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ARTICLE

In vivo activity of modafinil on dopamine transporter measured with positron emission tomography and [^{18}F]FE-PE2I

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Abstract

Modafinil, a wake-promoting drug used to treat narcolepsy, is a dopamine transporter inhibitor and is said to have very low abuse liability; this, however, is still up for debate. We conducted a dopamine transporter (DAT) occupancy study with modafinil (200 or 300 mg) in ten healthy volunteers using positron emission tomography (PET) with [^{18}F]FE-PE2I, a new PET radioligand with high affinity and selectivity for the dopamine transporter, to characterize its relation to abuse liability. Mean striatal DAT occupancies were 51.4% at 200 mg and 56.9% at 300 mg. There was a significant correlation between occupancy and plasma concentration, indicating dose dependency of DAT inhibition by modafinil in the striatum, and especially in the nucleus accumbens. This study showed that DAT occupancy by modafinil was close to that of methylphenidate, indicating that modafinil may be near the same level as methylphenidate in relation to abuse liability in terms of dopaminergic transmission.

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Key words: Abuse liability, dopamine transporter, [^{18}F]FE-PE2I, modafinil, positron emission tomography.

Introduction

Modafinil, which was first marketed nearly 20 years ago in Europe as an agent to offset excessive sleepiness associated with narcolepsy, was approved by the Food and Drug Administration (FDA) in 1998 and by the Pharmaceuticals and Medical Devices Agency (PMDA, Japan) in 2007. Modafinil may enhance cognition and is used off-label for the treatment of cognitive dysfunction in some psychiatric disorders (i.e. schizophrenia, attention-deficit/hyperactivity disorder [ADHD]) (Minzenberg and Carter, 2008). Modafinil is increasingly being diverted for nonmedical use by healthy individuals with the expectation of improving cognitive performance (Maher, 2008; Lynch et al., 2011). Although it is reported that modafinil has very low abuse liability (low reinforcing effects) in non-drug-abusing individuals (Jasinski and Kovacević-Ristanović, 2000; Myrick et al., 2004), the Physicians' Desk Reference (2006) cautions that it can produce psychoactive and euphoric effects typical of central nervous system (CNS) stimulant drugs (Physicians' Desk Reference, 2006), and there is debate about its potential for abuse (Kruszewski and Klotz, 2007). Amphetamine and methylphenidate are well-known typical stimulant drugs. Amphetamine acts by enhancing dopamine release and blocking dopamine transporter (DAT), resulting in dopamine increase, whereas methylphenidate acts mainly through blocking DAT at the synaptic clefts. Modafinil is known to have a blocking effect on DAT (IC_{50}=6.4 μM, Madras et al., 2006), thus increasing dopamine, in rhesus monkeys (Andersen et al., 2010). Although similar mechanisms are applicable to humans (Greenhill, 2006; Volkow et al., 2009b), the exact mechanism of the action of modafinil is not well known.

DAT plays a crucial role in the regulation of dopamine concentration in the synaptic cleft by dopamine reuptake. In the past, a study of modafinil use and DAT imaging with [^{11}C]cocaine was performed (Volkow et al., 2009b). However, [^{11}C]cocaine has various problems such as poor selectivity. Recently, a new ligand, N-(3-iodoprop-2E-enyl)-2β-carbomethoxy-3β-(4-methylphenyl)nortropane (PE2I), with high affinity and good selectivity for DAT, was developed (Emond et al., 1997; Halldin et al., 2003). In human positron emission tomography (PET) studies, [^{11}C]PE2I showed a high specific-to-nonspecific ratio (Halldin et al., 2003; Jucaite et al., 2006; Hirvonen et al., 2008; Seki et al., 2010). Further, a fluoroethyl analog of

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PE2I, ^{18}F-(E)-N-(3-iodoprop-2E-enyl)-2β-carbofluoroethoxy-3β-(4-methylphenyl)nortropane ([^{18}F]FE-PE2I) (inhibition constant, 12 nM), has been developed (Varrone et al., 2009). The quantification of DAT with [^{18}F]FE-PE2I is less biased than that with [^{11}C]PE2I (Sasaki et al., 2012).

Volkow et al. reported that DAT occupancy was 53.8% in the caudate, 47.2% in the putamen, and 39.3% in the nucleus accumbens (NAcc) (modafinil at 200 or 400 mg, single) measured by [^{11}C]cocaine (Volkow et al., 2009b). Because cocaine binds other monoamine transporters besides DAT (Ritz et al., 1987), the data in Volkow's study may be biased. On the other hand, [^{18}F]FE-PE2I has good selectivity for DAT in comparison to norepinephrine transporter (NET) and serotonin transporter (SERT). *In vitro*, FE-PE2I showed ~10 000 higher selectivity for DAT (Ki = 12 nM) as compared with SERT (Ki > 1 μM). In addition, the Ki value at rodent NET was not determined, as the NET inhibitor maprotiline at a concentration of 10 μM did not show any effect in autographic and PET studies (Varrone et al., 2009). In this study, we evaluated DAT occupancy of modafinil using PET with [^{18}F]FE-PE2I in healthy human subjects to assess its more precise pharmacokinetics.

