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REVIEW ARTICLE

# Dopamine transporter imaging with [$^{123}$I]FP-CIT SPECT: potential effects of drugs

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**Abstract**
*Background* [$^{123}$I]*N*-ω-fluoropropyl-2β-carbomethoxy-3β-{4-iodophenyl}nortropane ([$^{123}$I]FP-CIT) single photon emission computed tomography (SPECT) is a frequently and routinely used technique to detect or exclude dopaminergic degeneration by imaging the dopamine transporter (DAT) in parkinsonian and demented patients. This technique is also used in scientific studies in humans, as well as in preclinical studies to assess the availability of DAT binding in the striatum. In routine clinical studies, but also in scientific studies, patients are frequently on medication and sometimes even use drugs of abuse. Moreover, in preclinical studies, animals will be anesthetized. Prescribed drugs, drugs of abuse, and anesthetics may influence the visual interpretation and/or quantification of [$^{123}$I]FP-CIT SPECT scans.
*Discussion* Here, we discuss the basic principle of how drugs and anesthetics might influence the visual interpretation and/or quantification of [$^{123}$I]FP-CIT SPECT scans. We also review drugs which are likely to have a significant influence on the visual interpretation and/or quantification of [$^{123}$I]FP-CIT SPECT scans. Additionally, we discuss the evidence as to whether frequently prescribed drugs in parkinsonian and demented patients may have an influence on the visual interpretation and/or quantification of [$^{123}$I]FP-CIT SPECT scans. Finally, we discuss our recommendations as to which drugs should be ideally withdrawn before performing a [$^{123}$I]FP-CIT SPECT scan for routine clinical purposes. The decision to withdraw any medication must always be made by the specialist in charge of the patient's care and taking into account the pros and cons of doing so.

**Keywords** [$^{123}$I]FP-CIT SPECT · Dopamine transporter · Drugs · Withdrawal · Effects

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## Introduction

Idiopathic Parkinson's disease (PD) and several other parkinsonian syndromes are characterized neuropathologically by degeneration of dopaminergic cells, resulting in a loss of dopamine transporters (DATs) in the striatum [1, 2]. Several radiotracers for positron emission tomography (PET) and single photon emission computed tomography (SPECT) have been developed successfully to assess the integrity of presynaptic dopaminergic neurons end postsynaptic receptors in humans, including radiotracers for the DAT (Fig. 1) [3–12]. In the past decade, DAT imaging was shown to be a very sensitive means to detect loss of striatal DATs (particularly in the putamen) in early PD (for reviews, see [13, 14]), and recent studies even suggest that DAT imaging may be able to detect nigrostriatal dopaminergic degeneration in preclinical cases [15, 16]. Furthermore, and in line with autopsy studies, recent studies showed the ability of DAT imaging to differentiate dementia with Lewy bodies (DLB) from Alzheimer's disease (AD) [17–19]. In DLB, but not in AD, a loss of striatal DAT binding has been found. In clinical practice, it is sometimes difficult, but important, to discriminate parkinsonian patients with dopaminergic cell loss from those with other forms of parkinsonism not

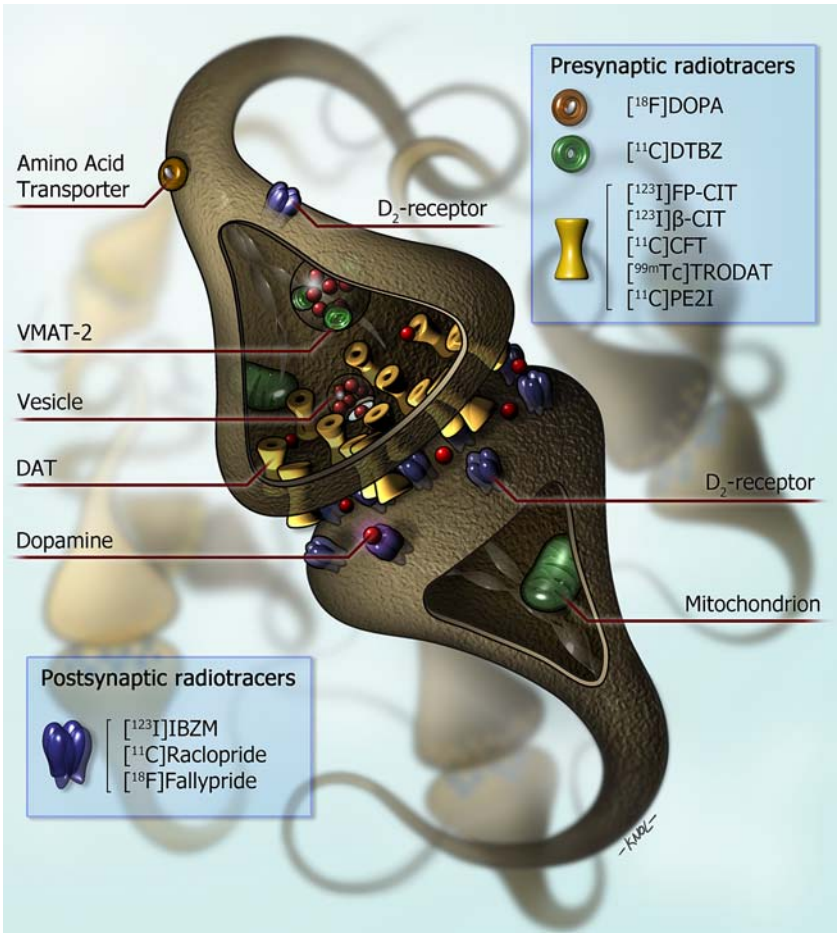


**Fig. 1** Simplified diagram of a striatal dopaminergic synapse. On the presynaptic side, potential markers for imaging of the integrity of dopaminergic neurons are shown. 6-[$^{18}$F]fluoro-L-3,4-dihydroxyphenylalanine (*[$^{18}$F]DOPA*) PET provides a measure of the structural and biochemical integrity of the dopaminergic neurons [3]. The radiotracer is taken up in the dopaminergic neuron via an amine acid transporter and is then decarboxylated to fluorodopamine by L-aromatic acid decarboxylase and temporarily stored in vesicles within the nerve terminals. [$^{11}$C]dihydroxytetrabenazine (*[$^{11}$C]DTBZ*) is a commonly used marker for the vesicular transporter [vesicular monoaminergic transporter-2 (*VMAT-2*)] in humans [4]. Substituted (nor)phenyltropanes (*[$^{123}$I]FP-CIT*, *[$^{123}$I]β-CIT*, *[$^{11}$C]PE2I*, *[$^{11}$C]CFT*, and *[$^{99m}$Tc]TRODAT*) are frequently used PET and SPECT tracers for imaging of DAT in humans [5–9]. Dopamine $D_2$ receptors are much more expressed on the postsynaptic side than on the presynaptic side of the dopaminergic synapse. Commonly used radiotracers for $D_{2/3}$ receptors are substituted benzamides (*[$^{123}$I]IBZM*, *[$^{11}$C]raclopride*, and *[$^{18}$F]fallypride*) [10–12]. For convenience, only $D_2$ receptors are shown on the postsynaptic cell, whereas other dopaminergic receptors (e.g., $D_1$ receptors) are also located on this side. *DAT* dopamine transporter, *VMAT-2* vesicular monoaminergic transporter-2

