Clinical utility of dopamine transporter single photon emission CT (DaT-SPECT) with \(^{123}\text{I}\) ioflupane in diagnosis of parkinsonian syndromes

Nin Bajaj,\(^1\) Robert A Hauser,\(^2\) Igor D Grachev\(^3\)

**ABSTRACT**

The diagnosis of movement disorders including Parkinson’s disease (PD) and essential tremor is determined through clinical assessment. The difficulty with diagnosis of early PD has been highlighted in several recent clinical trials. Studies have suggested relatively high clinical diagnostic error rates for PD and essential tremor. This review was undertaken to clarify the utility of DaT-SPECT imaging with \(^{123}\text{I}\) ioflupane (DaTSCAN or DaTscan or \(^{123}\text{I}\)FP-CIT) in assisting practitioners in their clinical decision making by visualising the dopamine transporter in parkinsonian cases. In some patients with suspected parkinsonian syndromes, SPECT imaging with \(^{123}\text{I}\) ioflupane is useful to assist in the diagnosis and to help guide prognosis and treatment decisions, including avoiding medications that are unlikely to provide benefit. Clinicians ordering \(^{123}\text{I}\) ioflupane SPECT should be aware of its limitations and pitfalls and should order scans when there is diagnostic uncertainty or when the scan will be helpful in clinical decision making.

**INTRODUCTION**

\(^{123}\text{I}\) ioflupane (Iodine-123-fluoropropyl (FP)-carboxymethoxy-3-β-(4-iodophenyltropane) (CIT) \(^{123}\text{I}\) FP-CIT or DaTSCAN or DaTscan) approved by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) for clinical use is the only approved in vivo diagnostic imaging agent for suspected parkinsonian syndromes (PS), including the most prevalent syndrome: Parkinson’s disease (PD) (figure 1A). EMA approved this agent under the trade name DaTSCAN in 2000.\(^1\) The US FDA approved it under the trade name DaTscan in 2011.\(^2\) This review was undertaken to clarify the utility of dopamine transporter visualisation through DaT-SPECT imaging to assist practitioners in their clinical evaluation diagnoses of suspected PS versus essential tremor (ET).

The role of \(^{123}\text{I}\) ioflupane is not to confirm the diagnosis of PD or other clinical syndromes in patients about whom there is no diagnostic doubt. If a patient fulfils the UK Parkinson’s Disease Brain Bank Criteria (UKPDBBC)\(^3\) for PD, no further tests are usually necessary. Hughes et al have shown that the diagnosis of PD using the UKPDBBC has a high degree of clinical accuracy when compared with subsequent pathology evaluation.\(^4\) Similarly, if the clinical picture is clearly characteristic of ET or dystonic tremor, no further diagnostic tests are usually required, although the accuracy of clinical diagnosis in these disorders remains to be formally evaluated.

**Labelled indications for \(^{123}\text{I}\) ioflupane**

The formal EMA indication\(^1\) for DaTSCAN is as follows:

‘This medicinal product is for diagnostic use only. DaTSCAN is indicated for detecting loss of functional dopaminergic neuron terminals in the striatum.

- In patients with clinically uncertain Parkinsonian Syndromes, in order to help differentiate Essential Tremor from Parkinsonian Syndromes related to idiopathic Parkinson’s Disease, Multiple System Atrophy and Progressive Supranuclear Palsy. DaTSCAN is unable to discriminate between Parkinson’s Disease, Multiple System Atrophy and Progressive Supranuclear Palsy (see figure 1B).
- To help differentiate probable dementia with Lewy bodies from Alzheimer’s disease. DaTSCAN is unable to discriminate between dementia with Lewy bodies and Parkinson’s disease dementia.’

The FDA-approved indication\(^2\) for DaTscan is similar:

‘DaTscan is a radiopharmaceutical indicated for striatal dopamine transporter visualisation using single photon emission computed tomography brain imaging to assist in the evaluation of adult patients with suspected parkinsonian syndromes. In these patients, DaTscan may be used to help differentiate ET from tremor due to parkinsonian syndromes (idiopathic Parkinson’s disease, multiple system atrophy and progressive supranuclear palsy). DaTscan is an adjunct to other diagnostic evaluations.’