Materials and methods

Subjects

Ten healthy volunteers (age range, 20–39 years; mean age ± S.D., 34 ± 1.6 years at 200 mg; 3 males, 2 females; 29.2 ± 3.8 years at 300 mg; 2 males, 3 females) were enrolled in the study. We recruited ten subjects, and none were excluded due to drug usage. None had a history of present or past psychiatric, neurological or somatic disorders, or alcohol-related problems. All subjects were non-smokers and stopped caffeine intake 48 h prior to PET scan. The study was approved by the review board of Nippon Medical School Hospital, Japan. After thorough explanation of the study, written informed consent was obtained from all participants.

Study design

The experiments were designed as an open-label protocol. Two PET scans were performed, separated by an interval of more than 1 wk. The first PET scan was done prior to, and the second scan 2.5 h after taking modafinil. We planned the second scan to aim at the T_{max} of modafinil, which is 2.5 h, where T_{max} is the time after administration of a drug when the maximum plasma concentration is reached. Each subject underwent PET scan with one dose of modafinil, either 200 or 300 mg.

PET procedures

PET scans were carried out with an Eminence SET-3000GCT-X (Shimadzu Corp., Japan) scanner to measure regional brain radioactivity. A head fixation device was used during the scans. A 10-min transmission scan was done to correct for attenuation. Dynamic PET scan was performed for 60 min after intravenous bolus injection of [^{18}F]FE-PE2I. Injected radioactivity was 185.5–191.1 (mean ± S.D.; 188.8 ± 1.90) MBq at baseline condition and 179.0–190.8 (185.5 ± 3.5) MBq at drug condition. Specific radioactivity was 100.1–253.2 (174.8 ± 63.9) GBq/μmol at baseline condition and 95.6–398.4 (195.0 ± 77.1) GBq/μmol at drug condition.

MRI procedures

Magnetic resonance (MR) images of the brain were acquired with 1.5 T MR imaging, Intera 1.5 T Achieve Nova (Philips Medical Systems, Best, Netherlands). T1-weighted MR images were obtained at 1-mm slices.

Plasma concentration of modafinil

The plasma concentration of modafinil was measured. Venous blood samples were taken 2.5 h after administration of modafinil (just before the second PET scan), collected in tubes containing EDTA-2Na, and centrifuged at 3000 rpm for 10 min at 4 °C. Separated plasma samples were stored at −80 °C until analysis. The plasma concentration of modafinil was measured by a validated method using high-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) with a target lower quantification limit of 0.1 μg/ml (Mitsubishi Chemical Medience Corp., Japan).

Data analysis

MR images were coregistered to summated PET images with the mutual information algorithm using PMOD (version 3.3; PMOD Technologies Ltd, Switzerland). Regions of interest (ROIs) were defined for the striatum (caudate, putamen, and NAcc) and cerebellar cortex. ROIs were drawn manually on overlaid summated PET and coregistered MR images of each subject. ROIs of caudate and putamen were drawn on horizontal slices, and that of NAcc was drawn on coronal slices, while also referring to the brain atlas.

The average values of right and left ROIs were used for the analysis. Group discussions were held between researchers and clinical technologists to confirm the scan quality. In fact, one participant (Subject 6) was re-scanned at baseline after a sufficient interval due to head motion. Data were not subjected to motion correction. DAT binding was quantified using a simplified reference tissue model (Lammertsma and Hume, 1996; Ito et al., 2001). The cerebellum was used as reference region because of its negligible DAT density (Sasaki et al., 2012).

These models allow the estimation of binding potential (BP_{ND}), which was defined as $f_{ND} \times B_{max}/K_d$, where f_{ND} is the free fraction of ligand in the nondisplaceable tissue compartment, B_{max} is the transporter density, and K_d is the dissociation constant (Innis et al., 2007).

Table 1. Subject Characteristics, Binding Potential, and Dopamine Transporter Occupancy