characterized by loss of presynaptic dopaminergic cells (e.g., psychogenic parkinsonism or drug-induced postsynaptic parkinsonism) [14]. The same is true for the differentiation between DLB and AD [18, 19]. Following the promising result of the initial SPECT studies in parkinsonian patients using [$^{123}$I]*N*-ω-fluoropropyl-2β-carbomethoxy-3β-{4-iodophenyl}nortropane ([$^{123}$I]FP-CIT) as a marker for the DAT [5, 20], registration studies for [$^{123}$I]FP-CIT were started in 1996 in Amsterdam. In 1998 and 1999, the results of phase-I and -II studies were published, respectively [21, 22], followed by multicenter phase-III and -IV studies in 2000 and 2004, respectively [23, 24].

In 2000, $^{123}$I-FP-CIT was licensed as DaTSCAN™ in Europe to differentiate patients suffering from parkinsonian syndromes, such as PD, multiple system atrophy, or progressive supranuclear palsy, from essential tremor (ET). In 2006, the same product received an additional registration for a new indication: to differentiate scintigraphically DLB from AD.

After registration in 2000, the use of [$^{123}$I]FP-CIT has increased dramatically. In 2006, more than 500 centers in 30 countries throughout Europe have been using [$^{123}$I]FP-CIT, both for routine clinical and experimental studies in animals and humans [25–29]. Nowadays, [$^{123}$I]FP-CIT is used extensively in clinical practice for the investigation of parkinsonian patients, as well as in experimental studies, and it is reasonable to expect that the use of this radiotracer will increase even further in the near future to discriminate DLB from AD. However, it is of paramount importance to evaluate potential effects of drugs on DAT imaging with

[$^{123}$I]FP-CIT. Therefore, in this review, we screened the literature to evaluate which kinds of drugs (of abuse) are likely to influence [$^{123}$I]FP-CIT SPECT imaging.

In the first part of this review, we constructed a theoretical framework to improve the understanding of potential influences of drugs on [$^{123}$I]FP-CIT SPECT images. In the second part, we described extensively what kind of medication will influence [$^{123}$I]FP-CIT SPECT images, based on studies performed with [$^{123}$I]FP-CIT or other radiotracers for the DAT. In addition, the possible influence of all groups of drugs on [$^{123}$I]FP-CIT SPECT imaging that are prescribed frequently in parkinsonian or demented patients will be discussed. In the third part, we describe the way we propose to deal with the information put forward in parts 1 and 2, both in an experimental and a routine clinical setting, although focused on the last setting.

## Part 1: how could drugs theoretically influence the results of [$^{123}$I]FP-CIT SPECT images

### *Drugs with affinity for monoaminergic transporters, or that may influence the affinity of [$^{123}$I]FP-CIT for monoaminergic transporters*

[$^{123}$I]FP-CIT is a $^{123}$I-labeled tracer for the DAT and is derived from cocaine [30]. Its in vitro affinity for the DAT is high (approximately 2 nM) ([31] please note that, in this particular paper, [$^{123}$I]FP-CIT is named RTI-313). The affinity for the serotonin transporter (SERT) is moderate, while the affinity for the norepinephrine transporter (NET) is low (16 and 140 nM, respectively) [31]. Based on these data, it is likely that the in-vivo binding of [$^{123}$I]FP-CIT is primarily to DAT and to a lesser amount to SERT. Consequently, drugs with high affinity for the DAT and SERT (such as reuptake inhibitors), but presumably not for the NET, may influence [$^{123}$I]FP-CIT images directly.

Within the striatum, the concentration of DAT is much higher than for SERT [32]. In line with this, initial biodistribution studies in rats [33] showed that striatal [$^{123}$I]FP-CIT uptake could be blocked with a selective ligand for the DAT (GBR12909), but not by a selective SERT blocker (fluvoxamine). Indeed, also human DAT imaging studies showed that drugs with (relatively) high affinity for the DAT influence radiotracer binding in the striatum. For example, the amphetamine-like drug methylphenidate blocks the specific striatal binding of [$^{123}$I]FP-CIT significantly [34].

Theoretically, a drug that affects the apparent affinity of [$^{123}$I]FP-CIT for the DAT or SERT might induce changes in striatal [$^{123}$I]FP-CIT binding ratios. For example, radiotracers for the dopamine $D_2$ receptors could be displaced by a large amount of endogenous dopamine (e.g., induced by amphetamines), which, among others, is reflected in an increase of the radioligand $K_d$ for the $D_2$ receptor [35]. It is remarkable that acute administration of amphetamine in monkeys induced a 50% decrease in striatal 2β-carboxymethoxy-3β-(4-iodophenyl)tropane (β-CIT) binding [32], but in that study, the reason for this decrease was not studied. However, other studies showed that amphetamines induced fast internalization of DATs, which will induce a decrease in the number of transporters ($B_{max}$) but not in affinity ($K_d$) [36]. On the other hand, it has been suggested that high plasma levels of the adrenergic agonists phenylephrine or norepinephrine may change the apparent affinity of radiotracers for the DAT. This suggests that drugs which increase plasma levels of phenylephrine or norepinephrine might be able to affect striatal binding of [$^{123}$I]FP-CIT [37].

In human studies, striatal [$^{123}$I]FP-CIT binding is, in the vast majority of studies, quantified as (specific) striatal binding over nonspecific binding in the occipital cortex or cerebellum. One has to take into account that, although the concentration of SERT is low in the striatum, occipital cortex, and cerebellum, it is not negligible [38]. Therefore, blockade of FP-CIT binding to SERTs by drugs may lead, at least theoretically, to an increase in the binding ratio because changes in the denominator of the ratio can induce larger changes in the value of the ratio than changes in the numerator. Interestingly, studies in rats showed that [$^{123}$I]FP-CIT binding in the occipital cortex could be displaced by a selective serotonin reuptake inhibitor (SSRI), but not by a selective blocker for the DAT [33]. Moreover, ecstasy (XTC) is a selective neurotoxin for serotonergic cells and consequently induces loss of SERT. Interestingly, DAT studies in XTC users showed significantly higher striatal-to-cerebellar [$^{123}$I]β-CIT binding ratios as compared to controls [39]. Taking all these data together, it may be suggested that DAT and SERT blockers (e.g., cocaine or SSRIs) and substrates for these transporters (e.g., amphetamines) may influence striatal [$^{123}$I]FP-CIT binding ratios.

