started immediately after injection of 4–8 mCi of \(^{11}\text{C}\) cocaine (specific activity > .2 Ci/\(\mu\)mol at time of injection). A series of 20 emission scans were obtained from time of injection to 54 min.

Subjects were scanned five times with \(^{11}\text{C}\) cocaine over a 2-day period; the first scan was done with no intervention and was used as a baseline, and the other four scans were performed 1 hour, 4 hours, 8 hours, and 24 hours after a single oral administration of 40 mg of radafaxine. Venous blood was drawn for quantification of plasma concentrations of radafaxine before and at 5, 1, 1.5, 2, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 8.5, 9, 12, 24, 24.5, and 25 hours after administration of radafaxine. Human plasma samples were assayed for radafaxine with a method based on protein precipitation with acetonitrile, followed by liquid chromatography/mass spectrometry/mass spectrometry (liquid chromatography with tandem mass spectrometry; LC/MS/MS) analysis with positive-ion Turbo Ionspray ionization (TISD) (lower limit of quantification, .5 ng/mL for a 100-\(\mu\)L aliquot of human plasma).

**Behavioral Measures**

To simulate an analogue rating scale, participants were instructed to orally respond to each descriptor with a whole number between 1 and 10 for the self-report of “high,” “mood,” “restlessness,” “anxiety,” “tired,” “alertness,” “desire for more drug,” and “control over intake if exposed to more drug.” Ratings were obtained 5, 27, and 47 min after each PET scan evaluation for the baseline scan, then 1, 4, 8, and 24 hours after radafaxine scans, as previously described (Wang et al 1997). Heart rate and blood pressure were monitored continuously.

**Analyses**

Emission data were corrected for attenuation and reconstructed with filtered back projection. For the purpose of region identification for the \(^{11}\text{C}\) cocaine scans, time frames from dynamic images taken at 10–54 min were summed and the summed image resliced along the anterior commissure–posterior commissure line. Planes were added in groups of 2 to obtain 12 planes encompassing the caudate, putamen, ventral striatum, and the cerebellum for region of interest placement. The caudate, putamen, ventral striatum, and cerebellum were measured on 4, 3, 1, and 2 planes, respectively, and right and left regions were averaged. These regions were then projected to the dynamic scans to obtain concentrations of \(^{11}\text{C}\) versus time. These time activity curves for tissue concentration were used to calculate distribution volume ratios in caudate, putamen, and ventral striatum, with a graphic analysis technique for reversible systems (Logan et al 1990), modified to avoid arterial sampling (Logan et al 1996). The distribution volume ratio, which is the ratio of the distribution volume (DV) in striatum to that in cerebellum (DVstr/DVcb) and which corresponds to the binding potential \(B_{\text{max}}/K_d + 1\), was used as an estimate of DAT availability (Logan et al 1994, 1996). Dopamine transporter occupancies were calculated as \([B_{\text{max}}/K_d\text{baseline } - B_{\text{max}}/K_d\text{radafaxine}]/B_{\text{max}}/K_d\text{baseline}] \times 100\).

To determine whether radafaxine significantly induced DAT blockade, we performed one-way repeated-measures analysis of variance (ANOVA), comparing the \(B_{\text{max}}/K_d\) at different times. Upon rejection of the ANOVA hypothesis of equal DAT blockade across time, we used the Dunnett method for comparison with a control to compare the \(B_{\text{max}}/K_d\) obtained at different times after radafaxine administration with the baseline, controlling the experimentwise error rate to be .05 (two-sided). To assess whether the levels of DAT occupancy differed for the different time points after radafaxine administration, we performed repeated-measures ANOVA, and post hoc pairwise comparisons were then done with the Tukey method, controlling the experimentwise error rate at .05 (two-sided) to assess at which time points the DAT occupancies differed. Stepwise regression and the least squares method were used to fit the temporal curves of plasma drug concentration and DAT occupancy and to find the parametric relationship between plasma radafaxine concentration and DAT occupancy in striatum. Spearman’s rank correlation analysis was used to further examine the relationship between DAT occupancy and the concentration of radafaxine in plasma. For the comparison of cardiovascular measures, we averaged the measures taken just before and during the first 30 min of each scan. For the comparisons of the descriptor of drug effects, we also averaged the measures obtained before and during each PET scan (three ratings). Paired-samples \(t\)-tests were used to assess whether there were differences in the cardiovascular and behavioral measures from the baseline scores. The normality assumption was examined with the Wilk-Shapiro test.