Subject Number	Gender	Age, yr	Dose, mg	Plasma Concentration of MF, μg/mL	BP_{ND} at striatum		DAT occupancy, %			
					Baseline	Modafinil	Striatum	Caudate	Putamen	Nucleus Accumbens
1	Male	25	300	0.5	3.58	3.00	16.3	17.6	13.0	26.2
2	Female	34	300	12.4	3.61	1.00	72.3	76.5	70.0	74.2
3	Male	34	300	8.4	3.96	1.54	61.0	67.0	60.2	54.8
4	Female	24	300	10.5	3.87	1.14	70.5	75.1	69.8	68.0
5	Female	29	300	9.0	3.27	1.17	64.2	64.7	64.7	65.3
Mean (SD)		29.2 (4.3)		8.2 (3.1)	3.66 (0.20)	1.57 (0.57)	56.9 (16.2)	60.2 (17.0)	55.5 (17.0)	57.7 (13.8)
6	Male	36	200	4.0	2.73	1.16	57.6	60.1	56.7	61.1
7	Male	31	200	5.0	3.22	1.41	56.2	59.0	56.3	45.2
8	Male	35	200	5.4	2.87	1.51	47.4	47.8	47.1	48.8
9	Female	35	200	5.0	2.65	1.62	39.1	44.3	38.7	33.0
10	Female	33	200	5.4	3.01	1.29	57.1	59.0	53.2	69.5
Mean (SD)		34 (1.8)		5.0 (0.4)	2.90 (0.17)	1.40 (0.14)	51.4 (6.6)	54.5 (6.7)	51.2 (6.6)	51.5 (11.0)

BP_{ND}; Binding Potential; DAT, Dopamine Transporter; MF, Modafinil; SD, Standard Deviation.

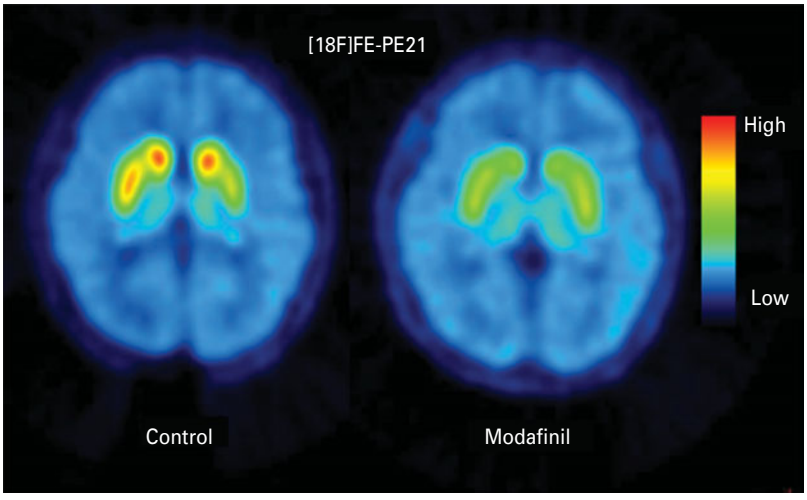

Fig. 1. Uptake of [^{18}F]FE-PE2I in a section of the striatum normalized to cerebellar uptake at baseline (left) and 2.5 h after the administration of modafinil (right) in subject 2.

DAT occupancy by modafinil in the striatum was calculated by the following equation:

$$\text{Occupancy}\,(\%) = (BP_{base} - BP_{drug})/BP_{base} \times 100,$$

where Occupancy is DAT occupancy, BP_{base} is BP_{ND} under drug-free condition, and BP_{drug} is BP_{ND} under drug-taking condition.

The relationship between dose or plasma concentration and DAT occupancy by modafinil is shown by the following equation:

$$\text{Occupancy}\,(\%) = D/(ED_{50} + D) \times 100 \,\text{or}\, C/(EC_{50} + C) \times 100.$$

D is the dose of modafinil, C is the concentration of modafinil, ED_{50} is the dose required to achieve 50% occupancy, and EC_{50} is the plasma concentration required to achieve 50% occupancy (Arakawa et al., 2010; Tateno et al., 2013). Correlations between dose or plasma concentration of modafinil and DAT occupancy in the striatum were examined.

Results

Figure 1 depicts the uptake of [^{18}F]FE-PE2I at baseline and post-dose scans for subject 2, whose data were typical of those of the other subjects. Subject characteristics, binding potentials, striatal DAT occupancies, and plasma concentrations are shown in Table 1. Subject 1, who had a very low plasma concentration, showed low DAT occupancy. Mean striatal occupancies were 51.4±6.6% at 200 mg and 56.9±16.2% at 300 mg. Plasma concentrations were 5.0±0.4 μg/ml at 200 mg and 8.2±3.1 μg/ml at 300 mg. Correlations between dose or plasma concentration of modafinil and DAT occupancy in the striatum

