

[¹²³I]FP-CIT (DaTscan) SPECT Brain Imaging in Patients with Suspected Parkinsonian Syndromes

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ABSTRACT

OBJECTIVE

To review [¹²³I]FP-CIT (Ioflupane I 123, DaTscan) SPECT imaging and its role in clinical practice.

BACKGROUND

[¹²³I]FP-CIT is a radiopharmaceutical that binds reversibly to striatal presynaptic dopamine transporters.

METHODS

We review the two principal multicenter clinical trials of [¹²³I]FP-CIT SPECT imaging and provide additional, previously unreported information. Study 1 was a trial of [¹²³I]FP-CIT SPECT in patients with early suspected parkinsonism that compared baseline scans to the consensus clinical diagnosis established 3 years later. Study 2 was a trial of [¹²³I]FP-CIT SPECT in patients with established diagnoses of parkinsonian syndrome (PS) or essential tremor (ET).

RESULTS

In Study 1, positive percent agreement (abnormal baseline scan and clinical diagnosis of PS at 36 months [$n = 71$]) was 78-79%. Negative percent agreement (normal baseline scan and a clinical diagnosis of non-PS at 36 months [$n = 28$]) was 97%. In study 2, positive percent agreement (abnormal scan and a clinical diagnosis of PS [$n = 158$]) was 92-97%. Negative percent agreement (normal scan and a clinical diagnosis of ET [$n = 27$]) was 74-96%.

CONCLUSION

[¹²³I]FP-CIT SPECT brain imaging is used to assist in the evaluation of adult patients with suspected PS and may help differentiate ET from PS as an adjunct to other diagnostic evaluations.

Introduction

Accurate diagnosis of patients with suspected parkinsonian syndromes (PS) is critical to predict the disease course and select appropriate therapies. Misdiagnosis can lead to unnecessary disability if effective treatment options are not instituted, and inappropriate therapies may unnecessarily expose patients to the risk of potential side effects. An important diagnostic distinction is that between Parkinson's disease (PD) and essential tremor (ET), but this can sometimes be difficult on clinical grounds alone. PD can present with postural tremor,¹ rigidity and bradykinesia may not be present early in the disease, and the initial levodopa response may be absent or minimal.² In ET, there may be asymmetry,³ rest tremor,⁴ cogwheeling, or subtle parkinsonian features that are particularly common in the elderly.⁵

Recent studies have highlighted the high misdiagnosis rate of PD. In one community-based study of 502 individ-

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uals with presumed PD, 103 (26%) were found not to have parkinsonism.⁶ Of these, 50 (29%) met criteria for ET. In another study ($N = 202$), a community-based diagnosis of PD was rejected according to clinical criteria in 15%, and 19% of individuals who had come to medical attention but were not diagnosed with PD met PD clinical criteria.⁷ In autopsy series, atypical PS (multiple system atrophy [MSA], progressive supranuclear palsy [PSP], and corticobasal degeneration [CBD]) accounted for half of PD misdiagnoses at specialized centers,^{8,9} while in the community, Alzheimer's disease and vascular parkinsonism were most common.^{6,7}

[¹²³I]FP-CIT (Ioflupane I 123, DaTscan) is a radiopharmaceutical used for single-photon emission-computed tomography (SPECT) brain imaging. In vitro, ioflupane binds reversibly to human recombinant dopamine transporters (DaT).¹⁰ Autoradiography of postmortem human brain slices exposed to radiolabeled ioflupane shows concentration of the radiolabel in the

striatum (caudate and putamen).^{10,11} The binding of ioflupane in the striatum is abolished by the dopamine reuptake inhibitor GBR 12909, thereby demonstrating the selectivity of ioflupane binding to striatal presynaptic DaT.^{10,11} Thus, [¹²³I]FP-CIT striatal uptake would be expected to be reduced in degenerative PS including PD, MSA, and PSP due to the loss of dopamine neurons and DaT positioned on dopamine neuron terminals in the striatum. In contrast, in ET there is no loss of dopamine neurons, and [¹²³I]FP-CIT striatal uptake would be expected to be normal.

