Age, Gender, and Diagnostic Performance of Ioflupane I123 Injection (DaTscan™) Brain Imaging in Patients with Movement Disorders and/or Dementia

Abstract

Background: Although numerous studies have established the sensitivity and specificity of Ioflupane I123 Injection (ioflupane (I123)), (I23)FP-CIT, DaTscan™, or DaTSCAN™ imaging in patients with movement disorders or dementia, no studies have examined the effects of gender and age on diagnostic performance.

Methods: We pooled data from four clinical trials in which patients with a movement disorder or dementia and healthy volunteers were administered ioflupane (I123). Panels of 3-5 blinded experts and/or on-site nuclear medicine physicians rated the images as normal or abnormal. Results were compared with expert clinical diagnosis (reference standard) to determine sensitivity and specificity. Subgroup and multiple logistic regression model (MLRM) analyses were performed to evaluate the effect of gender and age (two groups: <65 yrs and ≥75 yrs) on sensitivity and specificity.

Results: There were 421 males and 305 females in the intent-to-diagnose population. Sensitivity was higher for males with parkinsonian syndrome (PS) (93.3% vs. 87.6%; P=0.0029), whereas specificity was higher for females (96.4% vs. 89.5%; P=0.0126). Sensitivity was higher in the younger age groups (<65 yrs, 91.0% vs. ≥65 yrs, 86.8%; P=0.0240 and <75 yrs, 90.7% vs. ≥75 yrs, 78.4%; P < 0.0001). Specificity was higher in subjects <65 yrs (94.0% vs. 89.7% for ≥65 yrs, P=0.0384). Analysis using the 75 yrs cutoff showed no differences. When MLRM was used, all covariates (disease state, age, gender, reader type, and follow-up duration) were significant predictors of the model effect on sensitivity. For specificity, only disease state and reader type were significant predictors.

Conclusions: Sensitivity and specificity of ioflupane (I123) imaging was high in all age and gender subgroups, though statistically significant differences were observed with a slightly reduced, though still diagnostically useful, sensitivity above 75 yrs. This reduced sensitivity may be due to increased frequency of mixed pathologies in older people, which makes the clinical diagnosis (reference standard) less optimal. In PS, sensitivity was higher in males, whereas specificity was higher in females. MLRM analysis demonstrated that all tested covariates (including gender and age) were significant predictors for sensitivity, but not for specificity.

Keywords
Diagnostic accuracy; Sensitivity; Specificity; SPECT, Ioflupane I123 injection; Ioflupane (I123); (I23) FP-CIT; DaTscan™; DaTSCAN™; Gender; Age; Parkinsonian syndrome; Dementia; Lewy bodies

Introduction

The use of radiopharmaceuticals to augment clinical diagnosis of neurological diseases has facilitated greater accuracy and confidence in medical decision-making. Improved accuracy, particularly in the early stages of disease, allows for more suitable treatment selection and avoids unnecessary and potentially harmful exposure to inappropriate medications. Interpretation of the images requires expert understanding and ability to discriminate normal images from abnormal images. This expertise further relies upon the ability to understand and recognize the differences that exist and changes that occur based
on gender and the normal aging process, respectively. Early studies established that changes occur normally in the brain with aging [1,2]. Dopamine transporter (DaT) imaging studies performed in healthy volunteers have shown that DaT uptake decreases with age in a linear manner, declining 4.1-7.5% per decade, depending upon the region of the brain examined [3-6]. Likewise, specific-to-non-specific DaT binding ratios appear to be higher in healthy females than males [4-6] and this difference is not age-related [5]. In the PRamipexole On Underlying Disease (PROUD) study, a decline of 14.2%-15.5% was seen in early Parkinson's disease over 15 months, but effects of age and gender were not analyzed [7,8].

While some knowledge exists addressing the effects of gender and age on DaT uptake in healthy volunteers, no analyses have been performed to show the effects of gender and age on diagnostic performance in patients with movement disorders or dementia. Several clinical trials have evaluated the sensitivity (equivalent to positive percent agreement (PPA)) and specificity (equivalent to negative percent agreement (NPA)) of using ioflupane (123I) imaging to detect the presence or absence of a striatal dopaminergic deficit (SDD) in subjects with a movement disorder (PS, PD, PSP, MSA, or DLB) [9-15]. PS and DLB may have interrelated symptoms; cognitive impairment may be present in PS and motor symptoms may manifest in subjects with DLB. Hence, evaluating the disease states individually, as well as combined, may be informative. To perform such analyses, large datasets are needed. We pooled four clinical trials presented for the US new drug application of ioflupane (123I) to examine the effects of gender and age on the diagnostic performance of ioflupane (123I) imaging.

Materials and Methods

Four clinical trials [9-12,14,15] were used for this subgroup analysis. These clinical trials had been used to support the ioflupane (123I) US new drug application. Each study had evaluated the sensitivity (PPA) and specificity (NPA) of ioflupane (123I) (ioflupane I123 Injection or DaTscan™ or DaTSCAN™, GE Healthcare, Amersham, UK) imaging to detect the loss of dopaminergic nigrostriatal neurons in subjects thought to have a suspected movement disorder and/or dementia. The reference standard used in each of these trials was expert clinical diagnosis, made at baseline and 1-3 years post-scan, and classified as normal (SDD absent) or abnormal (SDD present). Expert clinical diagnosis made by neurologists or dementia specialists blinded to imaging results established whether the subject had an SDD (PD, PS, PSP, MSA, or DLB) or did not have an SDDD (ET, AD or VaD and a healthy volunteer). Ioflupane (123I) image results were compared with the corresponding subject's reference clinical diagnosis, made at baseline and 1-3 years post-scan, and classified as True Positive (TP), True Negative (TN), False Positive (FP) or False Negative (FN).

Statistical analysis

All statistical analyses were performed using Statistical Analysis Software (SAS Institute Inc., Cary, NC, USA). Demographic data are presented using descriptive statistics. Populations evaluated in this subgroup analysis were the Intent to diagnose (ITD; all subjects who underwent SPECT imaging and underwent the reference clinical diagnosis assessment for the relevant analysis) and Per protocol (PP; all subjects in the ITD population with no major protocol violations). Sensitivity was calculated as nTP / (nTP+nFN), (n = number of subjects). Specificity was calculated as nTN / (nTN+nFP). Sensitivity (PPA) and specificity (NPA) were calculated for the ITD and PP populations, and are reported with 95% confidence intervals (CI). Subgroup analyses were performed based on gender (male/female) and age, using 2 arbitrarily set thresholds, ≤ 65 yrs and ≥ 75 yrs. Fisher’s exact test was used to identify significant differences between subgroups. Due to the exploratory nature of this analysis, unadjusted P values were calculated. Single and multiple logistic regression analyses were performed on additional covariates; P values, odds ratios and 95% CI were calculated to identify statistically significant predictors.