**ACCURACY OF A CLINICAL DIAGNOSIS OF PD**

**Historical overview**

It is worth at this point revisiting the seminal 2002 Hughes et al paper, ‘Accuracy of Diagnosis of PD in a Specialist Movement Disorder Service’.\(^5\) The first notable point is in the title of the paper which refers to: ‘...a Specialist Movement Disorder service’. This study looked at the clinical and pathological data on 143 cases referred to the UK Parkinson’s Disease Society Brain Research Centre over a 10-year period by clinicians attached to the National Hospital for Neurology and Neurosurgery, The National Hospital for Neurology and
Figure 1  (A) $^{[123]}$Ioflupane selectively binds presynaptically to the DaT receptors within the striatum of the brain. Loss of DaT receptors is indicative of PS. (B): $^{[123]}$Ioflupane is used in the clinical differentiation of PS from ET—where signs and symptoms can overlap in early onset of disease. (C) Visual detection of DaT distribution in vivo.

- Grade 1: asymmetrical loss of putaminal tail—‘comma with full stop’
- Grade 2: bilateral loss of putaminal tails—‘two full stops’
- Grade 3: Partial to complete loss of caudate and putaminal signal—‘disappearing full stops’.

Reference: FDA prescribing information for DaTscan Website. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022454sOrig1s000Lbl.pdf.

(D) Diagnostic decision tree for patients with tremor and parkinsonism

UKPDBBC, UK Parkinson’s Disease Brain Bank Criteria; Dx, diagnosis; Rx, treatment.
Neurosurgery is the only national Centre for Neurology in the UK and uses a largely quaternary model of patient referral. Diagnostic decisions of physicians at such a specialised centre may have little predictive value for how movement disorder clinicians in general practice might behave.

Furthermore, the characteristics of patients whose brains are donated to a brain bank are worth examining. Unsurprisingly, the selection of patients in this study featured a high number of PS of aggressive nature, for example, multiple system atrophy (MSA). The likeliest candidates referred by patients’ relatives or their general practitioners (GPs) for brain donation would be patients in whom disease progression has been rapid or emotive, death has occurred in a hospital or a nursing home versus in the community, those with a family history or atypical features, or those having had a doubtful diagnosis in life. Less likely candidates would be patients with a slowly progressive, benign course of disease (eg, tremulous PD), or, in fact, patients with early, uncertain PS or scans without evidence of dopaminergic deficit (SWEDDs), as these patients are unlikely to die at that point in their disease or be subjects in an autopsy study. To some degree, these limitations have been acknowledged and discussed by Hughes et al. Little consideration has been given to whether a certain subtype of PD is over-represented in this series, but personal communication with the senior author (Andrew Lees) suggests patients with tremulous PD were under-represented.

A further consideration is when in the course of the disease the clinical diagnosis was initially made. In the Hughes et al study, the mean time from symptom onset to initial clinical diagnosis was 1.6 years. Crucially, this initial clinical diagnosis was revised in 44 of 122 cases after a mean of 3.4 years. Clearly, if this study had used the figures pertaining to initial diagnosis increased. This suggests that the original clinical diagnosis of PD was wrong.11 Consensus discussion regarding these cases suggested that the quaternary nature of this service. In this scenario modelling, assuming IPD to be the most prevalent of the pathological diagnoses, the negative predictive value falls to less than 50% of the sample: an acknowledgment from the authors that many cases of PD might be missed in general clinical practice. Although this study highlighted an underdiagnosis of PD, a large community-based study found the opposite, with 47% of patients diagnosed as having PD in the community not fulfilling the PDBBC.6

The difficulty with diagnosis of early PD has been highlighted in several recent clinical trials that included neuroimaging. In the CALM-PD (pramipexole vs L–dopa), REAL-PET (ropinirole vs L-dopa), and ELLDOPA (L-dopa vs placebo) studies, patients with a clinical diagnosis of early PD were enrolled by movement disorder physicians across centres in Europe and the USA. All patients had functional imaging assessment at baseline (β-CIT SPECT in CALM-PD and ELLDOPA, 18F–dopa in REAL-PET), after the clinical diagnosis was made and after subjects had been enrolled in the trials. Across the three trials, between 4% and 15% of subjects were found to have normal imaging findings, inconsistent with the clinical diagnosis of PD.