[¹²³I]FP-CIT has been approved for use in SPECT imaging in Europe since 2000, and the Food and Drug Administration (FDA) has now approved it for use in the United States.* The safety and efficacy of [¹²³I]FP-CIT SPECT imaging were evaluated in two principal multicenter clinical trials^{12,13} that are reviewed in this article.

Study 1

A phase III, multicenter study evaluated the use of [¹²³I]FP-CIT SPECT in patients with early suspected parkinsonism for whom there was diagnostic uncertainty.¹² The primary analysis was a comparison of [¹²³I]FP-CIT SPECT scans performed at baseline to the clinical diagnosis established 3 years later.

Eligible subjects were 30 to 90 years old and had Unified Parkinson's Disease Rating Scale (UPDRS) scores ≤ 16 . Individuals with secondary causes of parkinsonism, and those with features suggestive of MSA and PSP at screening were excluded. UPDRS and Hoehn-Yahr (H-Y) scoring (with subjects off antiparkinsonian medications for at least 12 hours) were performed at baseline and months 3, 18, and 36. The clinical diagnosis at 36 months was established by a consensus of two movement disorder specialists who were blind to SPECT findings and the site working diagnosis. Their diagnosis was based on clinical data collected over the 36 months, including a description of symptom onset, results of structural brain imaging, site UPDRS rigidity scores, H-Y scores, medication use, and a video recording of the UPDRS motor examination obtained at 36 months. Predefined options for clinical diagnosis were: probable PD (fulfilling Brain Bank criteria step 1, that is, bradykinesia plus at least 1 of rigidity, tremor, or postural instability),¹⁴ possible PD (not fulfilling Brain Bank criteria step 1), possible ET, or other. For the primary analysis, subjects were diagnosed as having a PS (which would be expected to have reduced dopamine transporter visualization on SPECT scan due to nigrostriatal degeneration), or non-PS (which would be expected to have normal dopamine transporter visualization on SPECT scan due to lack of nigrostriatal degeneration). PS included PD, MSA, and PSP whereas non-PS included ET, dystonic tremor, and vascular tremor.

[¹²³I]FP-CIT SPECT imaging was performed at baseline, 18 months, and 36 months. Dopaminergic medications were continued, but drugs that interfere with striatal uptake of [¹²³I]FP-CIT (eg, CNS stimulants, anti-anorexia and obesity treatments, and sympathomimetics) were discontinued for at least 4 weeks prior to baseline. Thyroid blockade was utilized where indicated, and subjects received an intravenous injection of 111-185

MBq (3-5 mCi) of [¹²³I]FP-CIT. Imaging was performed 3 to 6 hours after injection using either a multidetector single slice system or multiheaded gamma cameras.

Images were evaluated visually by three independent nuclear medicine physicians who were blind to clinical information other than the subject's age. Scans were assessed as normal (largely symmetrical, normal uptake in putamen and caudate) or abnormal (asymmetrically reduced putamen uptake, significantly reduced putamen uptake bilaterally, or virtually absent uptake bilaterally affecting both putamen and caudate) (Fig 1).

Ninety-nine subjects completed both [¹²³I]FP-CIT SPECT imaging at baseline and consensus clinical diagnosis at 36 months. The consensus clinical diagnosis at 36 months was PS in 71 cases (66 probable PD fulfilling Brain Bank criteria step 1, 5 possible PD not fulfilling Brain Bank criteria step 1) and non-PS in 28 cases.

Among the 71 subjects with a consensus clinical diagnosis of PS at 36 months, 78% to 79% (depending on the reader) had an abnormal [¹²³I]FP-CIT SPECT scan at baseline (ie, positive percent agreement was 78% to 79%) (Table 1). Among the 28 subjects with a consensus clinical diagnosis of non-PS at 36 months, 97% had a normal [¹²³I]FP-CIT SPECT scan at baseline (ie, negative percent agreement was 97%) (Table 1).

