REVIEW

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

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Received 26 October 2012
Revised 11 February 2013
Accepted 18 February 2013
Published Online First
13 March 2013

To cite: Bajaj N, Hauser RA, Grachev ID. *J Neurol Neurosurg Psychiatry* 2013;**84**:1288–1295.

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}I)ioflupane (DaTSCAN or DaTscan or (^{123}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}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}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}I)Ioflupane (Iodine-123-fluoropropyl (FP)-carbomethoxy-3 β-(4-iodophenyltropane) (CIT) (^{123}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}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}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 visualization 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

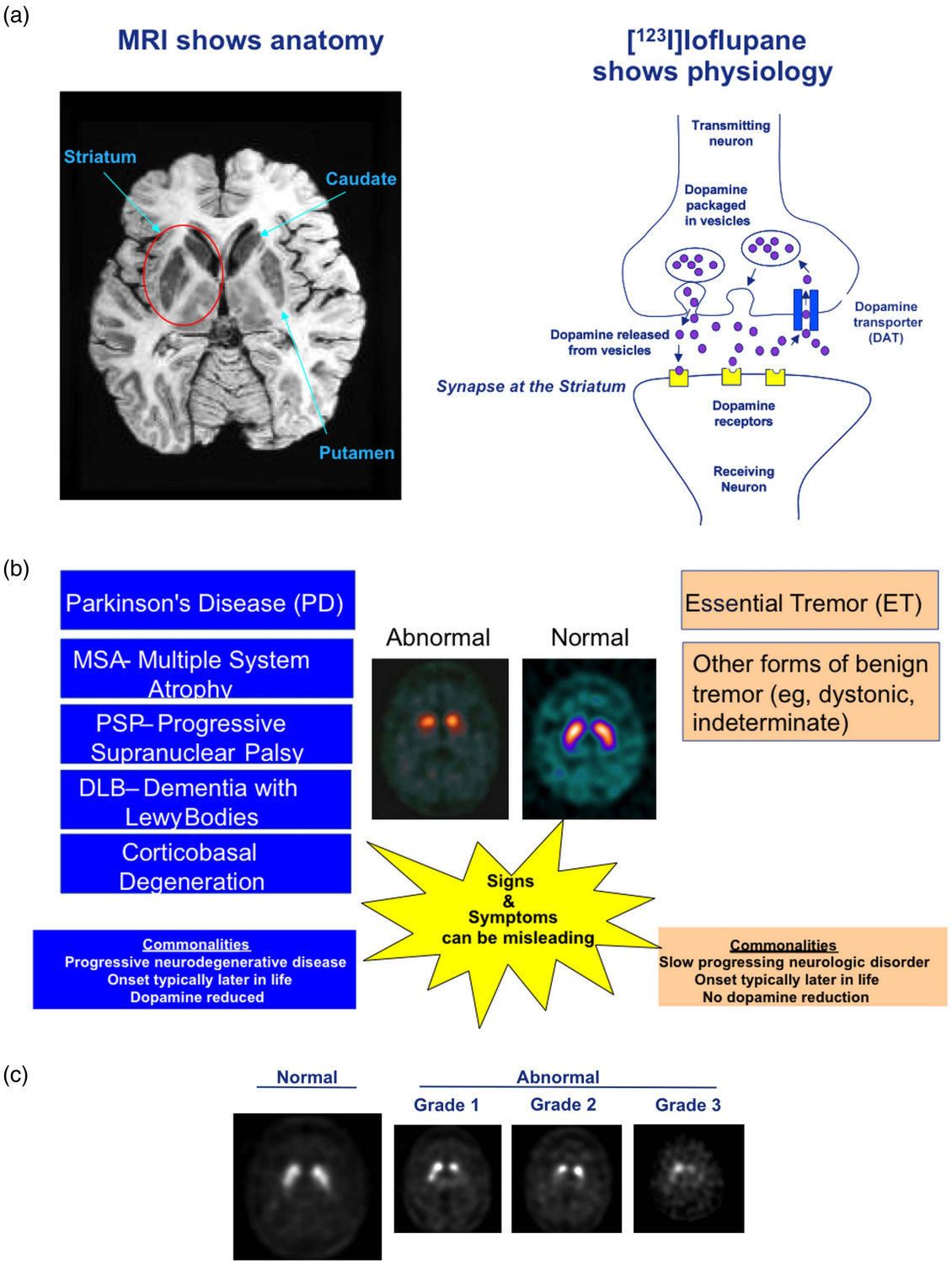

Figure 1 (A) (^{123}I)Ioflupane selectively binds presynaptically to the DaT receptors within the striatum of the brain. Loss of DaT receptors is indicative of PS. (B): (^{123}I)Ioflupane is used in the clinical differentiation of PS from ET—where signs and symptoms can overlap in early onset of disease. (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.

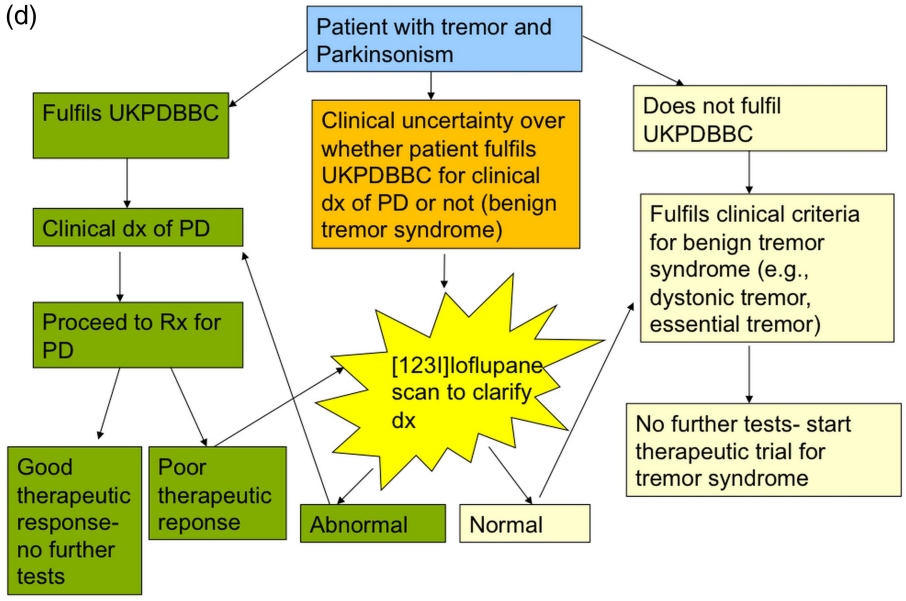

Figure 1 Continued.

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*[5] 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,[5] 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 clinical diagnosis alone, the specificity would not have looked as convincing. Fifty-four per cent of these cases were seen in the last year of life, again allowing plenty of time for clinical diagnostics to have been revised and refined. Despite this long time course for clinical decision making and an impressive positive predictive value for the diagnosis of idiopathic Parkinson's disease (IPD) of 98.6%, the negative predictive value of 90% meant a large number of cases of IPD were unrecognised in life. The authors extrapolated their findings to what might be expected in the community in a form of scenario modelling.[5] This was required, as only 51% of the 143 brains examined had IPD, with a significant over-representation of rarer conditions consistent with 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,[7–9] 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, ^{18}F–dopa in REAL-PET), after the clinical diagnosis was made and after subjects had been enrolled in the trials.[7–9] 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).[9] Marek *et al* followed some of these SWEDD patients and reported no deterioration in neurological features over time.[10] 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).[10] Consensus discussion regarding these cases suggested that the original clinical diagnosis of PD was wrong.[11]

Across these therapeutics trials enrolling subjects with PD, the percentage of enrollees with normal scans decreased as duration of time following initial diagnosis increased.[12] 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

diagnosis changes over time to come into agreement with the imaging results, rather than vice versa.[12]