Results

Study participants

The ITD population comprised 726 subjects and the PP population, 622. Subject baseline demographic characteristics and reference clinical diagnosis are shown by study and for the total ITD population in Table 3 and PP population in Table 4. There were no meaningful differences in baseline characteristics between the ITD and PP populations.
Table 1: Key characteristics of four clinical studies included in age and gender reported analysis.

| Study | Key Characteristics (Phase, Design) | Reference Standard | Subjects | Objectives | Investigational product dose information | No. of study sites | No. of subjects entered in the study/completed efficacy evaluations | Age of ITD population, range (mean) | Gender | Blinded image evaluations performed | Notes |
|-------|-----------------------------------|-------------------|----------|------------|----------------------------------------|------------------|-----------------------------|----------------------------------|--------|----------------|--------|
| A     | Phase 3, Multicenter, open-label, non-randomized, Single-dose, No control used | Expert clinical diagnosis at baseline according to published consensus criteria as the RCD | Healthy volunteers | Primary Sensitivity and specificity for detecting or excluding an SDD, Secondary Inter-reader agreement | Ioflupane (123I) 111-185 MBq (3 to 5 mCi) iv, 1 dose | 6 | 250/220 | 40, 80 (62.7) | 62% male, 38% female | Yes (5 central readers) | Primary objective was to assess clinical utility of ioflupane (123I) images, however, images were used for age and gender subgroup analysis. |
| B     | Phase 3, Multicenter, open-label, non-randomized, Single-dose, No control used | Expert clinical diagnosis at 12 months as the RCD | Subjects with dementia (possible DLB or other dementia types AD, VaD) | Primary Sensitivity and specificity for detecting or excluding an SDD, Secondary Inter-reader agreement | Ioflupane (123I) 111-185 MBq (3 to 5 mCi) iv, 1 dose | 40 | 351/288 | 54, 90 (73.9) | 57% male, 43% female | Yes (3 central readers) |
| C     | Phase 3, Multicenter, open-label, non-randomized, Repeat-dose (max. of 3), No control used | Expert clinical diagnosis at 36 months as the RCD | Healthy volunteers | Primary Sensitivity and specificity for detecting or excluding an SDD, Secondary Inter-reader agreement | Ioflupane (123I) 111-185 MBq (3 to 5 mCi) iv, 3 doses 18 months apart | 10 | 202/102 | 33, 79 (60.4) | 56% male, 44% female | Yes (3 central readers) |
| D     | Phase 4, Multicenter, open-label, non-randomized, Single-dose, No control used | Expert clinical diagnosis at 24 months as the RCD | Subjects with movement disorders (an uncertain clinical diagnosis of PS) | Primary Sensitivity and specificity for detecting or excluding an SDD, Secondary Sensitivity and specificity for detecting or excluding an SDD | Ioflupane (123I) 111-185 MBq (3 to 5 mCi) iv, 1 dose (73 subjects) or 2 doses 24 months apart (14 subjects) | 15 | 125/118 | 25, 84 (64.2) | 53% male, 47% female | No (on-site readers only) |

AD: Alzheimer’s disease; DLB: Dementia with Lewy Bodies; ITD: Intent to Diagnose; MBq: Megabecquerel; PS: Parkinsonian Syndrome; RCD: Reference Clinical Diagnosis; SDD: Striatal Dominergic Deficit; VaD: Vascular Dementia.

Table 2: Ethics committees for the four studies in the sub group analysis.

| Study A | Committee Name | City | Country | Chairman |
|---------|----------------|------|---------|----------|
| A       | Medical Research Ethics Committee, The Phillips University Clinic | Marburg | Germany | Dr. P Heubel |
|         | The Faculty of Medicine Ethics Committee, Ludwig Maximilian University of Munich | Munich | Germany | Prof. Dr. med. Dent. W Gernet |
|         | Southern General Hospital Medical Ethics Committee | Glasgow | UK | Rev. D Keddie |
|         | Medical Ethics Committee, Academic Medical Center, Amsterdam University | Amsterdam | The Netherlands | Prof. L Arisz |
|         | Joint UCL/UCLH Committees on the Ethics of Human Research | London | UK | Prof. A McLean |
|         | Ethics Review Committee, University Hospital | Ghent | Belgium | Prof. Dr. M Bogaert |