At 36 months, 17 of the 71 (24%) subjects with a consensus clinical diagnosis of PS were not taking anti-Parkinson medication, and in seven of these individuals, the [¹²³I]FP-CIT SPECT scan at baseline was abnormal (ie, positive percent agreement was 41%). Thus, there was a lower likelihood of an abnormal SPECT scan in subjects diagnosed with PS if they were not on anti-Parkinson medication at 36 months.

For almost all of the subjects, SPECT imaging results (normal vs. abnormal) remained the same through the study. The initial SPECT finding was changed from normal at baseline to abnormal at 36 months in one subject with a consensus clinical diagnosis at 36 months of possible PD. In addition, the initial SPECT finding of abnormal at baseline was changed to normal at 36 months in one subject with a consensus clinical diagnosis at 36 months of probable PD.

The inter-reader agreement with regard to visual interpretation of [¹²³I]FP-CIT SPECT scans (normal vs. abnormal) was very high at all time points. Notably, both positive and negative percent agreement between clinical diagnosis and imaging increased from baseline to 36 months (Table 2), suggesting that clinical diagnosis tended to move toward agreement with the imaging result as more clinical information became available (eg, progression of signs and symptoms, and response to medications).

Adverse events (AEs) were recorded from the first [¹²³I]FP-CIT administration until the 36-month telephone follow-up, and a total of 405 [¹²³I]FP-CIT SPECT scans were performed. Among the 179 subjects in the safety population, 122 experienced a total of 400 AEs during the 36-month period, a majority of which (376 AEs, 94%) were deemed by the investigator to be unrelated to [¹²³I]FP-CIT. During the 36-month study period, a total of 4 subjects died and 32 subjects (18%) experienced 71 nonfatal serious AEs (SAEs), none of which were deemed to be related to [¹²³I]FP-CIT. The most frequently reported AE was headache (15% of subjects). Only 24 AEs (6.0%) reported by 13 subjects were considered as having reasonable relationship to

*Correction added after online publication 22-March-2011: Sentence has been edited for grammatical clarity.