### *Drugs that may influence the expression of DAT and SERT*

As discussed in the previous section, [$^{123}$I]FP-CIT primarily labels in vivo the DAT, but also to some extent the SERT. The expression of DAT and SERT is extremely complex and dynamic [40, 41]. The DAT and SERT play critical roles in terminating dopaminergic and serotonergic transmission by reuptake of dopamine and serotonin from the synaptic cleft, respectively. Control of DAT and SERT activity and expression are therefore central to the spatial and temporal regulation of synaptic dopamine and serotonin levels. DATs and SERTs rapidly traffic between the plasma membrane and endosomal compartments in both constitutive and protein kinase C (PKC)-dependent manners [42]. Kinase activators, phosphatase inhibitors, and substrates for the transporter modulate DAT and SERT phosphorylation (and consequently modulate expression on

the cell membrane) and activity, but the underlying mechanisms and role of phosphorylation in these processes are poorly understood [43–46]. However, it is well accepted that phosphorylation of DAT or SERT, by activation of PKC or inhibition of protein phosphatases, will lead to reduction of transporter expression on the cell membrane. Therefore, at least theoretically, drugs which influence PKC (e.g, via activation of presynaptic receptors located on DAergic neurons) [47], influence phosphatase inhibitors, or are substrates for the transporter may induce alterations in the expression of the DAT and/or SERT and, consequently, may influence quantification of these transporters.

### *Potential effects of drugs on the metabolism of [$^{123}$I]FP-CIT and on cerebral blood flow*

The main metabolic pathway of cocaine is hydrolysis of the two ester functions, resulting in the formation of benzoylecgonine and ecgonine methyl ester [48, 49]. Hydrolysis of the 2β-caroboxymethyl-ester function, spontaneously and by esterases, is also the main metabolic pathway for [$^{123}$I]FP-CIT (Fig. 2), leading to [$^{123}$I]FP-CIT-acid [50]. However, FP-CIT-acid is probably not lipophilic enough to pass the blood–brain barrier [51], and it is therefore unlikely that drugs that do influence esterase activity will be able to influence [$^{123}$I]FP-CIT binding ratios to central DATs or SERTs. A second, minor metabolic pathway in cocaine bioactivation includes N-demethylation by microsomal cytochrome P-450. Also, for [$^{123}$I]FP-CIT, N-demethylation by microsomal cytochrome P-450 occurs in vivo in humans [51] (Fig. 2). Indeed, a radiotracer is then formed, called nor-β-CIT. Previous studies showed that the affinity for SERT is higher for nor-β-CIT than for [$^{123}$I]FP-CIT [52]. It is known that, in healthy volunteers, less than <4% of the total amount of activity is nor-β-CIT 1 h after injection of [$^{123}$I]FP-CIT [51]. Therefore, medication that influences cytochrome P-450 activity might influence the metabolism of [$^{123}$I]FP-CIT. However, one has to take into account that many isoenzymes of P-450 (CYP) exist. Because only CYP3A plays a significant role in the N-demethylation of cocaine [53] and consequently presumably also in the N-demethylation of [$^{123}$I]FP-CIT, only medications that influence CYP3A are potential influencers of the metabolism of [$^{123}$I]FP-CIT.

Finally, in human [$^{123}$I]FP-CIT SPECT studies, acquisition is started 3–6 h after injection of the radiotracer [22] because, in that time period, the specific striatal binding ratio is stable and a so-called pseudoequilibrium is reached. The relative slow kinetics of FP-CIT approximates the kinetics characteristics of a radiotracer with irreversible uptake [54]. It is known for radiotracers in which binding is irreversible that a change in binding is positively correlated with a change in cerebral blood flow [55]. Therefore, at least theoretically, a drug which influences cerebral blood flow may affect striatal FP-CIT binding ratios.

## Part 2: groups of drugs and their potential influence on [$^{123}$I]FP-CIT SPECT imaging

### *Definition of influence*

[$^{123}$I]FP-CIT is used in many centers in Europe for *routine clinical* studies. In most of these centers, FP-CIT SPECT scans are examined visually, based on the results of reports that show that visual examination of [$^{123}$I]FP-CIT images is a sensitive means to differentiate parkinsonian diseases with, from those without, dopaminergic degeneration [23]. In a typical early PD case, there is asymmetrical striatal [$^{123}$I]FP-CIT uptake, with severe loss of binding in the putamen, especially at the contralateral side, resulting in a "full stop" sign (at least at one side), while in ET, the

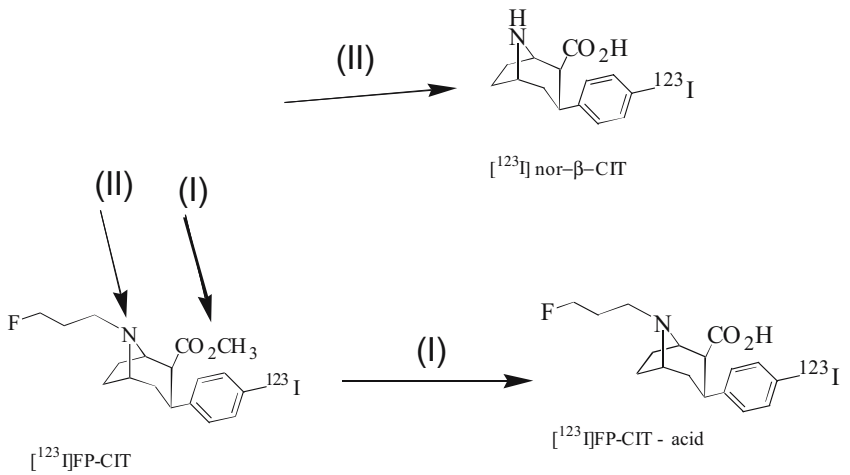


**Fig. 2** Metabolism of [$^{123}$I]FP-CIT in humans. Metabolism I represents the hydrolysis of ester function which leads to [$^{123}$I]FP-CIT-acid, the major metabolite found in plasma (>60% at 2 h p.i. [50]). Metabolism II represents the N-dealkylation of the radiotracer by P-450 cytochrome, which leads to the formation of [$^{123}$I]nor-β-CIT, a minor metabolite (<4% [51])