Clinical studies also suggest a substantial PD diagnostic error rate later in the disease. In a population-based study of patients with a diagnosis of parkinsonism, tremor with onset over age 50 years, or who had ever received antiparkinsonian medication, the diagnosis of PD was rejected in 15% after diagnosis according to standardised clinical criteria coupled with follow-up over at least 1 year.[13] Conversely, approximately 20% of patients with PD who had already come to medical attention had not been diagnosed as such.[13] Similarly, in a community-based sample of subjects on antiparkinsonian medication, evaluation based on standardised clinical diagnostic criteria indicated that at least a quarter of these individuals would not have derived any benefit from these medications.[6] Finally, a recent community-based survey of 610 patients across 92 Scottish general practices found that 1 in 20 patients taking PD medication did not have that diagnosis, with the revised diagnosis being ET or vascular parkinsonism (VP) in the majority.[14]

Diagnostic difficulties in making a PD diagnosis

A recent study from Bajaj *et al*[15] explored sources of diagnostic difficulty among experts. In that study, two blinded movement disorder experts were shown videos of a selection of patients with tremor. All patients were known to one of the authors and had had (^{123}I)ioflupane imaging and long-term subsequent clinical follow-up, including (for many) exposure to dopaminergic drugs, that allowed a reference clinical diagnosis to be generated. The two blinded experts were asked to make a diagnosis of PD or non-PD using UKPDBBC to assess the videos.[15] Their diagnostic error rates were high (false-positive results, 17.4% to 26.1%; false-negative results, 6.7% to 20%); furthermore, the concordance on final diagnosis between reviewers was poor (κ=0.24), highlighting the subjective nature of clinical opinion alone. Interestingly, the concordance of two blinded nuclear medicine physicians on abnormal versus normal scans in this study was 100%, although there was some variance on agreement on degree of abnormality (Grades 1–3) (figure 1C).

Assessment of fatigable bradykinesia, the *sine qua non* of the UKPDBBC, was particularly difficult in these patients with tremor. It is also clear that many parkinsonian features can be seen in cases of benign tremor. Reduced arm swing is a reported feature in cervical dystonia.[16 17] A further study from Marshall *et al* showed an initial tendency to overdiagnose PD in uncertain parkinsonian cases at baseline: again, this was likely due to the considerable overlap in clinical features between some benign tremor cases and cases with tremulous PD.[18] These studies indicate that even the most rigorous application of the UKPDBBC is subject to interpretation and can lead to diagnostic errors.

Diagnosis and medication response

The widely held clinical view is that if a patient responds adequately to a treatment trial of a drug for a hypothesised condition, the patient drug response is confirmatory of the proposed diagnosis. Although there is ample common sense inherent in this view, medication challenges have their own complications and are not necessarily straightforward. For instance, there has been little work on defining the magnitude of a significant clinical response. Alternatively, if a patient shows little clinical response to a drug, does it mean he does not have that condition or is simply unresponsive to that particular drug? The 'placebo' response is particularly problematic when dealing with dopaminergic therapies, given that dopamine forms part of the reward mechanism of the brain.[19]

Because patients with early PD may exhibit minimal signs, response to L-dopa or other dopaminergic medications may be difficult to assess and no benefit may be evident, especially if the most prominent feature is tremor, as tremor is highly variable in its response to medictions.[20] In the ELLDOPA study, in the group of subjects with dopaminergic deficits on SPECT scan and a clinical diagnosis of PD at the end of the study, at 24 weeks 16% of L-dopa-treated subjects were worse than at baseline and 27% had experienced 10% or less improvement.[21] Conversely, in two clinical trials of early PD subjects, 30% (DATATOP) and 64% (ELLDOPA) of subjects administered placebo experienced ≥50% improvement in motor Unified Parkinson's disease Rating scale score.[22]

Similarly, in ET, appropriate medications commonly have no appreciable effect. In one study, propranolol was found to be of no benefit in 30% of patients with ET while primidone was of no benefit in 32%.[23] To make matters even more confusing, PD tremor may improve with propranolol.[24]

In some cases, it is when the response to medication is less than expected that diagnostic uncertainty emerges. In these cases, it may not be clear whether the diagnosis is wrong or the patient is simply one of those who does not respond as well as expected to the chosen medication. In some of these patients, functional dopaminergic radioimaging may be useful to help guide further treatment decisions.