**Results**

Radafaxine significantly blocked DAT, as assessed by significant differences in the \(B_{\text{max}}/K_d\) measures in caudate \([F(4,28) = 8.7; p = .0001]\), putamen \([F(4,28) = 13.7; p < .0001]\), and ventral striatum \([F(4,28) = 6.6; p = .0007]\) (Figure 1, Table 1). Post hoc Dunnett test at the experimentwise error rate of .05 showed that with respect to baseline the differences were significant for all but the 1-hour measure in caudate and ventral striatum and were significantly different for all time points in putamen.

Peak DAT blockade did not occur until 4 hours after radafaxine administration, at which time blockade corresponded in caudate to 22% ± 5% (range, 15%–30%), in putamen to 20% ± 8% (10%–30%), and in ventral striatum to 20% ± 8% (10%–33%) (Figure 2). The maximal occupancy achieved for any one of the regions was 30%–33%. At the .05 significance level, DAT occupancy was found unequal across time in caudate and putamen, but this difference did not reach significance in ventral striatum \((p = .13)\). Post hoc Tukey pairwise comparison at the .05 level showed that in caudate and putamen, differences in DAT occupancy were significant between 1 and 4 hours but not between the other hours. Repeated-measures ANOVA to assess whether there were differences in DAT occupancy in the three striatal regions showed no significant differences for any of the time.

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points at the significance level of .05, which indicates that radafaxine has no special selectivity within the striatum. Because of this correlation measure with plasma, concentrations were performed only for the whole striatum (weighted average of caudate, putamen, and ventral striatum).

The pharmacokinetics of radafaxine are shown in Figure 3. The peak plasma concentration of radafaxine occurred between hours 6 and 5, which corresponds well with the time when peak DAT blockade was observed. A good fit ($R = .84$) for the plasma concentration of radafaxine was found by the least squares method, with the estimated plasma concentration at time $t$ being $104.8 - 2.3t - 112e^{-t} - 91t e^{-t}$. (Figure 3) a mixture of linear, inverse exponential, and gamma components. $e$ is a constant and the base of the natural logarithm ($e = 2.71828$). This fit has a coefficient of determination of .71, indicating that 71% of the variation in the data could be explained by this regression. Interpolation according to this curve showed that the peak plasma concentration occurred at approximately 5.4 hours after drug intake, with an estimated value of 89.7 ng/mL. The temporal curve for DAT occupancy in the entire striatum was found to be a combination of linear and inverse exponential terms, with the DAT occupancy at time $t$ being estimated as $21.0 - 3t - 29.9e^{-t}$

![Figure 1](image1.png) Distribution volume images of $[^{11}C]$cocaine for one of the subjects at baseline and at 1, 4, 8, and 24 hours after administration of 40 mg of radafaxine.

![Figure 2](image2.png) Dopamine transporter (DAT) occupancy by radafaxine at different times after its administration. Occupancy was significantly lower at 1 than at 4 hours after its administration for all striatal regions and also between 1 and 24 hours in caudate only. Values correspond to means and SDs.

![Figure 3](image3.png) Temporal curve for the concentration of radafaxine in plasma.

Table 1. Bmax/Kd Measures in Caudate, Putamen, and Ventral Striatum Before and at Different Times After Administration of Radafaxine

<table>
<thead>
<tr>
<th>Time</th>
<th>Caudate</th>
<th>Putamen</th>
<th>Ventral Striatum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>.82 ± .14</td>
<td>1.03 ± .17</td>
<td>.87 ± .14</td>
</tr>
<tr>
<td>1 h</td>
<td>.75 ± .11</td>
<td>.91 ± .14</td>
<td>.80 ± .16</td>
</tr>
<tr>
<td>4 h</td>
<td>.64 ± .08</td>
<td>.81 ± .10</td>
<td>.70 ± .15</td>
</tr>
<tr>
<td>8 h</td>
<td>.67 ± .09</td>
<td>.85 ± .10</td>
<td>.75 ± .09</td>
</tr>
<tr>
<td>24 h</td>
<td>.72 ± .13</td>
<td>.88 ± .13</td>
<td>.75 ± .09</td>
</tr>
</tbody>
</table>