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### Study B

| Committee Name                                                                 | City                  | Country       | Chairman                          |
|-------------------------------------------------------------------------------|-----------------------|---------------|-----------------------------------|
| Ethikkommission des Landes Oberösterreich                                      | Linz                  | Austria       | Univ. Prof. Prim Dr. Fisher       |
| Ethik-Kommission der Medizinischen Fakultät der Universität Wien und des Allgemeinen Krankenhauses der Stadt Wien AKH | Wien                  | Austria       | Univ. Prof. E. Singer             |
| Comité consultatif pour la protection des personnes dans la recherche biomédicale Bordeaux B | Bordeaux              | France        | Prof. MC Saux                     |
| Ethik-Kommission der Medizinischen Fakultät der Universität Leipzig            | Leipzig               | Germany       | Prof. Dr. med. R Preiß            |
| Ethik-Kommission, Campus Charité Mitte                                        | Berlin                | Germany       | Prof. Dr. med. R Uebelhack        |
| Ethik-Kommission der Ruhr-Universität Bochum, Medizinischen Fakultät           | Bochum                | Germany       | Prof. Dr. Zenz                    |
| Ethik-Kommission der Georg-August-Ruhr-Universität Göttingen                   | Göttingen             | Germany       | Prof. Dr. med. E Rüther           |
| Ethik-Kommission der Ärztekammer Hamburg                                       | Hamburg               | Germany       | Prof. Dr. med. Th. Weber          |
| Medizinischen Hochschule Hannover, Ethikkommission                             | Hannover              | Germany       | Prof. Dr. HD Tröger               |
| Landesärztakammer Rheinland-Pfalz, Ethikkommission                             | Mainz                 | Germany       | Prof. Dr. Rüttner                 |
| Kommission für Ethik in der ärztlichen Forschung, Bereich Humannmedizin, Klinik der Philippus-Universität Marburg | Marburg               | Germany       | Prof. Dr. Med. G Richter          |
| Regione Veneto, Azienda Ospedaliera di Padova, Comitato Etico per la Sperimentazione | Padova                | Italy         | Dr. R. Pegoraro                   |
| Azienda Ospedaliera Pisana, Comitato etico per la studio del farmaco sull’uomo | Pisa                  | Italy         | Prof. R. Barsotti                 |
| Regional komité for medisinsk forskningssetikk, Vest-Norge (REK Vest), Universitetet i Bergen, det medisinske fakultet | Bergen                | Norway        | A. Berstad                       |
| Comité Ético de Investigación Clínica                                          | Porto                 | Portugal      |                                   |
| Karolinska Institutet, Forskningsetikommitté Syd                               | Stockholm             | Sweden        | Prof. H. Glaumann                 |
| Regionala etikprøvningsnämnden i Stockholm                                     | Stockholm             | Sweden        | Prof. LE Rutquist                 |
| Clinic Barcelona, Hospital Universitari, Comité étic investigació clínica     | Barcelona             | Spain         |                                   |
| Comité Ético de Investigación Clínica, Hospital Universitario de Getafe         | Madrid                | Spain         |                                   |
| Comité etico de investigación clínica Hospital "La Fe" Valencia               | Valencia              | Spain         |                                   |
| Northern and Yorkshire Multi-Centre Ethics Committee                           | Durham                | UK            | J Kelly/S Brunton-Shiels          |
| Gateshead Local Research Ethics Committee                                      | Sunderland            | UK            | Dr. D. G. Raw                     |
| Northumberland, Tyne and Wear NHS Strategic Health Authority Local Research Ethics Committees, Newcastle General Hospital | Newcastle upon Tyne  | UK            | Dr. J. Lofthus, PD Carr           |
| Southampton & South West Hampshire Local Research Ethics Committee             | Southampton upon Tyne | UK            | C. Wright                        |
| Ethikkommission der Medizinischen Fakultät der Ludwig-Maximilians-Universität, LMU, Klinikum Großhadern | München               | Germany       | Prof. Dr. G. Paumgartner          |
| Ethikkommission der Fakultät für Medizin der Technischen Universität München   | München               | Germany       | Prof. Dr. A. Schömig              |
| Algemeines öffentliches Krankenhaus der Stadt Linz, Kommission zur Beurteilung klinischer Prüfungen von Arzneimitteln, Ethikkommission | Linz                  | Austria       | Primar Dr. H. Stekel             |
| Ospedali Civilì Brescia, Azienda Ospedaliera, Comitato Etico                   | Brescia               | Italy         | Prof. F. De Ferrari               |
| Facultni nemocnice v Motole, Etickakomise                                      | Prague                | Czech Republic| MUDr. V. Smelhaus                 |
| Brighton and Sussex Local Research Ethics Committee                            | Brighton              | UK            | Dr. P. Seddon                    |
| East Sussex Local Research Ethics Committee                                    | Brighton              | UK            | Dr. J. Rademaker                  |
| South Manchester Local Research Ethics Committee                                | Manchester            | UK            | Dr. W. Pettit                    |
| Central Manchester Research Ethics Committee                                    | Manchester            | UK            | Dr. D. Mandal                     |
| NHS Tayside Board, Tayside Committee on Medical Research Ethics, Ninewells Hospital & Medical School | Dundee              | UK            | NF Brown                         |
| Fazio-Fondazione San Raffaele Del Monte Tabor Milano, Comitato Etico             | Milano                | Italy         | Prof. E. Müller                  |
| dell’Istituto Nazionale Neurologico Basta di Milano                            | Milano                | Italy         | Prof. G. Zoppe                   |
| IRCSS – Fondazione San Raffaele Del Monte Tabor di Milano                        | Milano                | Italy         | Prof. G. Zoppe                   |
| Comité ético de investigación clínica, Servicio Andaluz de Salud, Consejería de Salud, Hospitales Universitarios Virgen de Rocio de Sevilla | Sevilla              | Spain         |                                   |
| Ethikkommission der stadt Wien                                                 | Wien                  | Austria       | Dr. H. Serban                    |
| North Sheffield Local Research Ethics Committee, Northern General Hospital      | Sheffield             | UK            | Dr. G. P. Clark                  |
| Glasgow West Local Research Ethics Committee                                   | Glasgow               | UK            | Dr. J. Hunter                    |
| NHS Greater Glasgow Primary Care Division Local Research Ethics Committee, Garnetval Royal Hospital | Glasgow              | UK            | Dr. P. Fleming                   |
| Frenchay Research Ethics Committee, North Bristol NHS Trust Headquarters        | Bristol               | UK            | Drs. J. Kendall and M. Shere      |
| Ärztekammer Berlin, Ethik-Kommission                                           | Berlin                | Germany       | C. Biondo                        |
| Ethikkommission des Landes Bremen, Institut für Klinische Pharmakologie, Klinikum Bremen-Mitte | Bremen                | Germany       | Dr. K. Boomgaarden-Brandeis      |
| Ethikkommission der Fakultät für Medizin der Technischen Universität München    | München               | Germany       | Prof. Dr. A. Schömig              |
### Study C

| Committee Name | City               | Country     | Chairman            |
|----------------|--------------------|-------------|---------------------|
| Ethics Committee of the Southern General Hospital NHS Trust, Glasgow | Glasgow | UK | Rev. D Keddie |
| Kommission für Eik in der ärztlichen Forschung, Klinikum der Philipps-Universität Marburg | Marburg | Germany | Prof. Dr. med. G Richter |
| New Cross Hospital Local Research Ethics Committee | Wolverhampton | UK | Dr. A Kermode |
| Southampton and South West Hampshire Joint Local | Southampton | UK | Prof. PA Heasman |
| Joint Ethics Committee Newcastle and North Tyneside Health Authority | Newcastle | UK | Prof. Dr. R Oertel |
| Comité Ético de Investigación Clínica Hospital Clinic I Provincial | Barcelona | Spain | Prof. J Rodes |
| Comité Ético de Investigación Clínica del Hospital de la Santa Creu i Sant Pau | Barcelona | Spain | Prof. S Casana |
| Comité d’ éthique hospitalier, Cliniques Universitaires de Mont-Godinne | Yvoir | Belgium | Prof. S Ertz |
| Hospitais da Universidade de Coimbra | Coimbra | Portugal | Prof. Dr. A Kermode |
| Ethikkommission der Medizinischen Fakultät der Universität Innsbruck | Innsbruck | Austria | Univ. Prof. Dr. E Singer |