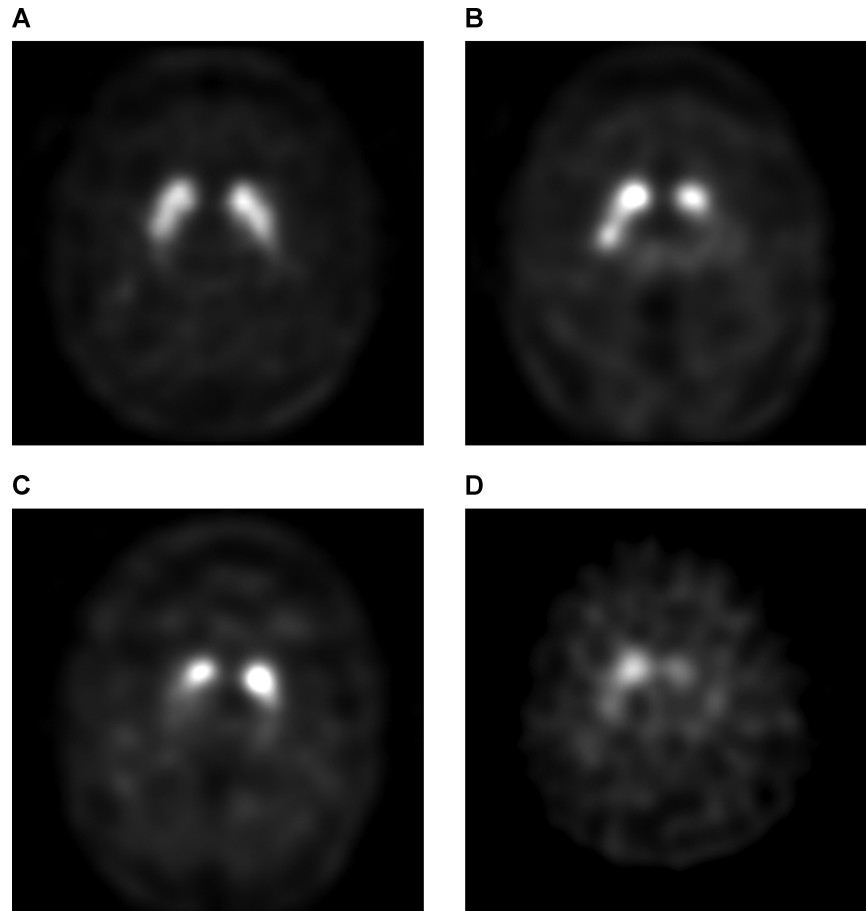


Fig 1. Normal and abnormal [^{123}I]FP-CIT SPECT images. [^{123}I]FP-CIT images are interpreted visually, based upon the appearance of the striata. Reconstructed pixel size should be between 3.5 and 4.5 mm with slices 1 pixel thick. Optimum presentation of the reconstructed images for visual interpretation is composed of transaxial slices parallel to the anterior commissure-posterior commissure line. Determination of whether an image is normal or abnormal is made by assessing the extent (as indicated by shape) and intensity of the striatal signal. (A) Normal: In transaxial images, normal images are characterized by two symmetric comma- or crescent-shaped focal regions of activity mirrored about the median plane. Striatal activity is distinct, relative to surrounding brain tissue. Abnormal [^{123}I]FP-CIT images fall into at least one of the following three categories (all of which are considered abnormal). (B) Abnormal: Activity is asymmetric, that is, activity in the region of the putamen of one hemisphere is absent or greatly reduced with respect to the other. Activity is still visible in the caudate nuclei of both hemispheres resulting in a comma or crescent shape in one and a circular or oval focus in the other. There may be reduced activity between at least one striatum and surrounding tissues. (C) Abnormal: Activity is absent in the putamen of both hemispheres and confined to the caudate nuclei. Activity is relatively symmetric and forms two roughly circular or oval foci. Activity of one or both is generally reduced. (D) Abnormal: Activity is absent in the putamen of both hemispheres and greatly reduced in one or both caudate nuclei. Activity of the striata with respect to the background is reduced.

[^{123}I]FP-CIT, most of which were mild in intensity (14, 3.5%). The most common AEs with reasonable relationship to [^{123}I]FP-CIT were headache ($n = 5$, 3%), nausea ($n = 3$, 2%), injection site hematoma, dizziness, and dysgeusia (each $n = 2$, 1%).

Study 2

Another multicenter study evaluated the use of [^{123}I]FP-CIT SPECT in patients with established diagnoses of PS or ET.¹³ Eligible subjects were 40 to 80 years old with either PS (meeting Brain Bank criteria step 1),¹⁵ or definite ET (meeting Findley and Koller criteria¹⁶). PS subjects were further classified as having PD (fulfilling Brain Bank criteria step 3, or if de novo, exhibiting an improvement of at least 30% on UPDRS motor score evaluation with a standard apomorphine or lev-

odopa challenge^{17–21}), MSA (fulfilling diagnostic criteria of the Consensus Committee of the American Autonomic Society and American Academy of Neurology²²), or PSP (fulfilling research diagnostic criteria of the National Institute of Neurological Disorders and Stroke and the Society for PSP²³). Patients with cerebrovascular disease, structural brain disease, dementia, head injury, or encephalitis were excluded. Central nervous system stimulants such as amphetamines, anti-anorexia or obesity treatments, sympathomimetics, benzotropine, and the antidepressants amoxapine and bupropion were not permitted in the 4 weeks prior to enrollment.