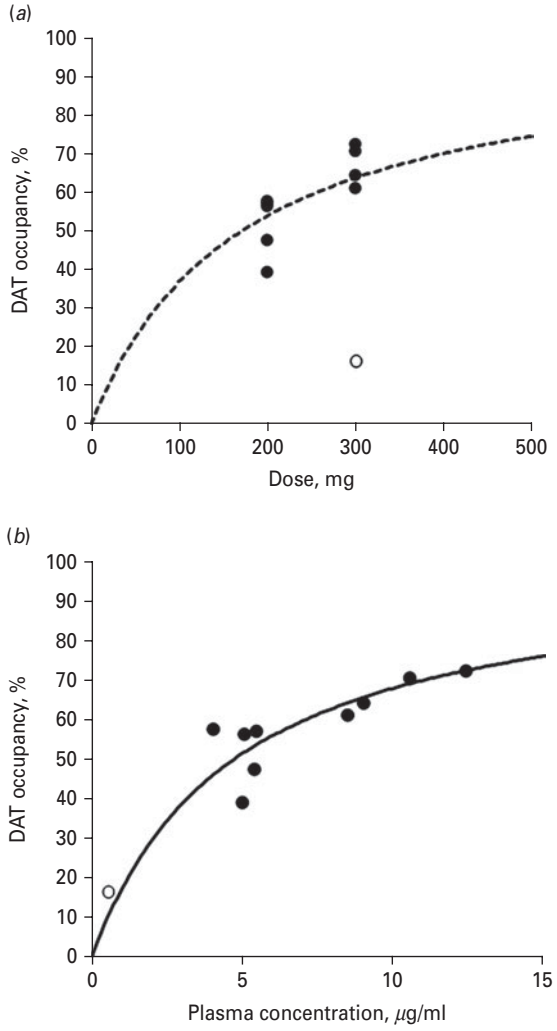

Fig. 2. (*a*) DAT occupancy in the striatum with [^{18}F]FE-PE2I and one dose of modafinil. Dotted line is fitted while excluding one sample for subject 1 (open circle) that showed extremely low occupancy. ED_{50} was 170.9 mg (r=0.72) except for one sample showing extremely low occupancy. (*b*) DAT occupancy in the striatum with [^{18}F]FE-PE2I and plasma concentration of modafinil. EC_{50} was 4.7 μg/ml (r=0.92). DAT=dopamine transporter.

are shown in Fig. 2*a*, *b*. There was a significant correlation between DAT occupancy and plasma concentration. The EC_{50} value was 4.7 μg/ml (r=0.92). Furthermore, when we viewed the three striatal regions separately, EC_{50} was 4.1 μg/ml (r=0.93) in the caudate, 4.9 μg/ml (r=0.93) in the putamen, and 4.7 μg/ml (r=0.70) in the NAcc. With the exception of the single data set of subject 1, showing extremely low plasma concentration and DAT occupancy, DAT occupancy correlated well with the modafinil dose, and the ED_{50} value was 170.9 mg (r=0.72).

Discussion

DAT occupancy was 51.4% (39.1–57.6%) at 200 mg and 56.9% (16.3–72.3%) at 300 mg in the striatum after single modafinil administration. Mean occupancy at 300 mg was 67.0±4.3% when we excluded the data of subject 1, who showed an irregularly low value of 16.3%. DAT occupancy at 300 mg was much higher than that at 200 mg except for that single sample with extremely low DAT occupancy. Furthermore, the correlation between DAT occupancy and the plasma concentration of modafinil was significant. As mentioned above, we confirmed that DAT occupancy by modafinil increased in a dose-dependent manner.

This is the first study of pharmacological PET with [^{18}F]FE-PE2I. Most PET studies of DAT in the past were performed with ([^{11}C]or[^{18}F])CFT (Wong et al., 1993; Laakso et al., 1998), [^{11}C]altropane (Madras et al., 1998), [^{11}C]cocaine (Fowler et al., 1989), [^{11}C]β-CIT (Farde et al., 1994), and other radioligands. Those radioligands have a rather low affinity, which is reflected by a low uptake in the striatum (Fowler et al., 1989). Additionally, they are not selective for DAT, having relatively high affinity for SERT and NET (Ritz et al., 1987). The pharmacological properties of PE2I have demonstrated that it has high affinity for DAT (Ki=17 nM) and is one of the most selective DAT ligands (Emond et al., 2008). [^{11}C]PE2I and [^{18}F]FE-PE2I have been utilized for PET studies (Seki et al., 2010; Varrone et al., 2011, 2012; Odano et al., 2012; Sasaki et al., 2012). Varrone et al. confirmed *in vivo* that [^{18}F]FE-PE2I, developed from [^{11}C]PE2I, has high affinity and selectivity for DAT and shows faster kinetics and more favorable metabolism than [^{11}C]PE2I, with less production of radiometabolites that could interfere with the quantification (Varrone et al., 2011). Quantification of DAT with [^{18}F]FE-PE2I should be able to produce less biased results compared to studies using [^{11}C]PE2I (Sasaki et al., 2012).