### Study D

| Committee Name | City               | Country     | Chairman            |
|----------------|--------------------|-------------|---------------------|
| Hospital Ethical Committee, University Hospital UCL Mont-Godinne | London | UK | Prof. E. Singer |
| Commission for Ethics, AZ St.-Jan AV | Brugge | Belgium | Prof. Dr. M. K Held |
| Comité Consultatif de Protection des Personnes Dans La Recherche Biomédicale de Lille, Hôpital Huriez | Lille | France | Prof. PY Hatron |
| Ethik-Kommission der Ärztekammer Hamburg Körperschaft des öffentlichen Rechts | Hamburg | Germany | Prof. Dr. K K Held |
| Ethikkommission des Klinikums der Universität Regensburg | Regensburg | Germany | Prof. Dr. R Andreaesn |
| Vorsitzenden der Ethikkommission Beider der Ärztekammer des Saarlandes | Saarbrücken | Germany | Prof. S Ertz |
| Spett. Le Comitato Etico | Milano | Italy | Prof. A. Randazzo |
| Comitato Etico Per La Sperimentazione Clinica Del Farmaci | Firenze | Italy | Prof. L. Zilletti |
| Ministério Da Saúde Hospitais Da Universidade De Coimbra | Coimbra | Portugal | Prof. Dr. J. Pedroso Lima |
| Comité Ético De Investigación Clínica Hospital Clinic I Provincial | Barcelona | Spain | Prof. MA Azenjo Sebastián |
| Comité Ético De Investigación Clínica Del Hospital De la Santa Creu i Sant Pau | Barcelona | Spain | Prof. S Casana |
| King’s College Hospital | London | UK | Prof. ER Howard |
| Southampton and South West Hampshire Local Research Ethics Committees | Southampton | UK | Prof. Dr. A. Kermode |
| Ethik-Kommission der Medizinischen Fakultät der Universität Wien | Vienna | Austria | Univ. Prof. Dr. E Singer |

### Table 3: Subject baseline demographics and clinical diagnosis (Reference Clinical Diagnosis) by study – ITD population

| Study | Study A (N = 220) | Study B (N = 326) | Study C (N = 102) | Study D (N = 78) | Total (N = 726) |
|-------|------------------|------------------|------------------|------------------|-----------------|
| Age (yr) | Mean (SD) | 62.7 (8.87) | 73.9 (7.17) | 60.4 (10.91) | 64.2 (11.99) | 67.6 (10.60) |
| Gender | Male | 136 (62%) | 187 (57%) | 57 (56%) | 41 (53%) | 42 (54%) |
| | Female | 84 (38%) | 139 (43%) | 45 (44%) | 37 (47%) | 35 (42%) |
| Race | Caucasian | 216 (99%) | 326 (100%) | 102 (100%) | 77 (99%) | 72 (99%) |
| | Black | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| | Asian | 3 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| | Other | 1 (<1%) | 0 (0%) | 0 (0%) | 1 (1%) | 3 (<1%) |
| PS (SDDD) | Possible PS | 158 (72%) | 0 (0%) | 71 (70%) | 48 (62%) | 277 (38%) |
| | Probable PS | 158 (72%) | 0 (0%) | 5 (5%) | 48 (62%) | 211 (29%) |
| DLB (SDDD) | Possible DLB | 0 (0%) | 116 (36%) | 0 (0%) | 0 (0%) | 116 (16%) |
| | Probable DLB | 0 (0%) | 27 (8%) | 0 (0%) | 0 (0%) | 27 (4%) |
| Non-PS/Non-DLB (no SDD) | ET | 62 (28%) | 126 (39%) | 31 (30%) | 30 (38%) | 249 (34%) |
| | AD | 0 (0%) | 125 (38%) | 0 (0%) | 0 (0%) | 125 (17%) |
| | Other | 35 (16%) | 1 (<1%) | 17 (17%) | 7 (9%) | 60 (9%) |
| SDD Present | SDD Absent | 158 (72%) | 116 (36%) | 71 (70%) | 46 (62%) | 393 (54%) |

*Includes Possible and Probable PS and Possible and Probable DLB diagnoses.
*22 subjects had no diagnosis, and 62 subjects were not assessed at 12-month visit.

AD: Alzheimer’s disease; ET: essential tremor; ITD: intent to diagnose; N: number of subjects in the study; PS: Parkinsonian syndrome; SD: standard deviation; SDD: striatal dopaminergic deficit; SDDD: striatal dopaminergic deficit disorder; yr: year.

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Parkinsonian syndrome; SD: standard deviation; SDDD: striatal dopaminergic deficit disorder.

AD: Alzheimer’s Disease; DLB: Dementia with Lewy Bodies; ET: Essential tremor; n = Number of subjects in the study; PP: Per protocol; PS: Parkinsonian Syndrome.

Table 4: Sensitivity (PPA)/specificity (NPA) for parkinsonian syndrome (PS) was calculated based on PS present vs. PS absent; Sensitivity (PPA)/specificity (NPA) for dementia with Lewy bodies (DLB) was calculated based on DLB present vs. DLB absent; Sensitivity (PPA)/specificity (NPA) for whole population was calculated based on SDDD present vs. SDDD absent.

Table 5: Sensitivity (PPA) and specificity (NPA) from blinded image evaluation between male and female subjects.

*Includes Possible and Probable PS and Possible and Probable DLB diagnoses.

AD: Alzheimer’s Disease; DLB: Dementia with Lewy Bodies; ET: Essential tremor; n = Number of subjects in the study; PP: Per protocol; PS: Parkinsonian syndrome; SD: standard deviation; SDDD: striatal dopaminergic deficit disorder.

Table 6: Summary result calculated across all readers for Studies A, B, C at baseline.

Table 7: Summary result calculated across all readers for Study B.

Table 8: Summary result calculated across all readers for Study C.