"comma" sign, representing symmetrical binding, both in caudate and putamen, is present (Fig. 3). Theoretically, *visual* assessment of [$^{123}$I]FP-CIT could be influenced by drugs in at least five ways: (1) A drug blocks [$^{123}$I]FP-CIT uptake in striatum (both in caudate and putamen) or lowers the numbers of DATs or the affinity of [$^{123}$I]FP-CIT for the DAT, resulting in an underestimating of the real number of striatal DATs, which may result in a misleading scan. (2) A drug *reduces* only uptake of [$^{123}$I]FP-CIT in the putamen or caudate nucleus, resulting in an abnormal scan. There is some indication that transporters may be differentially regulated in certain brain regions. Specifically, DAT regulation may differ in the dorsal striatum from that in the nucleus accumbens (part of the ventral striatum) [47]. Although it may be hard to differentiate FP-CIT binding in the caudate nucleus from that in the nucleus accumbens, it is important to note the volume of accumbens is much smaller than that of the caudate [56] and that the dorsal striatum contributes to 70–80% of the measured SPECT signal, as opposed to only 20–30% contribution of the ventral striatum [57]. Therefore, this is an unrealistic mechanism to induce a misleading abnormal FP-CIT scan. (3) A drug induces increases striatal [$^{123}$I]FP-CIT uptake (both in caudate and putamen), or lowers background activity, which induces a better contrast of striatal uptake vs background activity. However, in such a situation, a normal scan will still be judged as normal, and a "full stop" sign in, e.g., a PD patient will not change to a "comma" sign. (4) A drug induces an *increase* of [$^{123}$I]FP-CIT uptake in the putamen, but not in the caudate nucleus, or vice versa. However, this is only a theoretical possibility, not supported by data from literature. (5) A drug induces a significant change in rCBF.

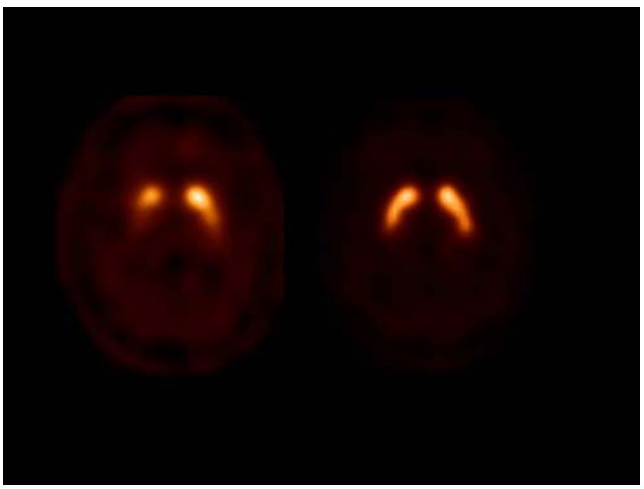

**Fig. 3** Transversal [$^{123}$I]FP-CIT SPECT images at the level of the striatum, in early PD (*left panel*) and in ET (*right panel*). *Left panel*: note the asymmetric binding, with less binding in the right vs the left striatum. At the right side, binding is only visible in the caudate nucleus (full stop sign), while at the left side, binding is visible in the caudate nucleus and anterior putamen. *Right panel*: intense binding both in the caudate nucleus and putamen, bilaterally (comma sign)

From this list of five theoretical ways that a [$^{123}$I]FP-CIT SPECT image could be influenced visually, the first one may be the most relevant one. For example, if a drug blocks 90% of specific striatal [$^{123}$I]FP-CIT uptake, it will be hard to visualize striatal uptake at all and it may lead to a misleading scan. However, because it has not been evaluated how many DATs should be blocked or down-regulated before a "normal" [$^{123}$I]FP-CIT scan might be misdiagnosed as an "abnormal" scan, it may be reasonable to assume that a more than 20% blockage of striatal DATs by drugs may induce a misleading scan (in case of visual assessment). Although 20% is an arbitrary threshold, it is a conservative one, giving the large variation in striatal DATs in a healthy control population [58].

In several institutions, [$^{123}$I]FP-CIT SPECT images are not only analyzed visually but also *quantitatively*, most frequently with a region-of-interest technique. From test/retest studies in healthy controls, it is known that the reproducibility is, on average, approximately 7% (SD 3%) when the scans were analyzed with a template with fixed regions for the striatum [59]. Therefore, it is reasonable to assume that for *an individual patient in a routine clinical setting*, a drug should have an effect on [$^{123}$I]FP-CIT binding ratios in the striatum that is larger than the test–retest measurements plus twice the SD or, in other words, larger than 13%. For *scientific studies*, all potential effects of drugs should be taken into account, as well as effects that may be within the reproducibility of the test, especially when there are small differences in striatal DAT densities between the groups under study, or if serial studies are performed in which a drug has been introduced, or as the dose has been changed after the baseline scan.

In this review, we will discuss the potential effects of drugs on the visual assessment and quantification of [$^{123}$I]FP-CIT SPECT scans. We will discuss drugs that are likely to influence FP-CIT SPECT scans, and we will also discuss the group of drugs that are frequently used in parkinsonian and demented patients in relation to their likelihoods to influence FP-CIT SPECT scans.

### *Effects of CNS stimulants, including DAT blockers and sympathicomimetics*

As [$^{123}$I]FP-CIT is derived from cocaine, it is straightforward that acute administration of cocaine will substantially occupy DATs in the striatum and consequently shall influence striatal [$^{123}$I]FP-CIT uptake. Although chronic cocaine intake may initially induce an upregulation of DATs (via a rapid recycling of internalized DATs to the membrane surface) [60, 61], the blocking effects after administration will overrule this effect and will have a major effect on DAT imaging. Volkow and coworkers [62] already showed in their seminal paper in 1997 that acute administration of

cocaine in doses used by addicts induces a high percentage of blockage of striatal DATs. In fact, only if 50% of DATs are blocked, a "high" is experienced by the cocaine abuser [62]. Therefore, acute administration of cocaine will not only influence quantification of DATs but will also influence the visual examination of [$^{123}$I]FP-CIT SPECT images (Table 1).

Amphetamines like methamphetamine or dexamphetamine are not only drugs of abuse. For example, d-amphetamine is a frequently prescribed drug as an appetite suppressant or in attention-deficit-hyperactivity-disorder (ADHD) patients. These amphetamines have a relatively low affinity for DATs [$K_i$ in the micromolar range; 52], but maybe more importantly, these drugs are substrates for the DAT and may induce fast internalization of DATs (and thereby reduce the surface expression to bind the FP-CIT) presumably via the PKC system [36]. For example, Laruelle and coworkers [32] have shown in monkeys that approximately 50% of striatal β-CIT binding is displaced by amphetamine, maybe by a fast internalization. Moreover, recent DAT SPECT and PET studies have shown that patients on methamphetamine or with a short abstinence period for methamphetamine (less than 6 months) had significantly lower striatal binding ratios than controls, ranging from 20 to 30% [63, 64]. Furthermore, several reports have shown that prolonged use of these drugs may have long-lasting effects on the expression of the DAT [65–67], although this phenomenon has been debated by the results of studies performed in methamphetamine abusers with protracted abstinence [66]. Nevertheless, acute or recent administration of these drugs will influence [$^{123}$I]FP-CIT SPECT quantification and visual assessments of images (Table 1) and may be an example of how a drug could influence the result of a [$^{123}$I]FP-CIT SPECT image by influencing the expression of the DAT.