Although several investigators have evaluated acute medication challenges as aids to clinical diagnosis, such challenges have not become widely accepted.[25–27] Indeed, the most recent UK National Institute of Clinical Excellence (NICE) guidance (2006) did not recommend the use of acute dopaminergic challenge in informing the clinical diagnosis in suspected parkinsonian conditions but supported the use of (^{123}I)ioflupane for differentiating ET from PD.[28]

Accuracy of a clinical diagnosis of ET

In the general population, ~40% of cases of ET are misdiagnosed and up to 50% of patients diagnosed with ET do not have it.[29] Jain *et al* applied Movement Disorder Society Consensus Statement Criteria to 71 consecutive patients at the Neurological Institute of New York with a pre-evaluation diagnosis of ET.[30 31] Sixty-three per cent (45/71) were found to have 'true' ET and 37% (26/71) were found to have 'false' ET. Eighty-eight per cent (23/26) of the patients with 'false' ET had been evaluated by a neurologist. Of the 26 patients found to have 'false' ET, 11 (42%) met clinical criteria for PD. An area of controversy attracting much recent discussion is the breadth of the definition of ET, and whether or not it should include asymmetrical tremor, parkinsonism or dystonia.[32] Clearly, extending the clinical definition too widely is bound to reduce diagnostic specificity while increasing sensitivity of detection. Appropriate use of (^{123}I)ioflupane scan in cases of possible ET with marked asymmetry or other parkinsonian features is recommended and would help in detection of tremulous PD cases or cases of PD with additional ET.

CLINICAL UTILITY OF (^{123}I)IOFLUPANE IN DIFFERENTIATING PS

Although (^{123}I)ioflupane is not licensed for the differentiation of other PS from PD, there has been much recent discussion on whether detailed/quantitative (^{123}I)ioflupane analysis might allow some indication of whether subjects had progressive supranuclear gaze palsy (PSP), MSA or VP rather than PD.[33–35]

Kalra *et al* systematically reviewed 25 studies comparing clinical and neuroimaging features that might distinguish VP from PD.[33] 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)ioflupane): two of these studies found significant differences in asymmetry of striatal hypoperfusion in PD versus VP cases. This would be in accord with the clinical hypothesis that PD is an asymmetrical clinical presentation with striatal hypoperfusion 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.[33]

Subregional patterns of preferential striatal dopaminergic transporter loss have also been examined in PSP and MSA versus PD.[34] A study using (^{123}I)ioflupane SPECT compared 70 patients with PD with 10 MSA, 10 PSP and 12 age-matched controls.[34] Although striatal hypoperfusion was a feature of all three PS, striatal decrement in binding was more significant in PSP with no statistical difference between binding in MSA versus PD cases. A more recent (^{123}I)ioflupane PET study has allowed greater resolution than SPECT, permitting quantitative analysis of ligand binding in anterior caudate and ventral putaminal areas.[35] 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)ioflupane 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[36] from scanning is not to be trivialised, this has to be weighed against the usefulness of (^{123}I)ioflupane 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) ioflupane in PD

Perlmutter 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.[37] The published 95% sensitivity/specificity of (^{123}I)ioflupane suggests that (^{123}I)ioflupane 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.[12] This is important to keep in mind when reviewing (^{123}I)ioflupane 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)ioflupane 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)ioflupane result versus final clinical diagnosis.[38]

Appropriate diagnostic setting

Only a clinician can make a diagnosis. (^{123}I)ioflupane 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)ioflupane imaging must understand the information that it provides and its limitations. (^{123}I)ioflupane 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)ioflupane in patients with tremor and parkinsonism is shown to illustrate this point in figure 1D.