Sensitivity (PPA)/specificity (NPA) for parkinsonian syndrome (PS) was calculated based on PS present vs. PS absent; Sensitivity (PPA)/specificity (NPA) for dementia with Lewy bodies (DLB) was calculated based on DLB present vs. DLB absent; Sensitivity (PPA)/specificity (NPA) for whole population was calculated based on SDDD present vs. SDDD absent.

CI: Confidence Interval; n: number of subjects included in the analysis; NPA: Negative Percent Agreement; PPA: Positive Percent Agreement; SDDD: Striatal Dopaminergic Deficit Disorder.

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Effect of gender on diagnostic performance

Figure 1 displays sensitivity (PPA) and specificity (NPA) in males vs. females in subjects with PS and DLB (ITD population), measured at baseline and upon follow-up, using BIE results. There were statistically significant differences at baseline in subjects with PS, with sensitivity being lower and specificity higher in females compared with males. This was also true for the whole population (Table 5). At month 18 and month 36, statistically significant differences were not observed. There were no differences between males and females observed in subjects with DLB at any time points. When on-site image reads were used (Table 6), no statistically significant differences were observed. There were differences between males and females in subjects with DLB at any time points. When on-site image reads were used were used (Table 6), no statistically significant differences were observed.

Effect of age on diagnostic performance

Figure 2 displays sensitivity (PPA) and specificity (NPA) in subjects < and ≥ 65 years (yrs) and 75 yrs, broken out by disease state (PS and DLB), in which BIE reads at baseline were used. In subjects with PS, sensitivity and specificity was lower in older subjects than younger subjects, however the difference was only statistically significant for specificity when using 65yrs as the cutoff. In subjects with DLB, sensitivity was higher in older subjects when using 65 yrs as the cutoff, but lower if 75 yrs was used. Sensitivity remained statistically significantly higher in older subjects using the 65-yr cutoff at the Month 12 assessment. Specificity was roughly equivalent, regardless of which age cutoff was used. In the whole population, sensitivity was statistically significantly higher in younger subjects using either cutoff; specificity was only higher in younger subjects when 65 yrs was used as the cutoff (Tables 7 and 8). When the on-site image reads were used, the only statistically significant differences noted were that specificity was higher at baseline in younger subjects using the 65-yr cutoff and the whole population (Tables 9 and 10).

Effect of disease state on diagnostic performance

Figure 3 displays sensitivity (PPA) and specificity (NPA) in subjects with PS vs. DLB, broken out by gender and age using both 65-yr and 75-yr cutoffs, using BIE results at baseline. Overall, sensitivity and specificity were numerically lower (not tested for P-value) in subjects with DLB compared with subjects with PS.

Effects of additional covariates on diagnostic performance

To identify the significant predictors for effects on sensitivity (PPA) and specificity (NPA), a multiple logistic regression model was used. The following covariates were included in the model: disease state (DLB vs. PS), age (as a continuous variable), gender (male vs. female), type of reader (blinded vs. on-site), and duration of follow-up (as a continuous variable). Table 11 summarizes the results for the ITD population. The numbers of observations is the total number of readings from all readers (blinded and on-site) across all time points in all studies (Table 12). For sensitivity, all covariates were significant independent predictors (P<0.05). For specificity, only disease state and type of reader were significant predictors. Results were similar for the PP population and for individual logistical regression for both populations (Tables 12 and 13).

Discussion

This subgroup analysis is the first to evaluate the effects of gender and age on the diagnostic performance of ioflupane ([123I]) imaging to detect the presence or absence of an SDD in subjects with a movement disorder or dementia. Pooling the 4 clinical trials provided a large dataset (ITD N =726) to enable this analysis. Although PS and DLB are different disorders, they share the common underlying pathology of striatal dopaminergic deficit. Additionally, there is some overlap in symptomatology, with cognitive impairment observed in patients with PS and DLB.
patients presenting with motor symptoms. These symptoms accumulate and become more profound with progression of the disease. For this reason, we analyzed the disorders individually as well as the whole population. The BIE image reads which were performed in 3 of the 4 studies, tended to yield more statistically significant differences between subgroups.

Overall, sensitivity and specificity were high in all subgroups analyzed. However, gender had some effect on diagnostic performance in PS and the whole population at baseline when BIE reads were used. Sensitivity was lower and specificity was higher in females compared with males. Studies evaluating gender in PD have shown that differences exist, such as increased prevalence in males (60%), delayed age at onset in females, as well as females more frequently presenting with tremor, for patients presenting with tremor, a slower rate of deterioration was observed [16]. Females also had 16% higher ioflupane (123I) binding than males at both the onset of disease and throughout 10 years of follow-up [16]. Differences in motor phenotypes have been observed, with males exhibiting symmetrical upper-body disease, whereas females exhibited more postural instability [17]. Non-motor phenotypic differences have also been noted, with males having more cognitive impairment, rapid eye movement sleep behavior disorder, orthostatic hypotension, and sexual dysfunction [17]. These findings suggest an overall milder course of disease in females, which might explain some of our observations in terms of potential relationships to accuracy of clinical diagnosis, the reference standard used in this study. Higher ioflupane (123I) binding in females may make it more difficult, or at a minimum, delay image interpretation as being abnormal, reducing the

Figure 2: Sensitivity (PPA) and specificity (NPA) in young vs. old subjects with PS and DLB. Sensitivity (PPA) and specificity (NPA), blinded image evaluation reads at baseline in subjects with PS (parkinsonian syndrome) and DLB (dementia with Lewy bodies). *P < 0.05; **P < 0.01.

Figure 3: Sensitivity (PPA) and specificity (NPA) in subjects with PS vs. DLB. Sensitivity (PPA) and specificity (NPA), read at baseline in subjects with PS (parkinsonian syndrome) and DLB (dementia with Lewy bodies).
Table 6: Sensitivity (PPA) and specificity (NPA) from on-site image reads between male and female subjects Intent to diagnose population.