Methylphenidate is also a drug derived from amphetamine and frequently prescribed for ADHD and narcolepsy. Vles et al. [34] reported recently that a therapeutic dose of methylphenidate decreased striatal [$^{123}$I]FP-CIT binding ratios up to 75% both in the putamen and the caudate nucleus. Moreover, a recent study showed that not only the immediate release form of methylphenidate but also the osmotic release form may induce a large occupancy of striatal DATs [68]. All in all, recent administration of methylphenidate is likely to influence the visual assessment of [$^{123}$I]FP-CIT SPECT scans, as well as the quantification of DATs by FP-CIT SPECT (Table 1), and it may be a typical example of how a drug with affinity for the DAT could influence the result of a [$^{123}$I]FP-CIT SPECT image.

Like amphetamines, the CNS stimulants (nor)ephedrine, pseudoephedrine, and phentermine are structurally similar to methamphetamine and were or are commonly used appetite suppressants. Chronic ephedrine use, in nutritional supplements, has been reported in female weightlifters [69], and ephedrines are frequently used as an ingredient in widely marketed herbal preparations. Phentermine is sometimes prescribed to induce weight loss. As compared to amphetamines, typical clinical doses of phentermine and ephedrines may not release central DA in humans [70]. Although the most potent actions of ephedrine-type compounds were as substrates of the NET transporter, some ephedrine derivatives showed affinity for the DAT in the low nanomolar or micromolar range, or they are substrates for the DAT [71–73]. Ephedrine and pseudoephedrine are also over-the-counter sympathomimetics to be used as bronchodilatators and nasal decongestants, respectively. Unfortunately, the influence of these drugs on DAT imaging has not been studied. However, taking all data together, we could not exclude an effect of these drugs on DAT studies, particularly when used as tablets. However, it is unlikely that ephedrine-like drugs used as bronchodilatators or nasal decongestants will significantly influence central DAT imaging because the plasma concentrations will be too low.

The combination of the amphetamine-derivatives fenfluramine (5-HT releaser) plus the DA releaser phentermine (fen-phen) has also been used widespread as anorectics to treat obesity. The adverse effects that came to be associated with fenfluramine and dexfenfluramine, valvular heart disease and primary pulmonary hypertension [74, 75], have led to their eventual withdrawal from the market in 1997 [76]. However, nowadays, fenfluramine is still used illicitly. Initial studies in small laboratory animals showed that acute administration of fenfluramines induced an increase in striatal DAT [77], which is remarkable because it is also

**Table 1** Medication and drugs of abuse which may influence significantly the visual and quantitative analysis of [$^{123}$I]FP-CIT SPECT studies

| |
|---|
| Cocaine[a] |
| Amphetamines (d-amphetamine, methamphetamine, methylphenidate)[a] |
| CNS stimulants phentermine or ephedrines (influences are likely when used as tablets)[a] |
| Modafinil[a] |
| Some antidepressants (mazindol, bupropion, radafaxine)[a] |
| Adrenergic agonists: phenylephrine or norepinephrine (influences are likely when infused at high doses)[b] |
| Anticholinergic drugs (benztropine may decrease striatal binding ratios; other anticholinergics might increase these ratios which will likely not affect visual assessments) |
| Opioids (only fentanyl)[a] |
| Anesthetics ketamine, PCP, and isoflurane (of interest particularly for animal SPECT studies, although ketamine and PCP are sometimes used illicitly)[a] |

[a] These drugs may decrease striatal [$^{123}$ I]FP-CIT binding
[b] These adrenergic agonists may increase striatal [$^{123}$ I]FP-CIT binding

known to increase PKC activity [78]. Fenfluramines (i.e., racemic fenfluramine and dexfenfluramine) cause dose-related, long-lasting reductions in serotonin axonal markers in all the animal species tested and with all the routes of drug administration used. Doses of fenfluramines that produce signs of brain serotonin neurotoxicity in animals are on the same order as those used to treat humans for weight loss when one takes into account known relations between body mass and drug clearance [79]. This may lead to lower FP-CIT binding to SERTs in fenfluramine users and, consequently, may influence FP-CIT DAT binding ratios. However, no human DAT imaging data on this topic are available, and therefore, it is still unknown if fenfluramine influences DAT imaging in humans.

Modafinil is a novel wakefulness-promoting agent that has been shown to have greater efficacy than placebo in the treatment of ADHD and narcolepsy. Modafinil has been shown to have a low affinity for the DAT [80]. However, the finding that modafinil and amphetamine induce similar increases in dopamine release at equipotent wake-promoting doses suggest a role for the DAT [81]. Indeed, a recent study showed that modafinil is able to block the DAT at "therapeutic doses" substantially in monkey brain [82]. Therefore, just like the other abovementioned drugs, this amphetamine analog may induce significant changes in [$^{123}$I]FP-CIT quantification and, possibly, also in the visual interpretation (Table 1).

The NET and DAT blocker mazindol is sometimes prescribed for the treatment of obesity or depression. A recent [$^{123}$I]β-CIT SPECT study in human cocaine abusers suggests that low doses of mazindol (i.e., 2–4 mg) occupy approximately 25% [83]. Therefore, this drug may affect [$^{123}$I]FP-CIT imaging, both visually and quantitatively (Table 1).

Bupropion is frequently prescribed as an antidepressant or as an antismoking drug. Several reports have shown that bupropion blocks DATs in vivo, although the results are not consistent. For example, a recent DAT SPECT study showed that after 4 weeks of bupropion in nine depressed patients, a 20% decrease in striatal DAT binding ratios was induced [84]. In addition, another PET study in depressed patients reported that the occupancy after bupropion treatment was 14% [85]. Although this effect may not necessarily indicate an effect of bupropion on DAT per se, a recent PET study performed in healthy controls showed that, 3 h after the last dose of bupropion SR, average DAT occupancy by bupropion and its metabolites was 26%. This level of occupancy was maintained through the last PET assessment at 24 h after dosing [86]. In contrast to this, another study performed in healthy controls found no effects of bupropion on DAT binding [87]. Nevertheless, although the effects of bupropion on DAT imaging are not consistent, a possible effect could not be excluded, and this effect may be approximately 20% and, thus, may influence visual and quantitative analyses of [$^{123}$I]FP-CIT SPECT studies (Table 1).

Byas-Smith and coworkers [37] showed in anesthetized monkeys that striatal DAT binding as assessed with 8-(2-[$^{18}$F]fluoroethyl)-2β-carbomethoxy-3β-(4-chlorophenyl) nortropane (FECNT) PET increased by approximately 50% during the phenylephrine or norepinephrine infusion. By performing additional in vitro studies, the authors were also convinced that a change in affinity of [$^{18}$F]FECNT for the DAT (rather than a change in DAT density) occurs during these manipulations. These data not only show that the DAT is considerably dynamic in its regulatory capacity but that sympathomimetics do have a potential effect on DAT imaging possibly by influencing the apparent affinity of the radiotracer for the DAT. However, one has to take into account that, in these experiments, the infusion rates were increased until the blood pressure increase precipitated a significant bradycardia or the mean arterial blood pressure increased by 25% [37]. Therefore, future studies are needed to study whether or not drugs used at clinical doses, which increase levels of phenylephrine or norepinephrine, do affect DAT imaging.