Only one PET study of modafinil was performed in the past. Volkow et al. reported DAT occupancy of 53.8% in the caudate, 47.2% in the putamen, and 39.3% in the NAcc (modafinil at 200 or 400 mg, single) as measured by [^{11}C]cocaine (Volkow et al., 2009b). In addition to obtaining almost the same occupancy in the caudate and putamen, we could calculate ED_{50} and confirm dose dependency in the striatum, and especially in the NAcc. There might be two reasons for this result. First, although the value of BP_{ND} by [^{11}C]cocaine is <1, that by [^{18}F]FE-PE2I is 2–4 at baseline. Second, because SERT exists, as does DAT, in the striatum, the binding of [^{11}C]cocaine does not precisely reflect the quantity of DAT (Staley et al., 1995; Gurevich and Joyce, 1996; Varnas et al., 2004). Based on the above-mentioned data, DAT occupancy as measured by [^{18}F]FE-PE2I in our study could possibly be the most precise figure to date.

Modafinil is increasingly being diverted for nonmedical use by healthy individuals with the expectation that it will improve cognitive performance (Lynch et al., 2011), although the degree of abuse liability of modafinil is controversial and there is debate surrounding its

potential for abuse (Kruszewski and Klotz, 2007). There are some arguments regarding the relationship between abuse liability and dopamine increase by blocking dopamine transporters (Greenhill, 2006; Volkow et al., 2009a). The dopamine-enhancing effects of modafinil in the striatum may help explain reports of its abuse, since this pharmacological effect is considered crucial for drug reinforcement (Myrick et al., 2004). Therefore, it is important to measure occupancy in the striatum (especially NAcc) for evaluating the degree of abuse.

Modafinil is used in doses ranging from 200 to 600 mg (Schwartz et al., 2005), and the dosage in our and Volkow's studies was within the clinical dosage range. Spencer et al. also reported that the DAT occupancy of armodafinil (optical isomer of modafinil) was 40.4% at 100 mg and 65.2% at 250 mg in the striatum measured by [11C]altropane (Spencer et al., 2010). From these reports, we can say with confidence that the DAT occupancy of modafinil (or armodafinil) at a clinical dose is approximately 40–70%. Additionally, the occupancies of methylphenidate and bupropion, representative of DAT inhibitors, have been measured by PET with various radioligands. As for bupropion, Meyer et al. reported its DAT occupancy (300 mg p.o.) as less than 22% in the striatum with [11C]RTI32 (Meyer et al., 2002), Learned-Coughlin et al. reported a DAT occupancy of bupropion sustained-release (SR) (150 mg p.o.) of 26% in the striatum with [11C]βCIT-FE (Learned-Coughlin et al., 2003), and Volkow et al. also reported a DAT occupancy of radafaxine ((+)-isomer of hydroxybupropion, 40 mg p.o) of 20% in the striatum with [11C]cocaine (Volkow et al., 2005). As for methylphenidate, Volkow et al. reported a DAT occupancy of 12–74% in the striatum with [11C]cocaine at clinically relevant doses of 5–60 mg (Volkow et al., 1998). Spencer et al. reported a DAT occupancy of dexmethylphenidate of 48–67% in the striatum with [11C]altropane at clinically relevant doses of 20–40 mg (Spencer et al., 2012). In general, it is said that abuse of methylphenidate is most common (Kollins et al., 2001; Maher, 2008; Bruggisser et al., 2012; Sembower et al., 2013), and a low risk of abuse by bupropion has been reported (Chevassus et al., 2012). The degree of abuse risk seems to correspond with DAT occupancy, considering the data of these two stimulants. Our study showed that DAT occupancy of modafinil was near that of methylphenidate at a clinical dose. So, we suggest that modafinil is at a level similar to methylphenidate with respect to abuse liability; modafinil may have not a little risk of abuse. Stimulant abuse is a serious public health problem that affects almost every community, and this also points to some potential adverse consequences for the modafinil user (Greenhill, 2006). This study suggests that the measurement of DAT occupancy by PET with [18F]FE-PE2I may be able to evaluate the risk of abuse by stimulants.

There are several limitations to the current study, urging caution in how these results are interpreted. First, in our study one sample showed an extremely low plasma concentration. This result may be ascribable to a personal diversity of absorption, distribution, metabolism and excretion (Robertson and Hellriegel, 2003). However, this subject also showed low DAT occupancy, and the data, in total, had no effect on our interpretation of this study. Second, in this study we measured DAT occupancy alone. Madras et al. reported that modafinil is a dopamine (IC_{50}=6.4 μM) serotonin (IC_{50}=35.6 μM) norepinephrine (IC_{50}>500 μM) reuptake inhibitor (Madras et al., 2006). Abuse is considered to have a relation with dopamine, but we should investigate the occupancy of SERT/NET to learn the properties of modafinil. Third, we measured drug concentrations in plasma only before PET-scan in this study. As the drug concentrations in plasma can change rapidly in time periods close to T_{max}, it might have been suitable to measure drug concentrations directly before and after the PET-scan for the purpose of assessing their more precise pharmacokinetics. Fourth, because we did not perform any respective motion corrections in the process analyzing the data, although we did confirm the scan quality, head motion may have had some influence on the data. Fifth, we performed PET-scan once only for a single administration. The relationship between chronic dosing and occupancy is unclear. There is a difference in abuse liability between short- and long-acting oral methylphenidate (Spencer et al., 2006). Therefore, we might be able to evaluate abuse liability better by measuring the time-course of DAT occupancy. Finally, this study was conducted with both genders as subjects. Modafinil is considered to have a gender effect mainly during the clearance process (Wong et al., 1999). In this regard, we must evaluate the abuse risk related to plasma concentration and/or DAT occupancy under strict consideration of the gender difference.