REFINING THE UTILITY OF (^{123}I)IOFLUPANE

Two phase 3 studies[18 39] were reviewed by Hauser and Grosset,[12] one of which compared baseline (^{123}I)ioflupane 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) ioflupane 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)ioflupane 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)ioflupane.[18]

The second phase 3 trial included subjects 40–80 years old with an established diagnosis of PS (n=158) or ET (n=27).[39] PPA (abnormal (^{123}I)ioflupane images among subjects with a clinical diagnosis of PS) was 92–97% from five blinded readers. NPA (normal (^{123}I)ioflupane 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)ioflupane is unknown. In these pivotal studies, (^{123}I)ioflupane was compared with clinical diagnoses, and it is not known how often the clinical diagnosis was wrong (especially when the (^{123}I)ioflupane and the clinical diagnosis were not in agreement). However, it is clear that there was generally good agreement between the (^{123}I)ioflupane result and the clinical diagnosis. Importantly, in early suspected PS, the initial clinical diagnosis was relatively inaccurate with a tendency to overdiagnose[18] 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*[18] as compared with the Benamer *et al*[39] study in diagnostically certain advanced patients. Whether the rate of agreement would continue to increase with further clinical

Table 1 Positive and negative per cent agreement rates in two studies with (^{123}I)ioflupane scans[12]

3-year European multicentre study with repeat (^{123}I)ioflupane study in subjects with PS[18] (Patients with early signs and/or symptoms and diagnostically uncertain PS)		Multicentre study in subjects with established diagnosis of PS or ET[39] (Patients with established diagnoses of PS or ET)	
Positive per cent agreement (95% CI) among subjects with PS; N=71 (% subjects with abnormal (^{123}I)ioflupane images)		**Positive per cent agreement (95% CI) among subjects with PS; N=158 (% subjects with abnormal (^{123}I)ioflupane images)**	
Reader A (n=99)	78 (66 to 87)	Reader A (n=185)	93 (88 to 97)
Reader B (n=99)	78 (66 to 87)	Reader B (n=185)	97 (93 to 99)
Reader C (n=99)	79 (67 to 88)	Reader C (n=185)	96 (92 to 99)
		Reader D (n=185)	92 (87 to 96)
		Reader E (n=185)	94 (90 to 97)
Negative per cent agreement (95% CI) among subjects with non-PS; N=28 (% subjects with normal (^{123}I)ioflupane images)		**Negative per cent agreement (95% CI) among subjects with non-PS; N=27 (% subjects with normal (^{123}I)ioflupane images)**	
Reader A (n=99)	97 (83 to 100)	Reader A (n=185)	96 (81 to 100)
Reader B (n=99)	97 (83 to 100)	Reader B (n=185)	74 (54 to 89)
Reader C (n=99)	97 (83 to 100)	Reader C (n=185)	85 (66 to 96)
		Reader D (n=185)	93 (76 to 99)
		Reader E (n=185)	93 (76 to 99)

ET, Essential tremor; PS, Parkinsonian syndrome.

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 (^{123}I)ioflupane in clinical decision-making. The most recent randomised, prospective, multicentre, global (US and Europe), controlled clinical trial demonstrated the impact of (^{123}I)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 to (^{123}I)ioflupane and 135 randomised to no imaging.[40] Significantly more patients in the (^{123}I)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 (^{123}I)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 (^{123}I)ioflupane for neurological practice. In the earlier study of patients with clinically uncertain PS, results of (^{123}I)ioflupane SPECT imaging of 36% of subjects with presynaptic PS and 54% with non-presynaptic PS were inconsistent with the initial diagnosis.[41] 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 (^{123}I)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 (^{123}I)ioflupane evaluations will be prescribed. Accordingly, we support the use of random audits of (^{123}I)ioflupane interpretation, as recently championed by the UK Royal College of Nuclear Medicine.[42]

Economic considerations of (^{123}I)ioflupane

The ability of (^{123}I)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 (^{123}I)ioflupane may be offset by patients' receiving appropriate therapy and avoiding the costs of inadequate management. Compared with current diagnostic strategies, use of (^{123}I)ioflupane may help lower total cumulative costs of care.[43–46]

Economic analyses in several European countries have demonstrated the economic advantages of using (^{123}I)ioflupane SPECT imaging. A study evaluating the cost-effectiveness of SPECT imaging using (^{123}I)ioflupane in patients with an uncertain clinical diagnosis of parkinsonism from the perspective of the Belgian healthcare system estimated that, with the use of (^{123}I)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 (^{123}I)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 (^{123}I)ioflupane patients gained 1.40 potentially beneficial

years of adequate treatment and that 5-year costs were €795 lower for those using (^{123}I)ioflupane.