Data are presented as Mean ± SD. Repeated-measures analysis of variance corresponded in caudate to $F(4,28) = 8.7, p = .0001$; in putamen to $F(4,28) = 13.7, p < .0001$; and in ventral striatum to $F(4,28) = 6.6, p = .0007$. Post hoc Dunnett test showed that with respect to baseline the differences were significant at the experimentwise error rate of .05 (two-sided) for all time points in caudate, putamen, and ventral striatum. Bmax/Kd refers to the ratio of the free receptor concentration and the equilibrium dissociation constant.
examine the monotone relationship between the plasma concentration and DAT occupancy on the whole striatum with and without time lag (Table 2). Using all available temporal measures (hours 1, 4, 8, and 24), we found a significant Spearman rank correlation between plasma concentration and DAT occupancy ($r = .51$, $p = .003$) and no evidence of a time lag effect of plasma radafaxine concentration toward DAT occupancy.

None of the behavioral (Figure 6) or cardiovascular effects (Figure 7) of radafaxine were significant.

**Discussion**

This study shows that radafaxine has a relatively low potency for blocking the DAT and exhibits slow kinetics in the human brain. At the proposed therapeutic dose, it blocked an average of 20%–22% of the DAT after a single dose. Moreover, the maximal blockade in any one subject was 33%. The low levels of DAT blockade achieved with radafaxine contrast markedly with the levels of DAT blockade induced by the DAT blocker methylphenidate (MP), which at the oral doses used therapeutically occupies on average 60% of the DAT in the human brain (Volkow et al 1998).

This study also shows that radafaxine exhibits slow brain pharmacokinetics (slow rate of DAT blockade, long-lasting blockade, and slow clearance from the DAT). In fact, at 1 hour after its administration, DAT blockade was only 10% and was significantly lower than the peak blockade, which was recorded at 4 hours after its administration. This slow DAT blockade also contrasts with that observed after oral MP, which 1 hour after its administration blocks on average 60% of the DAT.

The DAT blockade after radafaxine was long lasting, and there was still significant blockade at 24 hours after its administration. Moreover, DAT blockade at 24 hours in putamen and ventral striatum did not differ significantly from the levels observed at peak (4 hours). Indeed, the blockade of DAT by radafaxine was very stable, with a decrease from peak at 4 hours of 20%–22% to 12%–16% at 24 hours.

The relatively low potency of radafaxine at blocking DAT, its
slow pharmacokinetics, and its steady-state DAT blockade suggest that radafaxine is likely to have minimal or no reinforcing potential and is therefore unlikely to be abused. Specifically, we have shown that for DAT blockers to be perceived as reinforcing they need to block more than 50% of DAT (Volkow et al 1997, 1999a, 1999b). We have also shown that in addition to achieving a >50% DAT blockade, the rate of DAT blockade has to be fast for the reinforcing effects to occur (Volkow et al 1995a, 1998, 2000). Thus, when given orally, 50% DAT blockade is not perceived as reinforcing, but IV administration is. It therefore seems that it is the rate of DAT blockade (percent blockade per unit of time) that is relevant for the reinforcing effects to occur (Volkow and Swanson 2003).

It is known that the rapidity and abruptness of drug delivery to the brain affect the reinforcing effects of drugs; the shorter the interval between intake and perceived effects of the drug, the greater the reinforcing effects of the drug (Balster and Schuster 1973; Oldendorf 1992; Samaha et al 2004). This in turn provides an explanation for the differences in the reinforcing effects of drugs of abuse as a function of route of administration (Verebey and Gold 1988) because the latter affects the rate of drug delivery into the brain (Perez-Reyes et al 1982). For example, whereas a 50% DAT blockade is associated with a “high” when MP is injected IV and leads to peak concentrations in brain 8–15 min after its administration, this same level of blockade induced by oral MP, which leads to peak concentrations in brain 60–120 min after its administration, does not produce a “high” (Volkow et al 1998).