Subjects underwent thyroid blockade where appropriate, and received a single intravenous injection of [^{123}I]FP-CIT with SPECT imaging performed 3 to 6 hours later. A uniform reconstruction of raw data was performed at one center and hard copy

Table 1. Positive and Negative Percent Agreement Rates in Studies 1¹² and 2¹³

	Positive Percent Agreement (95% CI) (% patients with an abnormal [¹²³I]FP-CIT SPECT image among patients with PS)	Negative Percent Agreement (95% CI) (% patients with a normal [¹²³I]FP-CIT SPECT image among patients with non-PS)
Study 1 (patients with early suspected PS)		
	n = 71	n = 28
Reader A, n = 99	78 (66, 87)	97 (83, 100)
Reader B, n = 99	78 (66, 87)	97 (83, 100)
Reader C, n = 99	79 (67, 88)	97 (83, 100)
Study 2 (patients with established diagnoses of PS or ET)		
	n = 158	n = 27
Reader A, n = 185	93 (88, 97)	96 (81, 100)
Reader B, n = 185	97 (93, 99)	74 (54, 89)
Reader C, n = 185	96 (92, 99)	85 (66, 96)
Reader D, n = 185	92 (87, 96)	93 (76, 99)
Reader E, n = 185	94 (90, 97)	93 (76, 99)

images were produced using an identical color scale and format for each image. Hard copy images were randomized and evaluated by a blinded reading panel consisting of four experienced nuclear medicine physicians and a neurologist with limited experience in assessing [¹²³I]FP-CIT SPECT scans. These blinded readers rated the images of each case as normal or abnormal.

The intent-to-treat (ITT) population included 158 subjects with PS and 27 with ET. Of the 158 PS subjects, 130 (82.3%) had a diagnosis of PD, 18 (11.4%) had a diagnosis of MSA, and 10 (6.3%) had a diagnosis of PSP. In subjects with a diagnosis of PS, the [¹²³I]FP-CIT SPECT scan was read as abnormal in 92% to 97% of cases (positive percent agreement), depending on the individual reader (Table 1). For subjects with a diagnosis of ET, the [¹²³I]FP-CIT SPECT scan was read as normal in 74% to 96% of cases (negative percent agreement), depending on the individual reader (Table 1).

Table 2. Positive and Negative Percent Agreement for [¹²³I]FP-CIT SPECT Imaging Compared with Baseline Clinical Diagnosis and Compared with Consensus Clinical Diagnosis at 36 Months: Study 1¹²

	PS (Probable or possible PD) n	Positive Percent Agreement n (%)
Baseline clinical diagnosis	81	55/81 (67.9)
36-month consensus clinical diagnosis	71	56/71 (78.9)
	Non-PS (Non-PD) n	Negative percent agreement n (%)
Baseline clinical diagnosis	18	16/18 (88.9)
36-month consensus clinical diagnosis	28	27/28 (96.4)

Of the 158 subjects with PS, 150 (94.9%) had SPECT scans that were rated as abnormal by more than half of the reading panel. For these subjects (n = 158), all 5 readers rated the scan abnormal in 143 (90.5%), 4 of 5 readers rated the scan abnormal in 6 (3.8%), and 3 of 5 readers rated the scan abnormal in 1 (0.6%). In addition, of the 158 subjects with PS, all 5 readers rated the scan normal in 4 (2.5%), 4 of 5 readers rated the scan normal in 3 (1.9%), and 3 of 5 readers rated the scan normal in 1 (0.6%). Of the 8 PS subjects whose blinded consensus scan reading was normal, 5 had a clinical diagnosis of PD, 2 had a clinical diagnosis of MSA, and 1 had a clinical diagnosis of PSP. There was no effect of age, H-Y stage, or study center on abnormal/normal scan results. Also, the scan results did not differentiate among PD, MSA, and PSP.

Adverse events reported in more than 1% of the 189 subjects who underwent [¹²³I]FP-CIT SPECT scan were headache (n = 15, 7.9%), flulike symptoms (n = 4, 2%), injection site bleeding (n = 4, 2%), vertigo (n = 4, 2%), and paresthesia (n = 3, 1.5%). Of the 65 AEs reported in 36 subjects, fewer than half (n = 30) were thought to be probably or possibly related to [¹²³I]FP-CIT. There was one report of a SAE, consisting of extrapyramidal symptoms that the investigator judged to be unrelated to [¹²³I]FP-CIT.