A cost-effectiveness analysis from the perspective of the Italian healthcare system by Busca *et al* also demonstrated that (^{123}I)ioflupane 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}I) ioflupane 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}I)ioflupane 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}I)ioflupane 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}I)ioflupane 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}I)ioflupane may be an economically advantageous diagnostic tool.

Humanistic considerations in (^{123}I)ioflupane imaging

SPECT imaging with (^{123}I)ioflupane 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}I)ioflupane

In most cases the visual interpretation of (^{123}I)ioflupane 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 results in subtle asymmetric appearance on (^{123}I)ioflupane scans and can be observed in normal healthy controls. In some cases this can mimic the diagnostic asymmetry due to neurodegenerative process in PS.[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}I)ioflupane 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 DaT 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}I)Ioflupane should be used selectively for patients whose diagnosis is uncertain and for whom the result of a (^{123}I) ioflupane image would make a difference. In cases of uncertain PS, a (^{123}I)ioflupane image can help clinicians choose among medications that are most likely to provide benefit and avoid those that will not. (^{123}I)Ioflupane 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.

Acknowledgements The authors wish to thank Marjorie Winters, medical writing contractor, for her help in editing draft contents. Financial disclosure: N Bajaj: Honoraria: UCB, Teva, Genus, GE Healthcare; Grants: MRC, Parkinson's UK; Shares: none; RA Hauser: Allergan, Angiochem, Adamas Pharmaceuticals, AstraZeneca, Boehringer Ingelheim Pharm, Chelsea Therapeutics, Civitas Therapeutics, Clarion Healthcare, EMD Serono, GE Healthcare, Genzyme, GlaxoSmithKline, GSK, IMPAX, Ipsen, Lundbeck, Merck Serono, Merck Sharp & Dohme, Novartis, Novartis/Orion Pharmaceuticals, Novan Pharmaceuticals, Santhera Pharmaceuticals, Schering-Plough, Straken Pharmaceuticals, Synosia, Solvay, TEVA Neuroscience, TEVA Pharmaceuticals, UCB, Xenoport; ID Grachev, employee of GE Healthcare, Princeton, NJ, USA.

Contributors NB: contributed content, reviewed and added content to drafts; RAH: contributed content, revised drafts and added content to drafts; IDG: contributed content to drafts, reviewed and added content to drafts.

Competing interests NB: Since 2002, has received grants from GE Healthcare (2005), Parkinson's UK (2011, 2012), MRC (2011) and the Sarah Matheson Trust (2004); has received honoraria for lecture fees from GE Healthcare, UCB Pharma, Teva Lundbeck, GSK, Genus Pharma; has received honoraria for advisory boards for UCB, GSK, GE Healthcare. IDG is an employee of GE Healthcare. RAH has received honoraria or payments for consulting, advisory services, speaking services over the past 12 months as listed below: Abbott Laboratories, Allergan, Inc., AstraZeneca, Biotie Therapies Corporation, Ceregene, Chelsea Therapeutics, GE Healthcare, Impax Laboratories, Ipsen Biopharmaceuticals, Lundbeck, Med-IQ, Merck/MSD, Noven Pharmaceuticals, Straken Pharmaceuticals, Targacept, Teva Pharmaceuticals Industries, Teva Neuroscience, Upsher-Smith Laboratories, UCB, UCB Pharma SA, Xenoport, RAH's institution has received research support over the past 12 months as listed below: Abbot Laboratories, Addex Therapeutics, Allergan, AstraZeneca, Chelsea Therapeutics, GE Healthcare, Impax Laboratories, Ipsen Biopharmaceuticals, Merck/MSD, Merz, Michael J Fox Foundation for Parkinson's Research, Schering-Plough, Teva Neuroscience, UCB, Vita-Pharm. RAH has received royalties in the last 12 months: University of South Florida. In addition, RAH has consulted in litigation with lawyers representing various current and former manufacturers of welding consumables.

Provenance and peer review Not commissioned; externally peer reviewed.

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