| Reference Clinical Diagnosis | Parkinsonian Syndrome (PS; SDDD) | Dementia with Lewy Bodies (DLB; SDDD) | Whole Population |
|-----------------------------|----------------------------------|--------------------------------------|------------------|
|                             | Sensitivity % (95% CI)            | Specificity % (95% CI)                |                  |
| Mean Results*               | Male (n=352)                      | Female (n=262)                        |                  |
|                             | 91.3 (86.8, 94.6)                 | 87.6 (82.0, 92.0)                     |                  |
|                             | 0.2583                            | 0.1255                               |                  |
|                             | Sensitivity % (95% CI)            | Specificity % (95% CI)                |                  |
| Month 12b                   | Male (n=118)                      | Female (n=96)                         |                  |
|                             | 90.9 (80.0, 90.0)                 | 88.2 (72.5, 96.7)                     |                  |
|                             | 0.7271                            | 0.7271                               |                  |
|                             | Sensitivity % (95% CI)            | Specificity % (95% CI)                |                  |
| Month 18c                   | Male (n=56)                       | Female (n=45)                         |                  |
|                             | 82.9 (66.4, 93.4)                 | 80.0 (63.1, 91.6)                     |                  |
|                             | 1.0000                            | 0.2569                               |                  |
|                             | Sensitivity % (95% CI)            | Specificity % (95% CI)                |                  |
| Month 36c                   | Male (n=53)                       | Female (n=44)                         |                  |
|                             | 82.4 (65.5, 93.2)                 | 85.3 (68.9, 95.0)                     |                  |
|                             | 1.0000                            | 0.5920                               |                  |

*Summary results calculated across all studies and time points. For Study B, month 12 reference clinical diagnosis was used.

Table 7: Sensitivity (PPA) and specificity (NPA) from blinded image evaluation between <65 and ≥65 yrs subjects Values are mean results across all readers. Intent to diagnose population.

| Reference Clinical Diagnosis | Parkinsonian Syndrome (PS; SDDD) | Dementia with Lewy Bodies (DLB; SDDD) | Whole Population |
|-----------------------------|----------------------------------|--------------------------------------|------------------|
|                             | Sensitivity % (95% CI)            | Specificity % (95% CI)                |                  |
| Baseline*                   | Male (n=204)                      | Female (n=349)                        |                  |
|                             | 92.3 (89.7, 94.4)                 | 89.7 (86.5, 92.3)                     |                  |
|                             | 0.1808                            | 0.0108                               |                  |
|                             | Sensitivity % (95% CI)            | Specificity % (95% CI)                |                  |
| Month 12b                   | Male (n=23)                       | Female (n=42)                         |                  |
|                             | 47.6 (25.7, 70.2)                 | 81.5 (75.6, 86.4)                     |                  |
|                             | 0.0011                            | 0.3682                               |                  |
|                             | Sensitivity % (95% CI)            | Specificity % (95% CI)                |                  |
| Month 18c                   | Male (n=60)                       | Female (n=41)                         |                  |
|                             | 83.3 (75.4, 89.5)                 | 71.3 (60.6, 80.5)                     |                  |
|                             | 0.0903                            | 0.3255                               |                  |
|                             | Sensitivity % (95% CI)            | Specificity % (95% CI)                |                  |
| Month 36c                   | Male (n=58)                       | Female (n=41)                         |                  |
|                             | 80.7 (72.3, 87.5)                 | 71.3 (60.6, 80.5)                     |                  |
|                             | 0.1320                            | 0.2955                               |                  |

*Summary result calculated across all readers for Studies A, B, and C at baseline.

Citation: Grosset DG, O’Brien JT, Oertel WH, McKeith IG, Walker Z, et al. (2014) Age, Gender, and Diagnostic Performance of Ioflupane I123 Injection (DaTscan™) Brain Imaging in Patients with Movement Disorders and/or Dementia. J Neurol Stroke 1(2): 00008. DOI: 10.15406/jnsk.2014.01.00008
Sensitivity (PPA)/specificity (NPA) for parkinsonian syndrome (PS) was calculated based on PS present vs. PS absent. Sensitivity (PPA)/specificity (NPA) for dementia with Lewy bodies (DLB) was calculated based on Probably DLB vs. Non-DLB. Sensitivity (PPA)/specificity (NPA) for whole population was calculated based on SDD present vs. SDD absent. 

**Table 8:** Sensitivity (PPA) and specificity (NPA) from blinded image evaluation between <75 and ≥75 yrs subjects. Values are mean results across all readers. Intent to diagnose population.

| Reference Clinical Diagnosis | Parkinsonian Syndrome [PS; SDDD] | Dementia with Lewy Bodies [DLB; SDDD] | Whole Population |
|-----------------------------|----------------------------------|--------------------------------------|------------------|
|                             | Sensitivity % (95% CI) | Specificity % (95% CI) | Sensitivity % (95% CI) | Specificity % (95% CI) | Sensitivity % (95% CI) | Specificity % (95% CI) |
| Baseline                    | 91.4 (89.3, 93.1) | 88.4 (80.2, 94.1) | 92.9 (89.8, 95.3) | 86.1 (70.5, 95.3) | 85.9 (78.7, 91.4) | 91.9 (87.7, 95.1) |
| P value                      | 0.2814 | 0.0400 | 0.0836 | 0.0183 | 0.0468 | 0.1837 |
| Month 12                    | 82.8 (75.1, 88.9) | 73.4 (64.1, 81.4) | 91.7 (86.3, 95.5) | 93.6 (89.2, 96.5) | 90.7 (88.8, 92.4) | 78.4 (72.1, 83.9) |
| P value                      | 0.2400 | 0.0040 | 0.5423 | 0.0242 | 0.0001 | 0.0001 |
| Month 36                    | 77.7 (71.0, 83.5) | 64.7 (38.3, 85.8) | 96.4 (89.9, 99.3) | 100 (54.1, 100) | 91.2 (88.5, 93.4) | 91.1 (87.1, 94.2) |
| P value                      | 0.2814 | 1.0000 | 0.0001 | 1.0000 | 0.0183 | 0.0183 |

- Summary result calculated across all readers for Studies A, B, and C at baseline.
- Summary result calculated across all readers for Study B.
- Summary result calculated across all readers for Study C.
- Sensitivity (PPA)/specificity (NPA) for parkinsonian syndrome (PS) was calculated based on PS present vs. PS absent.
- Sensitivity (PPA)/specificity (NPA) for dementia with Lewy bodies (DLB) was calculated based on Probably DLB vs. Non-DLB.
- Sensitivity (PPA)/specificity (NPA) for whole population was calculated based on SDD present vs. SDD absent.
- P value is from Fisher's exact test.
- CI: Confidence Interval; n: Number of subjects included in the analysis; NPA: Negative Percent Agreement; PPA: Positive Percent Agreement; SDDD: Striatal Dopaminergic Deficit disorder.