In conclusion, this is the first study of pharmacological PET by [18F]FE-PE2I. Modafinil blocked DAT dose-dependently in the human brain with similar numerical values of earlier literature, but our data suggest that the present results with [18F]FE-PE2I are more precise. There was a significant correlation between DAT occupancy and plasma concentration of modafinil, and DAT occupancy by modafinil was at almost the same level as that of methylphenidate, so we suggest that modafinil may resemble methylphenidate in terms of abuse liability. By this study, we found with considerable certainty the possibility that the DAT occupancy of stimulants may reflect abuse liability at a clinical dose.

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References

Andersen ML, Kessler E, Murnane KS, McClung JC, Tufik S, Howell LL (2010) Dopamine transporter-related effects of modafinil in rhesus monkeys. Psychopharmacology (Berl) 210:439–448.

Arakawa R, Okumura M, Ito H, Takano A, Takahashi H, Takano H, Maeda J, Okubo Y, Suhara T (2010) Positron emission tomography measurement of dopamine D_2 receptor occupancy in the pituitary and cerebral cortex: relation to antipsychotic-induced hyperprolactinemia. J Clin Psychiatry 71:1131–1137.

Bruggisser M, Bodmer M, Liechti ME (2012) [Methylphenidate misuse]. Praxis (Bern 1994) 101:299–305.

Chevassus H, Farret A, Gagnol JP, Ponçon CA, Costa F, Roux C, Galtier F, Petit P (2012) Psychological and physiological effects of bupropion compared to methylphenidate after prolonged administration in healthy volunteers (NCT00285155). Eur J Clin Pharmacol 69:779–787.

Emond P, Garreau L, Chalon S, Boazi M, Caillet M, Bricard J, Frangin Y, Mauclaire L, Besnard JC, Guilloteau D (1997) Synthesis and ligand binding of nortropane derivatives: N-substituted 2beta-carbomethoxy-3beta-(4′-iodophenyl)nortropane and N-(3-iodoprop-(2E)-enyl)-2beta-carbomethoxy-3beta-(3′, 4′-disubstituted phenyl)nortropane. New high-affinity and selective compounds for the dopamine transporter. J Med Chem 40:1366–1372.

Emond P, Guilloteau D, Chalon S (2008) PE2I: a radiopharmaceutical for *in vivo* exploration of the dopamine transporter. CNS Neurosci Ther 14:47–64.

Farde L, Halldin C, Muller L, Suhara T, Karlsson P, Hall H (1994) PET study of [11C]beta-CIT binding to monoamine transporters in the monkey and human brain. Synapse 16:93–103.

Fowler JS, Volkow ND, Wolf AP, Dewey SL, Schlyer DJ, Macgregor RR, Hitzemann R, Logan J, Bendriem B, Gatley SJ, Christman D (1989) Mapping cocaine binding sites in human and baboon brain *in vivo*. Synapse 4:371–377.

Greenhill LL (2006) The science of stimulant abuse. Pediatr Ann 35:552–556.

Gurevich EV, Joyce JN (1996) Comparison of [3H]paroxetine and [3H]cyanoimipramine for quantitative measurement of serotonin transporter sites in human brain. Neuropsychopharmacology 14:309–323.

Halldin C, Erixon-Lindroth N, Pauli S, Chou YH, Okubo Y, Karlsson P, Lundkvist C, Olsson H, Guilloteau D, Emond P, Farde L (2003) [(11)C]PE2I: a highly selective radioligand for PET examination of the dopamine transporter in monkey and human brain. Eur J Nucl Med Mol Imaging 30:1220–1230.

Hirvonen J, Johansson J, Teräs M, Oikonen V, Lumme V, Virsu P, Roivainen A, Någren K, Halldin C, Farde L, Hietala J (2008) Measurement of striatal and extrastriatal dopamine transporter binding with high-resolution PET and [11C]PE2I: quantitative modeling and test-retest reproducibility. J Cereb Blood Flow Metab 28:1059–1069.

Innis RB et al. (2007) Consensus nomenclature for *in vivo* imaging of reversibly binding radioligands. J Cereb Blood Flow Metab 27:1533–1539.

Ito H, Sudo Y, Suhara T, Okubo Y, Halldin C, Farde L (2001) Error analysis for quantification of [(11)C]FLB 457 binding to extrastriatal D(2) dopamine receptors in the human brain. Neuroimage 13:531–539.