*Effects of antidepressants*

Recent studies using [$^{123}$I]β-CIT SPECT to label DATs in vivo showed that the use of SSRIs, as well as the use of a selective serotonergic neurotoxic (XTC), induced a significant increase in the striatal [$^{123}$I]β-CIT uptake ratios [87–89]. However, β-CIT (or RTI-55) has a higher affinity and less selectivity for the SERT than [$^{123}$I]FP-CIT [31]. Interestingly, we recently showed that, while one dose of 20 mg of citalopram leads to a significant increase of β-CIT striatal binding ratios of approximately 20%, two doses of 20 mg paroxetine leads to less increase of striatal [$^{123}$I]FP-CIT SPECT (approximately 10% [90]). This finding is in line with the observation that [$^{123}$I]FP-CIT is a more selective radiotracer for the DAT than β-CIT. In this study, paroxetine has been used as a SERT blocker. Although we have no direct evidence that other SSRIs will have the same effects on striatal FP-CIT binding ratios, it is likely that other SSRIs will also show the same effect. Yet, within the group of SSRIs, one of the SSRIs has a relatively high affinity for the DAT that is sertraline (affinity for DAT approximately 20–25 nM) [91, 92]. It could be hypothesized that the DAT blocking effects of sertraline on striatal FP-CIT binding ratio are counterbalanced by its SERT blocking effects. However, initial studies in mice did not confirm this hypothesis by showing a significant increase of striatal β-CIT binding after administration of sertraline [93]. All in all, although there is evidence to suggest that at least one SSRI significantly influences the quantification of

FP-CIT to DAT in humans, these effects are too small to hinder the interpretation of visual assessments and will lead to increases of striatal to occipital ratios of approximately 10%.

Serotonin–norepinephrine reuptake inhibitors (SNRIs) (e.g., venlafaxine and clomipramine) are in use today for the treatment of anxiety disorders and depression. Studies in mice and rats [94, 95] showed that clomipramine induced an increase in striatal β-CIT binding comparable to the situation with SSRIs. Moreover, Shang and coworkers recently showed a significantly 10% increase of striatal β-CIT ratio by venlafaxine in humans [96]. Therefore, it is likely that the same statements on their potential effects on [$^{123}$I]FP-CIT imaging could be made for SNRIs as for SSRIs (see above).

Reversible monoamine oxidase-A inhibitors like befloxatone or moclobemide are frequently prescribed for depression. These drugs increase serotonin levels by inhibition of its breakdown, but they do not have a high affinity for the DAT or SERT. Although the effects of these kinds of drugs on DAT imaging have not been evaluated, it is not very likely that they will influence FP-CIT binding to SERTs and indirectly to DATs.

Antidepressants like mirtazapine, buspirone, and nefazodone are α2-adrenergic antagonists, 5-HT$_{1A}$ receptor agonist, and antagonists of 5-HT$_{2C}$ receptors, respectively. While mirtazapine did not increase PKC activity, nefazodone did [78]. However, until now, no studies have evaluated the effects of these drugs on DAT imaging.

Bupropion or mazindol are prescribed in several countries as antidepressants. As described earlier, these drugs may influence DAT imaging. Moreover, radafaxine is a new antidepressant that blocks DAT (and NET) in vivo significantly. In healthy controls, peak blockade of striatal DAT (as assessed with [$^{11}$C]cocaine PET) occurred at about 4 h after oral intake and was 22% [97]. Based on these data, it is likely that this drug will also decrease striatal FP-CIT binding ratios significantly (Table 1). On the other hand, "older" tricyclic antidepressants such as amitryptiline, imipramine, or mianserine are not potent at the DAT [92], and they are not PKC activators [78]. One study, however, suggested that subchronic treatment (for 10 consecutive days) with desipramine in rats induced a significant increase in striatal DATs [98]. However, unfortunately, DATs were measured with the nonselective DAT tracer [$^{3}$H]mazindol; therefore, it is not clear if the effects are specific for the DAT. Likewise, Thibaut and coworkers [99] found increased striatal [$^{3}$H]mazindol uptake in mice after administration of desipramine. They suggested that this phenomenon occurred due to the enhanced availability of radioligand as a consequence of displacement from cerebellar NET binding by desipramine. Overall, although the effects of tricyclic antidepressants on DAT imaging in humans have not been evaluated, it is unlikely that these kinds of drugs will influence DAT imaging significantly.

*Effects of neuroleptics*

Of the group of neuroleptics, only pimozide ($K_d$=69 nM) and ziprasidone ($K_d$=76 nM) had notable potency at the human DAT [100]. In addition, only clozapine induced changes in the PKC level; more specifically, it decreased its level [101]. Until now, one human DAT imaging study specifically examined the effects of a neuroleptic on [$^{123}$I]FP-CIT binding to DATs. Mateos and coworkers [102] showed in schizophrenic patients that 4 weeks of treatment with risperidone did not influence striatal FP-CIT binding ratios significantly. Moreover, [$^{123}$I]FP-CIT SPECT studies in schizophrenic patients showed no difference in striatal uptake between drug-free patients and patients on neuroleptics [29], and acute as well as subacute administration of different neuroleptics did not influence striatal FP-CIT binding in rats [103]. These data suggest that if neuroleptics will induce changes in DAT imaging, such changes will presumably not be large enough to influence quantification or visual assessments of [$^{123}$I]FP-CIT SPECT in routine clinical studies.

*Effects of cholinergic and anticholinergic drugs*

Anticholinergic drugs are frequently used in parkinsonian patients, and cholinesterase inhibitors (functional cholinergic agonists) are frequently used in demented parkinsonian patients, including DLB patients [104, 105]. Tsukada and coworkers [106] showed that cholinergic neuronal modulations affect striatal DAT activity in the conscious monkey brain. In their study, they showed lower binding potential after acute *intravenous* administration of the cholinesterase inhibitor donepezil. Importantly, a recent FP-CIT SPECT study compared striatal FP-CIT uptake ratios between large groups of patients on cholinesterase inhibitors with those not on cholinesterase inhibitors and found no significant differences. The results of this study suggest that the use of cholinesterase inhibitors may not influence striatal FP-CIT binding ratios significantly in humans [107]. Therefore, although a small influence of cholinesterase inhibitors on DAT imaging in humans could not be excluded, it is unlikely that cholinesterase inhibitors will significantly influence the interpretation of [$^{123}$I]FP-CIT SPECT scans in a routine clinical setting.