Discussion

[¹²³I]FP-CIT SPECT brain imaging is used to assist in the evaluation of adult patients with suspected PS. In these patients, [¹²³I]FP-CIT SPECT imaging may help differentiate ET from tremor due to PS (PD, MSA, PSP) and is an adjunct to clinical and other diagnostic evaluations.

It is important to note that in the studies reviewed above, there was no autopsy confirmation of diagnosis, and thus no confirmed “gold standard.” Rather, the agreement rates between clinical diagnosis and SPECT readings were evaluated. However, as reported in study 1, imaging results rarely changed over 36 months whereas the clinical diagnosis tended to move into alignment with the imaging results (Table 2). The baseline [¹²³I]FP-CIT SPECT scans better correlated with the clinical diagnosis after time had passed and more clinical information was available, including progression of signs and symptoms and response to medications. This is in agreement with the observation by Seibyl et al.²⁴ that as the duration of diagnosis of patients enrolled in PD disease progression trials increased, the percentage of patients with normal scans decreased, suggesting that with longer disease duration more clinical information is available to enhance the accuracy of diagnosis. In addition, at the end of study 1, approximately 20% of subjects (15/71) with a 36-month consensus clinical diagnosis of PS had normal baseline scans. These patients exhibited significantly less progression of mean UPDRS scores over 36 months (Table 3) than subjects with a consensus clinical diagnosis of PS who had abnormal scans. Moreover, in the five subjects with a consensus clinical diagnosis of possible PD and a normal scan, mean UPDRS scores did not worsen over 36 months, suggesting that these patients did not have a degenerative parkinsonism (Table 4).

Table 3. Mean Baseline UPDRS and 36-Month UPDRS in Subjects with a Consensus Clinical Diagnosis of PS at 36 Months, According to Baseline [¹²³I]FP-CIT SPECT Results¹²

	All Patients with 36-Month Consensus Clinical Diagnosis of Probable or Possible PD (Study 1), ¹² n = 71			
	Normal [¹²³ I]FP-CIT SPECT at Baseline		Abnormal [¹²³ I]FP-CIT SPECT at Baseline	
	n	Mean UPDRS	n	Mean UPDRS
Baseline (T = 0)	15	11.0	56	11.0
36 months (T = 36)	15	14.4	55	21.1
UPDRS Change	15	3.4	55	10.2*

*P = 0.003 vs. all patients with normal DaTscan at baseline.

These observations suggest that in cases of early, suspected PS, [¹²³I]FP-CIT SPECT is more accurate than clinical diagnosis, but this remains to be proven. [¹²³I]FP-CIT SPECT imaging currently constitutes an additional piece of information for the clinician to consider. Based on the clinical studies described above, patients with clinical diagnostic uncertainty between PS and ET have a higher likelihood of PS in the presence of abnormal [¹²³I]FP-CIT SPECT, and a very low likelihood of PS when the [¹²³I]FP-CIT SPECT is normal.

The interrater agreement with regard to visual assessment of [¹²³I]FP-CIT SPECT imaging was very high in these studies. This indicates good consistency in scan results regardless of being performed at different sites, utilization of different cameras, and interpretation by different readers. Nonetheless, the small amount of variability from reader to reader, even when the same hard copy color image was evaluated indicates that the true accuracy of visual inspection of [¹²³I]FP-CIT SPECT brain imaging is not 100% and it would be a mistake to simply base the diagnosis of PS versus non-PS on the imaging result alone.