Though much less investigated, the rate of clearance of the drug from brain also affects its reinforcing effects and abuse potential because it is likely to limit the frequency at which the drugs can be self-administered. In this respect, DAT-blocking drugs with very fast rates of clearance, such as cocaine, are much more likely to promote frequent self-administration, because the reinforcing effects are associated with the rapid blockade of more than 50% of the DAT (Volkow et al 1995a). If DAT drugs are blocking more than 50% of DAT with a single administration, then slow pharmacokinetics will lead to DAT saturation with repeated frequent administration and will eventually interfere with further administration (Volkow et al 1995a). Thus, even if radafaxine were to be injected IV at doses large enough to induce more than 50% DAT blockade, its long DAT blockade is likely to interfere with its repeated administration.

We also postulate that fluctuating versus steady-state drug concentrations in brain will affect the drug’s reinforcing effects. We postulate this because animal studies have shown that the rate at which animals self-administer DAT-blocking or DA-releasing drugs, such as cocaine and amphetamine, is predicted by the downward slope of DA that follows the drug-induced increases in nucleus accumbens (Ranaldi et al 1999; Wise et al 1995). Although such studies have not been done in humans, studies in human cocaine abusers have shown that craving increases as the “high” induced by cocaine decreases (Breiter et al 1997). Because we have shown that the “high” in humans from IV MP is associated with DA increases (Volkow et al 1999c), it is also possible that in humans the craving is triggered by the decreases in DA that follow the peak after drug administration. Also, because the reinforcing effects of DAT blockers are associated with the fast change in DA (Δ in DA concentration) (Volkow et al 1999c), we postulate that drugs that have long-lasting steady-state concentrations are less likely to induce drug craving than those that do not.

The temporal course of DAT blockade corresponded well with the pharmacokinetics of the drug in plasma, which peaked at approximately 4–6 hours after drug intake and had a clearance rate at 24 hours of 13%. Moreover, the concentration of radafaxine in plasma predicted the peak levels of DAT blockade. At the estimated peak radafaxine in plasma, concentrations of 89.7 ng/mL that also occurred at approximately 4–6 hours after drug intake, the induced DAT blockade corresponds to 19%. The significant correlation between plasma and DAT blockade suggests that plasma concentration of radafaxine is a good surrogate marker for monitoring radafaxine delivery to the brain.

In this study, a 40-mg dose of oral radafaxine was devoid of any observable behavioral or cardiovascular effects. The lack of these adverse effects with 20% DAT blockade is not surprising because we had previously shown that drug doses that induced DAT blockade of less than 40% had behavioral and cardiovascular effects that did not differ from those of placebo (Volkow et al 1997). We postulate that this is due to an excess of DAT, such that under baseline conditions (without stimulation) the excess
DAT can compensate for the low level of blockade. In fact, a simulation model to predict the relationship between DAT blockade and changes in DA predicted that with stable DA release, 40% DAT blockade would not change extracellular DA (Gatley et al 1997). However, low/lower DAT blockade might be relevant during phasic DA cell firing, which might amplify the magnitude and duration of extracellular DA. Failure of radafaxine to induce a “high,” change “mood,” or induce desire for more drug is concordant with its lack of reinforcing effects. Because descriptors of drug effects, such as the “high,” are the best predictor of drug self-administration in humans (Fischman and Foltin 1991), this also predicts that the abuse and diversion of radafaxine would be unlikely.

In interpreting the findings from this study, it is important to comment on [11C]cocaine as a tracer for the DAT, as well as on the model used in this study to assess DAT occupancy (Bmax/Kd = DVSTR/DVCB - 1). Although cocaine binds to the DAT, the norepinephrine transporter, and the serotonin transporter (Ritz et al 1987), the binding of [11C]cocaine in the striatum as measured by PET has been shown to represent only the DAT (Volkow et al 1995b). More specifically, studies in humans have shown that striatal [11C]cocaine binding is insensitive to pretreatment with desipramine (Fowler et al 1988), demonstrating that binding to the norepinephrine transporter is negligible. Similarly, studies in the baboon have shown that [11C]cocaine binding in the striatum is not affected by drugs that bind to the serotonin transporter (citalopram and fluoxetine) (Volkow et al 1995b). Dopamine transporter occupancy is assessed by graphic analysis of [11C]cocaine time–activity data, which allows the measurement of the distribution volume (DV) (Logan et al 1990, 1996). The DV is an “equilibrium” measure representing the ratio of tissue radioactivity (metabolite corrected) to plasma radioactivity. Because it is an equilibrium property, it does not depend on blood flow. The DV calculated for [11C]cocaine with the graphic method has been shown to be the same as that obtained from a compartmental model approach and to be a stable parameter that does not change with time (Logan et al 1990, 1996). Furthermore, estimates of DAT occupancy have been shown to be reproducible (Volkow et al 1997) and to lead to similar measures whether one uses [11C]cocaine or [11C]Cl-threo methylphenidate as the DAT radioligand (Fowler et al 1998).