In the ELLDOPA study of 142 subjects, 21 subjects (15%) examined by β-CIT-SPECT were classified as subjects without evidence of dopaminergic deficiency (SWEDDs). Marek et al followed some of these SWEDD patients and reported no deterioration in neurological features over time. These patients also had normal imaging results at 9 months (19/19 cases), 18 months (17/17), 36 months (12/12) and 48 months (10/10). Consensus discussion regarding these cases suggested that the original clinical diagnosis of PD was wrong.

Across these therapeutics trials enrolling subjects with PD, the percentage of enrollees with normal scans decreased as duration of time following initial diagnosis increased. This suggests that the clinical diagnosis becomes more accurate over time as clinical features evolve and response to medication becomes clearer. Notably, in patients with early suspected PS, the clinical
Multiple studies have shown that dopamine plays a crucial role in epithelial differentiation, with various studies confirming its role in the development of various tissue types. However, the exact mechanisms by which dopamine regulates tissue differentiation remain unclear. Further research is needed to elucidate the complex role of dopamine in epithelial differentiation.
Kalra et al systematically reviewed 25 studies comparing clinical and neuroimaging features that might distinguish VP from PD. Clinical features that helped differentiate the diagnostic distinction of VP from PD included older age; shorter duration of illness; presentation with symmetrical gait abnormality; reduced L-dopa responsiveness; and more postural instability, falls, and dementia in patients with VP. Three of the reviewed studies used presynaptic dopaminergic imaging with SPECT (TRODAT, β-CIT or (123)I)iodoipamidil): two of these studies found significant differences in asymmetry of striatal hyperperfusion in PD versus VP cases. This would be in accord with the clinical hypothesis that PD is an asymmetrical clinical presentation with striatal hyperperfusion being most marked contralateral to the most clinically affected side. The third study found striatal binding in VP to be preserved or only mildly reduced compared with a 40% predominately putaminal reduction of binding in PD cases. Clearly, further studies are needed in this area and the review authors have highlighted the importance of an accurate clinical diagnosis of VP as underpinning future work.

Subregional patterns of preferential striatal dopaminergic transporter loss have also been examined in PSP and MSA versus PD. A study using (123)I)iodoipamidil PET study has allowed greater resolution than SPECT, permitting quantitative analysis of ligand binding in anterior caudate and ventral putaminal areas. This study comparing 49 patients with PD with 19 PSP, 24 MSA and 21 healthy controls found that PSP cases had more prominent and earlier dopamine transporter loss in the anterior caudate (allowing 94% sensitivity and 92% specificity of distinction of PSP vs PD) and MSA cases in the ventral putamen (allowing 90% sensitivity and 45% specificity of distinction of PSP vs PD).

Although these studies in other PS indicate there may be merits in quantitative and subregional binding analysis of ligand binding in (123)I)iodoipamidil scans, the licensed indication does not extend to the diagnostic distinction of PD and other PS, and more studies need to be done in this area.

CONSIDERATIONS IN DECISION MAKING

Radiation risk

Although the cancer risk of 1 in 5000 to 7500 suggested by de la Fuente-Fernández from scanning is not to be trivialised, this has to be weighed against the usefulness of (123)I)iodoipamidil imaging to help avoid side effects of inappropriate medications, or an unnecessary delay in instituting appropriate therapy to alleviate disability. However, it is certainly a good reason to avoid unnecessary scans.