The results of the studies reviewed above are consistent with other recent investigations. In another study of patients with clinically uncertain PS,²⁵ clinical diagnosis at 2 years follow-up

agreed with the initial [¹²³I]FP-CIT SPECT result in 69 of 77 patients (90%) in whom a specific diagnosis was established. In addition, a follow-up [¹²³I]FP-CIT SPECT scan helped establish a diagnosis in 7 of 8 patients with a previously inconclusive diagnosis. Another study²⁶ evaluated [¹²³I]FP-CIT SPECT in 20 patients with ET, 13 with PD, and 23 healthy controls. PD patients had reduced DaT binding compared to ET patients and healthy controls, and demonstrated an annual decline rate of 7.3% in the contralateral putamen. There were no mean uptake differences between ET patients and healthy controls, and no uptake loss over time in ET patients. In a study evaluating the accuracy of PD diagnoses in 610 general practice patients,²⁷ expert clinical evaluation was undertaken in 64 patients who were identified by screening criteria. Of these, 14 were confirmed as likely to have PD, 25 were considered unlikely to have PD, and 25 were deemed clinically uncertain. In the clinically uncertain cases, [¹²³I]FP-CIT SPECT was normal in 14 and abnormal in 11. Notably, all 14 patients with normal scans were able to be withdrawn from antiparkinsonian medications without worsening, thereby eliminating unnecessary medication costs and risk of side effects. An analysis of the cost-effectiveness of [¹²³I]FP-CIT SPECT in the differential diagnosis of ET and Parkinson's disease concluded that [¹²³I]FP-CIT SPECT is likely to be economically advantageous and lower overall cost to the healthcare system.²⁸

It is important to recognize that an abnormal [¹²³I]FP-CIT SPECT scan does not necessarily indicate a diagnosis of PD and a normal scan does not necessarily indicate a diagnosis of ET, as multiple other conditions must be considered. Abnormal striatal uptake of [¹²³I]FP-CIT would be expected in all degenerative parkinsonisms associated with a loss of nigrostriatal dopamine neurons including PD, MSA, PSP, CBD, and others, and [¹²³I]FP-CIT SPECT imaging does not differentiate among these disorders. Striatal uptake of [¹²³I]FP-CIT would be expected to be normal in ET, dystonic tremor, medication- or drug-induced parkinsonism with blockade of postsynaptic dopamine receptors, medication- or drug-induced tremor, most vascular parkinsonism, Alzheimer's disease, psychogenic

Table 4. Mean Baseline UPDRS and 36-Month UPDRS in Subjects with a Consensus Clinical Diagnosis of PS at 36 Months, According to Clinical Confidence, and Subdivided According to Baseline [¹²³I]FP-CIT SPECT Results¹²

	All Patients with 36-Month Consensus Clinical Diagnosis of Probable or Possible PD (Study 1), ¹² n = 71							
	Probable PD				Possible PD			
	n		Mean UPDRS		n		Mean UPDRS	
Baseline (T = 0)	66		10.9		5		12.2	
36 months (T = 36)	65		20.3		5		12.2	
	Normal [¹²³ I]FP-CIT SPECT at Baseline		Abnormal [¹²³ I]FP-CIT SPECT at Baseline		Normal [¹²³ I]FP-CIT SPECT at Baseline		Abnormal [¹²³ I]FP-CIT SPECT at Baseline	
	n	Mean UPDRS	n	Mean UPDRS	n	Mean UPDRS	n	Mean UPDRS
Baseline (T = 0)	10	10.4	56	11.0	5	12.2	0	–
36 Months (T = 36)	10	15.5	55	21.1	5	12.2	0	–
UPDRS Change	10	5.1	55	10.2 [†]	5	0 [‡]		

[†]P = 0.135 vs. patients with probable PD and normal [¹²³I]FP-CIT SPECT at baseline.

[‡]P = 0.033 vs. all patients with abnormal [¹²³I]FP-CIT SPECT at baseline.

tremor or psychogenic parkinsonism, other disorders, and in normal individuals. Thus, the differential diagnosis remains large with either a normal or abnormal [¹²³I]FP-CIT SPECT scan, and clinical assessment and judgment are critical. In addition, in some cases there may be a need to obtain a brain CT or MRI to exclude a structural lesion. Physicians ordering an [¹²³I]FP-CIT SPECT scan should be familiar with the clinical conditions under consideration, the meaning of the imaging results, and their limitations.

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