Kilbourn and coworkers [108] examined DAT binding in rat brain with and without prior intravenous administration of the anticholinergic drug scopolamine (muscarinic receptor blocker; 5 mg/kg body weight). Drug-treated animals exhibited a 30% increase in d-threo-[$^{3}$H]methylphenidate binding to the DAT in the striatum relative to controls.

Also, Tsukada et al. showed a significant increase of DAT binding in monkeys after intravenous scopolamine administration. In parkinsonian patients, anticholinergic drugs, particularly orphenadrine, benztropine, or trihexyphenidyl, are frequently used in particularly younger patients because their psychotoxic, cognitive, and autonomic adverse events make them inappropriate for the treatment of the elderly [109]. Particularly benztropine has a modest affinity for the DAT [110], while the affinity of trihexyphenidyl is in the low micromolar range. Interestingly, a recent study showed that the benztropine analog difluoropine (this is a drug not on the market for human use) occupied DATs up to 76% in monkeys [110]. Consequently, it may be that benztropine induces a lower [$^{123}$I]FP-CIT binding to DAT due to its potency to occupy the DAT, which influences the quantification and visual examination of FP-CIT SPECT studies. On the other hand, other anticholinergics such as scopolamine (sometimes used as plaster for the prevention of motion sickness), orphenadrine, or trihexyphenidyl may induce an *increased* [$^{123}$I]FP-CIT binding to striatal DATs, which may influence quantification but not the visual assessment of scans (see part 2 "Definition of influence").

*Effects of levo-dopa, catechol-O-methyltransferase-inhibitors, monoamine oxidase type B inhibitors, dopamine agonists, and NMDA antagonists*

Although the availability of drugs for treatment of PD has multiplied, L-dopa, in its fourth decade of clinical use, is still the most potent and effective medication [111]. Several studies have examined the acute and subchronic effects of levo-dopa on DAT imaging, and the majority of them did not find a significant effect (for a review see [112]). Moreover, the results of a recent study suggested that chronic treatment in PD did not influence [$^{123}$I]FP-CIT binding. Schillaci and coworkers [113] studied 15 PD patients under stable levo-dopa/carbidopa monotherapy and after at least 20 days of treatment wash-out, and they did not find a significant difference. Therefore, it is unlikely that levo-dopa will have a significant influence on DAT imaging, visually as well as quantitatively. On the other hand, the Parkinson Study Group [114] studied the effects of levo-dopa on the progression of PD. At baseline, PD patients were scanned with [$^{123}$I]β-CIT SPECT to measure striatal DATs and subsequently treated with levo-dopa at different doses or placebo for 40 weeks. After 40 weeks of treatment, the patients were rescanned (while on treatment) and clinically examined after drug withdrawal for 2 weeks. While the severity of PD increased more in the placebo than in the levo-dopa-treated groups, the decline in striatal DAT binding was significantly greater with levo-dopa than with placebo [−4 to −7.2% among those receiving levo-dopa (dose-dependent effect), as compared with −1.4% among those receiving placebo]. As stated by the authors, they could not exclude the possibility that levo-dopa simply down-regulates the DAT, which may illustrate that drugs may not interfere significantly with [$^{123}$I]FP-CIT SPECT imaging in routine clinical cases; effects on scientific studies could not be excluded.

The short plasma half-life limits the antiparkinsonian efficacy of levo-dopa/carbidopa. Coadministration of a catechol-*O*-methyltransferase (COMT) inhibitor extends the plasma half-life of levo-dopa. Therefore, COMT inhibitors are sometimes used in parkinsonian patients, particularly in the more advanced disease stages. Effects of these groups of drugs on DAT imaging have not been studied, but because levo-dopa per se does not significantly interfere with the interpretation of FP-CIT SPECT scans in routine clinical studies, it is unlikely that COMT inhibitors will do so.

The effects of monoamine oxidase type B inhibitors on DAT binding in PD patients have been examined by two groups. Innis and coworkers [115] and Fowler and coworkers [116] showed no significant effects of selegeline on striatal DAT binding in PD patients and healthy controls, respectively. This is remarkable because selegiline is metabolized into amphetamine and methamphetamine [117].

Dopamine $D_2$ agonists, such as pramipexol or pergolide are also frequently prescribed in PD [109, 111]. Several DAT studies examined the subchronic effects of DA agonists in PD patients. While three studies did not find a significant effect [114, 118, 119], one study showed a slight but significant (7%) decrease in striatal DAT binding [120]. These data indicate that DA agonists will not influence the examination of [$^{123}$I]FP-CIT images visually or quantitatively *in routine clinical* studies.

The NMDA antagonist amantadine is frequently used in PD, while memantine is used in patients suffering from dementia [121]. Human DAT imaging has not been performed to assess the effects of these drugs on DAT binding. However, binding assays with [$^{3}$H]GBR-12935 on membranes prepared from animals treated with amantadine revealed no difference in the density and the affinity of striatal DAT binding sites as compared to control, which may indicate that there was no modification at the level of the DAT expression [122]. In contrast, Gordon and coworkers [123] showed an increase of 25–30% of DATs in rats after 3 weeks of intraperitoneal treatment with amantadine.

*Effects of estrogen replacement therapy*

A growing body of research has shown that the brain dopaminergic system is modulated by estrogen and other sex steroids (for a review, see [124]). Recently, Best and coworkers [125] studied the influence of the menstrual cycle on the DAT availability in humans with β-CIT SPECT. Ten female subjects aged 18–40 years were scanned twice during

the early follicular and the midluteal phases to detect any hormone-mediated changes in DAT availability in the striatum. In the 10 menstrual cycle subjects, DAT availability in the striatum did not differ between follicular and luteal phases. Interestingly, Gardiner and coworkers [126] studied 13 postmenopausal women who were administered estrogen replacement therapy and underwent DAT imaging with [$^{99m}$Tc]TRODAT-1 SPECT. In this 6-week pilot study, subjects underwent SPECT before estrogen replacement therapy, after 4 weeks of 0.625 mg/day of conjugated estrogens, and after an additional 2 weeks of 0.625 mg/day CEE plus 10 mg/day of medroxyprogesterone acetate. They showed that short-term administration of estrogen replacement therapy in postmenopausal women is associated with a modest increase in DAT in the putamen but not in the caudate nucleus. Because these effects are small, it is not likely that estrogen replacement therapy will significantly influence the visual interpretation of FP-CIT SPECT scans nor the quantification in routine clinical studies. Finally, the authors' findings are in contrast to our earlier remarks that it is unlikely that within the dorsal striatum the regulation of the DAT is region-specific (see earlier remark in the paragraph on the "Definition of influence," first paragraph part 2).