**Table 9:** Sensitivity (PPA) and specificity (NPA) from on-site image reads between <65 and ≥65 yrs subjects. Intent to diagnose population.

| Reference Clinical Diagnosis | Parkinsonian Syndrome [PS; SDDD] | Dementia with Lewy Bodies [DLB; SDDD] | Whole Population |
|-----------------------------|----------------------------------|--------------------------------------|------------------|
|                             | Sensitivity % (95% CI) | Specificity % (95% CI) | Sensitivity % (95% CI) | Specificity % (95% CI) | Sensitivity % (95% CI) | Specificity % (95% CI) |
| Mean Results                | 89.7 (85.0, 93.4) | 94.2 (87.8, 97.8) | 77.8 (40.0, 97.2) | 91.3 (82.8, 96.4) | 81.3 (54.4, 96.0) | 91.0 (58.5, 93.3) |
| P value                      | 1.0000 | 0.0468 | 0.0242 | 0.0834 | 0.0001 | 0.0242 |
| Month 12                    | 77.8 (40.0, 97.2) | 91.3 (82.8, 96.4) | 81.3 (54.4, 96.0) | 91.0 (58.5, 93.3) | 92.4 (86.1, 96.5) | 83.1 (76.9, 88.1) |
| P value                      | 0.2814 | 0.0242 | 0.0001 | 0.0242 | 0.0001 | 0.0242 |
| Month 18                    | 82.1 (66.5, 92.5) | 95.0 (75.1, 99.9) | 81.8 (48.2, 97.7) | 0.2814 | 0.0242 | 0.0242 |
| P value                      | 1.0000 | 0.2814 | 1.0000 | 0.2814 | 1.0000 | 0.2814 |
| Month 36                    | 82.1 (66.5, 92.5) | 95.0 (75.1, 99.9) | 81.8 (48.2, 97.7) | 0.2814 | 0.0242 | 0.0242 |
| P value                      | 1.0000 | 0.2814 | 1.0000 | 0.2814 | 1.0000 | 0.2814 |

- Summary results calculated across all studies and time points. For Study B, month 12 reference clinical diagnosis was used.
- Summary result calculated for Study B.
- Summary result calculated for Study C.
- Sensitivity (PPA)/specificity (NPA) for parkinsonian syndrome (PS) was calculated based on PS present vs. PS absent.
- Sensitivity (PPA)/specificity (NPA) for dementia with Lewy bodies (DLB) was calculated based on Probably DLB vs. Non-DLB.
- Sensitivity (PPA)/specificity (NPA) for whole population was calculated based on SDD present vs. SDD absent.
- P value is from Fisher's exact test.
- CI: Confidence Interval; n: Number of subjects included in the analysis; NPA: Negative Percent Agreement; PPA: Positive Percent Agreement; SDDD: Striatal Dopaminergic Deficit disorder.

**Citation:** Grosset DG, O’Brien JT, Oertel WH, McKeith IG, Walker Z, et al. (2014) Age, Gender, and Diagnostic Performance of Ioflupane I123 Injection (DaTscan™) Brain Imaging in Patients with Movement Disorders and/or Dementia. J Neurol Stroke 1(2): 00008. DOI: 10.15406/jnsk.2014.01.00008
Table 10: Sensitivity (PPA) and specificity (NPA) from on-site image reads between <75 and ≥75 yrs subjects. Intent to diagnose population.

| Reference Clinical Diagnosis | Parkinsonian Syndrome (PS; SDDD) | Dementia with Lewy Bodies (DLB; SDDD) | Whole Population |
|------------------------------|----------------------------------|--------------------------------------|------------------|
|                              | Sensitivity % (95% CI) | Specificity % (95% CI) | Sensitivity % (95% CI) | Specificity % (95% CI) | Sensitivity % (95% CI) | Specificity % (95% CI) |
| Mean Results<sup>a</sup> | | | | | | |
| <75 yrs (n=460) | 89.2 (85.6, 92.2) | 93.0 (80.9, 98.5) | 89.8 (77.8, 96.6) | 90.0 (76.3, 97.2) | 89.3 (86.0, 92.1) | 91.6 (83.4, 96.5) |
| ≥75 yrs (n=154) | 89.1 (83.3, 93.4) | 100 (81.5, 100) | 78.2 (65.0, 88.2) | 84.3 (73.6, 91.9) | 86.4 (81.1, 90.6) | 87.5 (78.7, 93.6) |
| P value | 0.6004 | 0.0000 | 0.4864 | 0.0000 | 0.8547 | 0.0000 |
| Month 12<sup>b</sup> | | | | | | |
| <75 yrs (n=104) | 89.8 (77.8, 96.6) | 90.0 (76.3, 97.2) | 89.3 (86.0, 92.1) | 91.6 (83.4, 96.5) | 86.4 (81.1, 90.6) | 87.5 (78.7, 93.6) |
| ≥75 yrs (n=110) | 100 (81.5, 100) | 84.3 (73.6, 91.9) | 86.4 (81.1, 90.6) | 87.5 (78.7, 93.6) | 86.4 (81.1, 90.6) | 87.5 (78.7, 93.6) |
| P value | 0.2237 | 0.0000 | 0.4864 | 0.0000 | 0.8547 | 0.0000 |
| Month 18<sup>c</sup> | | | | | | |
| <75 yrs (n=92) | 81.0 (69.1, 91.9) | 85.7 (42.1, 99.6) | 89.1 (83.3, 93.4) | 100 (81.5, 100) | 90.0 (76.2, 97.8) | 100 (81.5, 100) |
| ≥75 yrs (n=9) | 89.7 (72.6, 97.8) | 100 (15.8, 100) | 100 (81.5, 100) | 100 (81.5, 100) | 90.0 (76.2, 97.8) | 100 (15.8, 100) |
| P value | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 |
| Month 36<sup>c</sup> | | | | | | |
| <75 yrs (n=89) | 83.9 (72.3, 92.0) | 83.3 (35.9, 99.6) | 89.1 (83.3, 93.4) | 100 (81.5, 100) | 89.1 (83.3, 93.4) | 100 (81.5, 100) |
| ≥75 yrs (n=8) | 85.2 (66.3, 95.8) | 100 (15.8, 100) | 100 (81.5, 100) | 100 (81.5, 100) | 89.1 (83.3, 93.4) | 100 (81.5, 100) |
| P value | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 |

<sup>a</sup>Sensitivity results calculated across all studies and time points. For Study B, month 12 reference clinical diagnosis was used.