Accuracy of (123)I)iodoipamidil in PD

Perlmuter and Eidelberg make the point that after several years, follow-up of individuals with negative DAT SPECTs revealed that some develop PD or another PS. The published 95% sensitivity/specificity of (123)I)iodoipamidil suggests that (123)I)iodoipamidil will not be 100% accurate in predicting the diagnosis. In fact, readers of the scans performed in the pivotal trials failed to achieve total agreement, further confirming that results of the scan cannot be 100% accurate. This is important to keep in mind when reviewing (123)I)iodoipamidil results, considering them in the overall diagnostic and decision-making process, and in discussing them with patients.

Nevertheless, the overall error rate appears to be low. Recent audit data indicate that of 743 (123)I)iodoipamidil cases performed at a UK National Centre of Excellence for PD over a 9-year period, there were five false-positive and two false-negative results yielding a specificity of 98.6%, sensitivity of 99.4%, positive predictive value of 98.7%, negative predictive value of 99.4% and overall accuracy of 99.1% for (123)I)iodoipamidil result versus final clinical diagnosis.

Appropriate diagnostic setting

Only a clinician can make a diagnosis. (123)I)iodoipamidil is simply a tool that can be used to help inform that diagnosis through an understanding of functional dopaminergic status. Clinicians who order (123)I)iodoipamidil imaging must understand the information that it provides and its limitations. (123)I)iodoipamidil is not licensed to distinguish among conditions in which there is a loss of striatonigral dopamine neurons (eg, PD, PSP, MSA, corticobasal degeneration syndrome, Lewy body disease), even though future work may prove utility for this indication. Similarly, it does not distinguish among conditions in which there is no loss of dopamine neurons (eg, healthy individuals, ET, dystonic tremor, psychogenic conditions, parkinsonism induced by dopamine receptor antagonists). Therefore, a scan should not be ordered if the clinical uncertainty is whether a patient has PD versus MSA or ET versus psychogenic tremor. An appropriate diagnostic tree for use of (123)I)iodoipamidil in patients with tremor and parkinsonism is shown to illustrate this point in figure 1D.

REFINING THE UTILITY OF (123)I)IODOIPAMIDIL

Two phase 3 studies were reviewed by Hauser and Grosset, one of which compared baseline (123)I)iodoipamidil scans in patients with early suspected parkinsonism to a consensus clinical diagnosis established 3 years later. Among the 71 subjects with a consensus clinical diagnosis of PS at 36 months, there was positive per cent agreement (PPA) (ie, abnormal (123)I)iodoipamidil scan at baseline) in 78% to 79%, depending on the reader. Among the 28 subjects with a consensus clinical diagnosis of non-PS at 36 months, there was negative per cent agreement (NPA) (ie, normal (123)I)iodoipamidil scan at baseline) in 97% (see table 1).

PPA and NPA increased over the 36 months, with the clinical diagnosis moving towards agreement with the imaging result rather than vice versa. No serious adverse events were reported as related to (123)I)iodoipamidil. The second phase 3 trial included subjects 40–80 years old with an established diagnosis of PS (n=158) or ET (n=27). PPA (abnormal (123)I)iodoipamidil images among subjects with a clinical diagnosis of PS was 92–97% from five blinded readers. NPA (normal (123)I)iodoipamidil images among subjects with a clinical diagnosis of non-PS was 74–96% (see table 1).

It is vital to recognise that the true accuracy of (123)I)iodoipamidil is unknown. In these pivotal studies, (123)I)iodoipamidil was compared with clinical diagnoses, and it is not known how often the clinical diagnosis was wrong (especially when the (123)I)iodoipamidil and the clinical diagnosis were not in agreement). However, it is clear that there was generally good agreement between the (123)I)iodoipamidil result and the clinical diagnosis. Importantly, in early suspected PS, the initial clinical diagnosis was relatively inaccurate with a tendency to overdiagnose and over time the clinical diagnosis tended to move into better agreement with the imaging result. This was reflected in slightly inferior PPA results in Marshall et al as compared with the Benamer et al study in diagnostically certain advanced patients. Whether the rate of agreement would continue to increase with further clinical
follow-up is unknown. Pathology correlation would be ideal, but would be difficult to obtain in a systematic fashion in early disease, as few early cases come to autopsy.