*Effects of analgesics (opioids)*

Opioids can activate at least four types of opioid receptors (δ, κ, μ, and σ). Activation of opioid receptors may induce changes in striatal DAT densities in rats [127]. It has been shown that the opiate fentanyl (selective μ receptor agonist, frequently used transdermally as an analgestic) may cause reduced [$^{123}$I]β-CIT binding to striatal DAT [128] in humans (case report; after intrathecal administration) and after acute intraperitoneal administration in rats, although the mechanism is not fully understood. Furthermore, the opioid analgesic meperidine (sometimes used as injection to reduce pain) has atypical opioid receptor agonist effects and shares some structural features with the phenyltropane analogs of cocaine [129]. In addition, meperidine appears to interact predominantly with the high-affinity component of the DAT, although with relatively low affinity (but relatively high affinity for the SERT [130]). On the other hand, the $IC_{50}$ to inhibit DA uptake is relatively high [131]. Interestingly, Xiao and coworkers [132] showed in a DAT SPECT study in rhesus monkey that acute morphine (agonist for the μ and κ receptor) injection has both rapid and lasting effects on DAT by down-regulating its function. The decline was partially reversible following morphine abstinence. On the other hand, chronic but not acute treatment of rats with morphine significantly decreased DAT density in the anterior basal forebrain that includes the nucleus accumbens but had no such effect on binding in the striatum [133]. Additionally, Kish and coworkers studied biochemical indices of monoaminergic neurotransmitter activity and integrity in postmortem striatum of chronic heroin users who died from an overdose of heroin. Striatal levels of the vesicular monoamine transporter were normal, suggesting that the density of dopamine nerve terminals is not reduced in heroin users [134]. All in all, it cannot be excluded that opiates influence binding of [$^{123}$I]FP-CIT imaging to DATs, but data are not consistent.

*Effects of anesthetics*

PET and SPECT studies in animals play an important role in the characterization of new radiotracers, and these studies present an in vivo means to measure neuroreceptors in animal models of disease or to evaluate treatment. Particularly, in the past few years, PET and SPECT imaging of small laboratory animals has been improved substantially (for reviews see [135, 136]). In the vast majority of such studies, the animal will be anesthetized. Particularly, the famous PET studies in conscious monkeys by Tsukada's group have highlighted the potential effects of anesthetics on DAT imaging. For example, these studies showed clear effects of ketamine and isoflurane on DAT imaging [137, 138], presumably by a fast internalization of DATs from the cell membrane and/or blockade of DAT binding [139, 140]. These data are relevant for the interpretation of animal studies in which [$^{123}$I]FP-CIT was used to label the DAT. For clinical studies, this information may be of relevance because ketamine is sometimes used as a drug of abuse [141] (Table 1). Similar to ketamine, the dissociative anesthetic phencyclidine (PCP) may exert some direct effects through the DAT [142], and it is sometimes used as a drug of abuse (Table 1).

## Part 3: drugs interactions in imaging DAT with FP-CIT in routine clinical studies: recommendations for withdrawal of drugs before the scan

In scientific studies, even small differences may be relevant. Therefore, all kinds of drugs, even levo-dopa (and herbals such as St John's Wort or ephedra; for discussion, see part 2), may influence DAT imaging with [$^{123}$I]FP-CIT SPECT. However, most centers use [$^{123}$I]FP-CIT more frequently, or even exclusively, only for routine clinical studies. From data published and discussed in part 2, it is suggested that some medications or drugs of abuse are likely to influence the interpretation of [$^{123}$I]FP-CIT SPECT images, which may lead to a misleading scan. Therefore, it is relevant prior to administration of [$^{123}$I]FP-CIT to check the patient's present and recent past medication record.

Cocaine and amphetamines including methylphenidate are the most clear examples of drugs (of abuse) that will

influence the visual and quantitative analysis of [$^{123}$I]FP-CIT SPECT scans. Therefore, to prevent a significant occupancy of the DAT, for routine clinical studies we recommend that the patient stop taking them at least five plasma clearance half-lives before the scan. This is a rather conservative approach because, in clinical trials, four plasma clearance half-lives is suggested to be an appropriate washout period for drugs [143]. However, the decision to withdraw any medication must always be made by the specialist in charge of the patient's care, taking also into account the advantages and disadvantages of a withdrawal. Also, phentermine and ephedrines (as tablets; phentermine has previously been a prescription drugs but now is not generally available), modafinil, and some antidepressants (bupropion, radafaxine, and mazindol; mazindol has previously been a prescription drug but now is not generally available) are likely to influence the scan significantly, and should be stopped (if allowed; five half-lives). There are data to suggest that anticholinergics, and particularly benzatropine, may influence the visual and quantitative interpretation of FP-CIT SPECT scan significantly by reducing [$^{123}$I]FP-CIT binding to the DAT due to its relatively high affinity for the DAT. Therefore, we recommend stopping benzatropine to prevent a misleading [$^{123}$I]FP-CIT SPECT scan. Based on studies in rats and monkeys, other anticholinergics (such as scopolamine) might *increase* striatal [$^{123}$I]FP-CIT binding ratios. For a visual analysis of FP-CIT scans, it is therefore not necessary to withdraw this medication. On the other hand, these drugs might lead to an overestimation of striatal FP-CIT binding ratios in humans. This increased striatal uptake may possibly affect the results of a quantitative analysis. There are also some data to suggest that opioids may influence the interpretation of FP-CIT SPECT scans. Therefore, fentanyl should not be used when [$^{123}$I]FP-CIT is administered (at least five half-lives). For other opioids, the evidence that they may influence DAT imaging is not strong enough to advocate withdrawing them before a routine [$^{123}$I]FP-CIT SPECT scan. Ketamine and PCP are sometimes used illicitly, and it is likely that these drugs will significantly influence the interpretation of the scan visually as well as quantitatively.

SSRIs and SNRI will significantly increase striatal FP-CIT binding ratios. However, because the effects will only be around 10%, we believe that, for an individual patient, such an effect will be too small to misinterpret an individual scan. Therefore, we do not recommend withdrawing this medication for routine clinical studies. Based on literature, antipsychotic medication and cholinesterase inhibitors should not be stopped prior to a routine [$^{123}$I]FP-CIT SPECT scan. Finally, amantadine is frequently used in parkinsonian patients. Although animal studies showed effects on DAT, no human studies have been performed so far. Although it may be of value to test the influence of amantadine on [$^{123}$I]FP-CIT SPECT in humans, until now there is no direct evidence which support an effect. Therefore, at this moment, we do not recommend stopping this medication.

## Conclusion

In conclusion, based on published data, it is likely that several drugs (of abuse), e.g., amphetamines, will influence the visual interpretation and quantification of [$^{123}$I]FP-CIT SPECT scans in routine clinical studies. Ideally, such medication should be stopped before the administration of the radiotracer. The decision to withdraw any medication must always be made by the specialist in charge of the patient's care, taking into account the pros and cons of a withdrawal.

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