Jasinski DR, Kovacević-Ristanović R (2000) Evaluation of the abuse liability of modafinil and other drugs for excessive daytime sleepiness associated with narcolepsy. Clin Neuropharmacol 23:149–156.

Jucaite A, Odano I, Olsson H, Pauli S, Halldin C, Farde L (2006) Quantitative analyses of regional [11C]PE2I binding to the dopamine transporter in the human brain: a PET study. Eur J Nucl Med Mol Imaging 33:657–668.

Kollins SH, MacDonald EK, Rush CR (2001) Assessing the abuse potential of methylphenidate in nonhuman and human subjects: a review. Pharmacol Biochem Behav 68:611–627.

Kruszewski SP, Klotz SG (2007) Modafinil: mischaracterization. J Clin Psychiatry 68:970–971; author reply 971–972.

Laakso A, Bergman J, Haaparanta M, Vilkman H, Solin O, Hietala J (1998) [18F]CFT [(18F)WIN 35428], a radioligand to study the dopamine transporter with PET: characterization in human subjects. Synapse 28:244–250.

Lammertsma AA, Hume SP (1996) Simplified reference tissue model for PET receptor studies. Neuroimage 4:153–158.

Learned-Coughlin SM, Bergström M, Savitcheva I, Ascher J, Schmith VD, Långstrom B (2003) *In vivo* activity of bupropion at the human dopamine transporter as measured by positron emission tomography. Biol Psychiatry 54:800–805.

Lynch G, Palmer LC, Gall CM (2011) The likelihood of cognitive enhancement. Pharmacol Biochem Behav 99:116–129.

Madras BK, Meltzer PC, Liang AY, Elmaleh DR, Babich J, Fischman AJ (1998) Altropane, a SPECT or PET imaging probe for dopamine neurons: I. Dopamine transporter binding in primate brain. Synapse 29:93–104.

Madras BK, Xie Z, Lin Z, Jassen A, Panas H, Lynch L, Johnson R, Livni E, Spencer TJ, Bonab AA, Miller GM, Fischman AJ (2006) Modafinil occupies dopamine and norepinephrine transporters *in vivo* and modulates the transporters and trace amine activity *in vitro*. J Pharmacol Exp Ther 319:561–569.

Maher B (2008) Poll results: look who's doping. Nature 452:674–675.

Meyer JH, Goulding VS, Wilson AA, Hussey D, Christensen BK, Houle S (2002) Bupropion occupancy of the dopamine transporter is low during clinical treatment. Psychopharmacology (Berl) 163:102–105.

Minzenberg MJ, Carter CS (2008) Modafinil: a review of neurochemical actions and effects on cognition. Neuropsychopharmacology 33:1477–1502.

Myrick H, Malcolm R, Taylor B, LaRowe S (2004) Modafinil: preclinical, clinical, and post-marketing surveillance–a review of abuse liability issues. Ann Clin Psychiatry 16:101–109.

Odano I, Varrone A, Savic I, Ciumas C, Karlsson P, Jucaite A, Halldin C, Farde L (2012) Quantitative PET analyses of regional [11C]PE2I binding to the dopamine transporter–application to juvenile myoclonic epilepsy. Neuroimage 59:3582–3593.

PDR Network (2006) Provigil (modafinil). In: Chesanow N, Fleming H (eds) Physicians' desk reference, 60th edn, pp1002–1007. New Jersey: Thompson PDR.

Ritz MC, Lamb RJ, Goldberg SR, Kuhar MJ (1987) Cocaine receptors on dopamine transporters are related to self-administration of cocaine. Science 237:1219–1223.

Robertson P Jr., Hellriegel ET (2003) Clinical pharmacokinetic profile of modafinil. Clin Pharmacokinet 42:123–137.

Sasaki T, Ito H, Kimura Y, Arakawa R, Takano H, Seki C, Kodaka F, Fujie S, Takahata K, Nogami T, Suzuki M, Fujiwara H, Takahashi H, Nakao R, Fukumura T, Varrone A, Halldin C, Nishikawa T, Suhara T (2012) Quantification of dopamine transporter in human brain using PET with 18F-FE-PE2I. J Nucl Med 53:1065–1073.

Schwartz JR, Feldman NT, Bogan RK (2005) Dose effects of modafinil in sustaining wakefulness in narcolepsy patients with residual evening sleepiness. J Neuropsychiatry Clin Neurosci 17:405–412.

Seki C, Ito H, Ichimiya T, Arakawa R, Ikoma Y, Shidahara M, Maeda J, Takano A, Takahashi H, Kimura Y, Suzuki K, Kanno I, Suhara T (2010) Quantitative analysis of dopamine transporters in human brain using [11C]PE2I and positron emission tomography: evaluation of reference tissue models. Ann Nucl Med 24:249–260.

Sembower MA, Ertischek MD, Buchholtz C, Dasgupta N, Schnoll SH (2013) Surveillance of diversion and nonmedical use of extended-release prescription amphetamine and oral methylphenidate in the United States. J Addict Dis 32:26–38.