In reviewing the results of the phase three trials, it is clear that the readers were not in complete agreement in their interpretation of the scans. This ensures that results of the scans as currently conceived cannot be 100% accurate. It also suggests that some readers are more accurate than others. Experience and training may make a difference but this remains to be proven.

Additional studies have highlighted the role of (123I)ioflupane in clinical decision-making. The most recent randomised, prospective, multicentre, global (US and Europe), controlled clinical trial demonstrated the impact of (123I)ioflupane on clinical management, diagnosis and confidence of diagnosis during a 1-year follow-up in 273 patients with clinically uncertain PS of whom 138 were randomised in (123I)ioflupane and 135 randomised to no imaging.40 Significantly more patients in the (123I)ioflupane imaging group had at least one change in their actual clinical management after 12 weeks (p=0.002) and after 1 year (p<0.001) compared with patients in the control group. In addition, significantly more (123I)ioflupane patients had changes in diagnosis and an increased confidence of diagnosis at 4 weeks, 12 weeks and 1 year (all p<0.001) compared with control patients. This recent study, together with a previously published retrospective study,41 confirmed the clinical utility of (123I)ioflupane for neurological practice. In the earlier study of patients with clinically uncertain PS, results of (123I)ioflupane SPECT imaging of 36% of subjects with presynaptic PS and 54% with non-presynaptic PS were inconsistent with the initial diagnosis.42 After imaging, the clinical diagnosis was changed in 52% of patients. All patients with a final diagnosis of presynaptic PS had an abnormal image, whereas 94% of patients with non-presynaptic PS had a normal scan. Imaging increased confidence in diagnosis, leading to changes in clinical management in 72% of patients.

In practice, clinical diagnosis is sufficient and accurate for many patients with advanced and typical manifestations of PD. However, there is a subset of patients with suspected PS, particularly those with early-stage disease or atypical signs and symptoms, who can benefit from further diagnostic evaluation.

While we agree that further neuropathological correlation studies to evaluate the accuracy of (123I)ioflupane would be useful and feasible in advanced/late stages of the disease, traditional pathological correlation is not feasible for patients with early PD—the stage with the highest prevalence of clinical uncertainty and the time during which the majority of (123I)ioflupane evaluations will be prescribed. Accordingly, we support the use of random audits of (123I)ioflupane interpretation, as recently championed by the UK Royal College of Nuclear Medicine.42

### Table 1 Positive and negative per cent agreement rates in two studies with (123I)ioflupane scans12

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<th>Positive per cent agreement (95% CI) among subjects with PS; N=71 (% subjects with abnormal (123I)ioflupane images)</th>
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<th>Negative per cent agreement (95% CI) among subjects with non-PS; N=28 (% subjects with normal (123I)ioflupane images)</th>
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ET, Essential tremor; PS, Parkinsonian syndrome.

**Economic considerations of (123I)ioflupane**

The ability of (123I)ioflupane SPECT imaging to help differentiate ET from tremor due to PS may translate into economic advantages by avoiding the medical resource use and costs associated with misdiagnosis and inappropriate treatment of patients with PS.

The initial cost of (123I)ioflupane may be offset by patients’ receiving appropriate therapy and avoiding the costs of inadequate management. Compared with current diagnostic strategies, use of (123I)ioflupane may help lower total cumulative costs of care.43–46

Economic analyses in several European countries have demonstrated the economic advantages of using (123I)ioflupane SPECT imaging. A study evaluating the cost-effectiveness of SPECT imaging using (123I)ioflupane in patients with an uncertain clinical diagnosis of Parkinsonism from the perspective of the Belgian healthcare system estimated that, with the use of (123I)ioflupane, clinical management would change in 48.5% of patients and that, over a 5-year period, 1.2 adequately treated years would be gained at a yearly additional cost of €72.47 The authors concluded that the treatment of patients with clinically uncertain PS based on using (123I)ioflupane as a diagnostic adjunct is an economically favourable strategy due to the increase in time on appropriate therapy achieved at modest extra cost to the healthcare system.