Limitations of this study include the fact that the studies were done with acute and not chronic administration. The long-lasting DAT blockade of DAT with radafaxine predicts that chronic administration should result in higher levels of DAT occupancy. Even if greater DAT blockade is achieved with chronic administration, however, this does not affect the interpretation that its low potency predicts poor reinforcing effects because the increase would occur over a long period. Also, because the route of administration affects the reinforcing effects of drugs (Verebey and Gold 1988), we cannot rule out that if radafaxine were to be injected IV it would not be perceived as reinforcing. Indeed, PET studies of the relationship between DA increases induced by MP and its reinforcing effects showed that for equivalent DA increases, oral MP was not reinforcing, whereas IV MP was (Volkow et al 1999c, 2001). In extrapolating data from MP to radafaxine, however, one has to consider that MP is significantly more potent at blocking DAT than radafaxine (ED50 or dose required for MP to block 50% of DAT is .23 mg/kg) (Volkow et al 1998). Because preclinical studies have shown that DAT inhibitors with low DAT occupancies do not maintain drug self-administration, it is not evident that even if injected radafaxine would be self-administered (Lindsey et al 2004). Also, because the relevant variable for drug reinforcement is not just DA increases but “fast DA increases” (Volkow and Swanson 2003), even if radafaxine were to be injected (at large enough doses), and assuming that it would have reinforcing effects, its very low clearance from brain would result in saturation of DAT, which would interfere with its frequent repeated administration (DAT would be occupied, so subsequent doses would not be able to further change DA).

In this study, we used subjective self-reports to assess the reinforcing effects of radafaxine in healthy subjects. Although we did not use other tests for reinforcing effects, such as choice procedures, self-reports of drug effects have been shown to be reliable and to predict drug self-administration in humans (Fischman and Foltin 1991). In addition, this study was done in non–drug abusers, so we cannot rule out the possibility that drug abusers might have perceived radafaxine as reinforcing. This is unlikely, however, because comparison of the rewarding effects of MP is not greater in addicted than in nonaddicted subjects (Volkow et al 1997). Moreover, when cocaine is given to cocaine abusers at doses that do not induce more than 50% DAT blockade, they do not recognize the drug as different from placebo (Volkow et al 1997). Thus, it is unlikely that a dose that control subjects do not differentiate from placebo would be recognized as reinforcing by cocaine abusers.

A final limitation concerns the statistical analysis used to assess the correlation analysis, owing to the relatively small sample size (n = 8) and the fact that measures were obtained for the same subjects at different time points, so that these observations are not independent from one another, which violates statistical assumptions in modeling. Nonetheless, the results predicted from the modeling of the data are in agreement with the results obtained with the PET measures and thus provide preliminary evidence that plasma measures might serve as an estimate for brain DAT occupancy.

The findings from this study can only “predict” but do not “indicate” that the radafaxine will not be reinforcing. Indirect evidence that this prediction is correct is given by the frequency of abuse of bupropion (Margolin et al 1995; Miller and Griffith 1983; Peck et al 1979; Rush et al 1998), which has pharmacologic properties similar to those of radafaxine. In fact there is no evidence of abuse or diversion of bupropion when given to cocaine abusers with attention-deficit/hyperactivity disorder (Levin et al 2002; Montoya et al 2002). Nonetheless, future epidemiologic data will allow us to evaluate whether this prediction is correct.

In summary, we have shown significant though relatively low levels of DAT blockade in the human brain after oral administration of radafaxine. Its relatively low potency in blocking DAT, its slow rate of DAT blockade, and its long-lasting blockade predict a very poor reinforcing profile for this drug. This study is the first in which PET technology was used to investigate the potency and pharmacokinetics of a new psychoactive drug at its molecular target in humans, to predict its potential reinforcing effects and hence abuse liability.

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