Spencer TJ, Biederman J, Ciccone PE, Madras BK, Dougherty DD, Bonab AA, Livni E, Parasrampuria DA, Fischman AJ (2006) PET study examining pharmacokinetics, detection and likeability, and dopamine transporter receptor occupancy of short- and long-acting oral methylphenidate. Am J Psychiatry 163:387–395.

Spencer TJ, Madras BK, Bonab AA, Dougherty DD, Clarke A, Mirto T, Martin J, Fischman AJ (2010) A positron emission tomography study examining the dopaminergic activity of armodafinil in adults using [^{11}C]altropane and [^{11}C]raclopride. Biol Psychiatry 68:964–970.

Spencer TJ, Bonab AA, Dougherty DD, Mirto T, Martin J, Clarke A, Fischman AJ (2012) Understanding the central pharmacokinetics of spheroidal oral drug absorption system (SODAS) dexmethylphenidate: a positron emission tomography study of dopamine transporter receptor occupancy measured with C-11 altropane. J Clin Psychiatry 73:346–352.

Staley JK, Boja JW, Carroll FI, Seltzman HH, Wyrick CD, Lewin AH, Abraham P, Mash DC (1995) Mapping dopamine transporters in the human brain with novel selective cocaine analog [125I]RTI-121. Synapse 21:364–372.

Tateno A, Arakawa R, Okumura M, Fukuta H, Honjo K, Ishihara K, Nakamura H, Kumita S, Okubo Y (2013) Striatal and extrastriatal dopamine D2 receptor occupancy by a novel antipsychotic, Blonanserin: a PET study with [11C]Raclopride and [11C]FLB 457 in schizophrenia. J Clin Psychopharmacol 33:162–169.

Varnas K, Halldin C, Hall H (2004) Autoradiographic distribution of serotonin transporters and receptor subtypes in human brain. Hum Brain Mapp 22:246–260.

Varrone A, Steiger C, Schou M, Takano A, Finnema SJ, Guilloteau D, Gulyas B, Halldin C (2009) *In vitro* autoradiography and *in vivo* evaluation in cynomolgus monkey of [18F]FE-PE2I, a new dopamine transporter PET radioligand. Synapse 63:871–880.

Varrone A, Tóth M, Steiger C, Takano A, Guilloteau D, Ichise M, Gulyás B, Halldin C (2011) Kinetic analysis and quantification of the dopamine transporter in the nonhuman primate brain with 11C-PE2I and 18F-FE-PE2I. J Nucl Med 52:132–139.

Varrone A, Gulyás B, Takano A, Stabin MG, Jonsson C, Halldin C (2012) Simplified quantification and whole-body distribution of [18F]FE-PE2I in nonhuman primates: prediction for human studies. Nucl Med Biol 39:295–303.

Volkow ND, Wang GJ, Fowler JS, Gatley SJ, Logan J, Ding YS, Hitzemann R, Pappas N (1998) Dopamine transporter occupancies in the human brain induced by therapeutic doses of oral methylphenidate. Am J Psychiatry 155:1325–1331.

Volkow ND, Wang GJ, Fowler JS, Learned-Coughlin S, Yang J, Logan J, Schlyer D, Gatley JS, Wong C, Zhu W, Pappas N, Schueller M, Jayne M, Carter P, Warner D, Ding YS, Shea C, Xu Y (2005) The slow and long-lasting blockade of dopamine transporters in human brain induced by the new antidepressant drug radafaxine predict poor reinforcing effects. Biol Psychiatry 57:640–646.

Volkow ND, Fowler JS, Wang GJ, Baler R, Telang F (2009a) Imaging dopamine's role in drug abuse and addiction. Neuropharmacology 56 (Suppl. 1):3–8.

Volkow ND, Fowler JS, Logan J, Alexoff D, Zhu W, Telang F, Wang GJ, Jayne M, Hooker JM, Wong C, Hubbard B, Carter P, Warner D, King P, Shea C, Xu Y, Muench L, Apelskog-Torres K (2009b) Effects of modafinil on dopamine and dopamine transporters in the male human brain: clinical implications. JAMA 301:1148–1154.

Wong DF, Yung B, Dannals RF, Shaya EK, Ravert HT, Chen CA, Chan B, Folio T, Scheffel U, Ricaurte GA, Neumeyer JL, Wagner HN Jr., Kuhar MJ (1993) *In vivo* imaging of baboon and human dopamine transporters by positron emission tomography using [11C]WIN 35428. Synapse 15:130–142.

Wong YN, King SP, Simcoe D, Gorman S, Laughton W, McCormick GC, Grebow P (1999) Open-label, single-dose pharmacokinetic study of modafinil tablets: influence of age and gender in normal subjects. J Clin Pharmacol 39:281–288.