A similar cost-effectiveness model for the German healthcare system demonstrated cost savings due to improved medical services to patients with uncertain PS.48 The model demonstrated that (123I)ioflupane patients gained 1.40 potentially beneficial
years of adequate treatment and that 5-year costs were £795 lower for those using (123)Iioflupane.

A cost-effectiveness analysis from the perspective of the Italian healthcare system by Busca et al also demonstrated that (123)Iioflupane versus current diagnostic practice results in an additional 1.8 adequately treated years at a cost saving of £482 per patient over a 5-year period.44

An economic evaluation from the UK perspective found (123)Iioflupane to be economically advantageous, with the overall financial impact estimated to be £16 859, which equates to £56 per patient per year.49 Cost savings were attributable to fewer hospital outpatient visits, fewer community nurse visits, fewer general practitioner visits, earlier appropriate management of patients, and the avoidance of unnecessary antiparkinsonian therapy and its attendant morbidity.45 49

A retrospective database study by Hesse et al evaluated the possible impact of (123)Iioflupane on decision making for drug treatment in PS at a hospital in Germany.46 The authors found that almost 25% of patients treated with antiparkinsonian medication prior to (123)Iioflupane did not show evidence of a presynaptic dopaminergic deficit, whereas 37% of untreated patients were diagnosed as having PD.46 The authors concluded that use of (123)Iioflupane may support establishing or refuting the clinical diagnosis and, therefore, help make the decision for or against dopaminergic treatment in patients with PS.46

Based on the results of these studies, (123)Iioflupane may be an economically advantageous diagnostic tool.

**Humanistic considerations in (123)Iioflupane imaging**

SPECT imaging with (123)Iioflupane may have an impact on patient-reported quality of life through enabling timely diagnosis that can lead to prompt and appropriate treatment. Patients who remained untreated after a PD diagnosis experienced deteriorations in mobility, activities of daily living, emotional well-being, social support and bodily discomfort.50 51

**Limitations and pitfalls of (123)Iioflupane**

In most cases the visual interpretation of (123)Iioflupane SPECT is simple and straightforward. However, the ease of visual interpretation may be challenged by patient positioning, motion, use of different colour scales and the lack of experience of some readers with subtle anatomical asymmetry as pathological uptake. Mild anatomical asymmetry of the striata may result in subtle asymmetric appearance on (123)Iioflupane scans and can be observed in normal healthy controls. In some cases this can mimic the diagnostic asymmetry due to neurodegenerative process in PD.52

In such challenging cases, quantitative assessment could be used as a diagnostic adjunct to improve the diagnostic confidence in addition to the visual read. There are several commercial software packages—some under development for full FDA 510 (k) submission—that will analyse (123)Iioflupane scans and from which striatal binding ratios may be compared against a standard age-matched and gender-matched database of healthy controls. Efforts in this direction will be extremely important, given that there is normal loss of DA receptor density with aging.53 However, without a formal validation of software in clinical trials and regulatory approval, the routine clinical use of quantification as a stand-alone approach remains challenging and cannot be recommended for current clinical practice without a visual read.

**CONCLUSION**

(123)Iioflupane should be used selectively for patients whose diagnosis is uncertain and for whom the result of a (123)Iioflupane image would make a difference. In cases of uncertain PS, a (123)Iioflupane image can help clinicians choose among medications that are most likely to provide benefit and avoid those that will not. (123)Iioflupane may be an economically advantageous diagnostic tool, avoiding costs related to inappropriate treatment of non-PD cases with expensive and unnecessary visits by medical personnel, and conversely avoiding the costs of cumulative disability related to a missed diagnosis of PD, thereby lowering the total cost of care of these patients to health economies.

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**Competing interests**

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