<sup>b</sup>Sensitivity result calculated for Study B.

<sup>c</sup>Sensitivity result calculated for Study C.

Sensitivity (PPA)/Specificity (NPA) for Parkinsonian Syndrome (PS) was calculated based on PS present vs. PS absent; Sensitivity (PPA)/Specificity (NPA) for Dementia with Lewy Bodies (DLB) was calculated based on Probably DLB vs. Non-DLB; Sensitivity (PPA)/specificity (NPA) for whole population was calculated based on SDD present vs. SDD absent. P value is from Fisher’s exact test.

Table 11: Logistic regression for ioflupane (123I) sensitivity (PPA) and specificity (NPA) with covariate(s)-ITD population.

| Logistic Regression with All Covariates | Individual Logistic Regression |
|----------------------------------------|--------------------------------|
| Statistics | P-value | Odds ratio (95% CI) | P-value | Odds ratio (95% CI) |
| Sensitivity (PPA) | | | | |
| Number of Observations | 2485 | | | |
| Number of Observations with True Positive | 2139 (86.1%) | | | |
| Disease state (DLB vs. PS) | 0.0028 | 0.642 (0.480, 0.859) | 0.0001 | 0.612 (0.481, 0.780) |
| Age (yrs)<sup>a</sup> | 0.0086 | 0.982 (0.968, 0.995) | 0.0001 | 0.977 (0.966, 0.989) |
| Gender (Male vs. Female) | 0.0031 | 1.421 (1.126, 1.794) | 0.0030 | 1.412 (1.124, 1.773) |
| Reading (Blinded vs. On-site)<sup>b</sup> | 0.0016 | 0.622 (0.463, 0.835) | 0.0063 | 0.667 (0.499, 0.892) |
| Duration of follow-up (months)<sup>c</sup> | <0.0001 | 0.970 (0.961, 0.979) | <0.0001 | 0.974 (0.966, 0.982) |
| Specificity (NPA) | | | | |
| Number of Observations | 1811 | | | |
| Number of Observations with True Negative | 1632 (90.1%) | | | |
| Disease state (DLB vs. PS) | 0.0048 | 0.547 (0.360, 0.832) | 0.0017 | 0.588 (0.423, 0.819) |
| Age (yrs)<sup>a</sup> | 0.4975 | 1.006 (0.988, 1.024) | 0.1189 | 0.989 (0.975, 1.003) |
| Gender (Male vs. Female) | 0.0039 | 0.754 (0.548, 1.038) | 0.1981 | 0.814 (0.595, 1.114) |
| Reading (Blinded vs. On-site)<sup>b</sup> | <0.0001 | 2.307 (1.674, 3.180) | <0.0001 | 2.322 (1.688, 3.194) |
| Duration of follow-up (months)<sup>c</sup> | 0.0710 | 1.017 (0.999, 1.037) | 0.0491 | 1.018 (1.000, 1.036) |

<sup>a</sup>Age and duration of follow-up are treated as continuous in the logistic regression model.

<sup>b</sup>PDT408 only has institutional (on-site) reads.

CI: Confidence Interval; DLB: Dementia with Lewy Bodies; ITD: Intent to Diagnose; n: Number of subjects included in the analysis; NPA: Negative Percent Agreement; PPA: Positive Percent Agreement; PS: Parkinsonian Syndrome; yrs: years

Sensitivity of detecting an SDDD in the early stages of the disease. This is borne out by the fact that sensitivity in females approximated that in males later in the disease process (month 18 and month 36, Figure 1). On the other hand, because a diagnosis of PD in males is more common (2/3 of all cases) and relatively straightforward, it may be easier to exclude a diagnosis of PD in
Effect on diagnostic performance, with sensitivity and specificity. The observed fluctuation in diagnostic performance between age groups was more likely associated with less precision in the reference standard than in inaccuracies of the interpretation of the SPECT images. This is particularly true, because the 18- and 36-month clinical diagnoses were established based on independent review by movement disorder specialists of videotapes, not by a clinical consensus panel (Study C) [12]. Furthermore, the inter-reader agreement, as measured by kappa, was very good/almost perfect [9,12,18,19], which further supports our contention that the observed fluctuations in diagnostic performance were not due to inaccuracies in the interpretations of the SPECT images.

A comparison of diagnostic performance between age groups is shown in Table 12. Differences associated with gender in PS were not observed in subjects with DLB, despite recent observations that the incidence of DLB is higher in males [20]. This can be explained by the smaller sample size of DLB subjects as compared to PS in our analysis, which was also substantiated by Savica et al. [20] by their finding that the overall incidence rate of DLB is higher in males [20]. This can likely be explained by the fact that dementia subtype is more difficult to diagnose than PS, and the reduced accuracy can be attributed to less precision in the reference standard (i.e., the clinical diagnosis of DLB [21] or other dementia subtypes (with or without SDD), rather than inaccuracies in the interpretations of the SPECT images.

When a multiple logistic regression model was used, all covariates (disease state DLB vs. PS), age, gender (male vs. female), type of reader (blinded vs. on-site) and duration of follow-up were significant predictors of the model effect on sensitivity. For specificity, only disease state and type of reader were significant predictors. The observation that age and gender did not affect specificity in the multiple logistic regression model is important and supports the robust performance and high accuracy of this diagnostic test. Age and gender had a statistically significant effect on sensitivity, which may be explained by the differences in the diagnostic performance between age groups. This subgroup analysis had some limitations. This was an exploratory analysis, and as such, unadjusted p-values were calculated. If corrections for multiple comparisons had been made, the results may have been different. Image assessments were only performed visually. If quantification procedures had been included, differences may have been observed in the sensitivity and specificity results. Although clinical diagnosis is considered a valuable reference standard in developing radiopharmaceuticals for movement disorders and dementia [22], the definitive truth standard is neuropathological confirmation of brain tissue at autopsy. However, it is impractical to design clinical trials to span the life-expectancy of the study subjects, and so clinical diagnosis is the best alternative. For this reason, in our paper, in addition to sensitivity and specificity, we also used the terms PPA and NPA (mathematically identical calculations, but emphasizing our limitations of not being the truth standard). Despite taking measures to minimize errors in clinical diagnosis, such as using panels of experts, inaccuracies likely occurred, and may be responsible for the reductions observed in sensitivity and specificity. Additionally, age and gender had some statistically significant effects on the diagnostic performance of ioflupane ([123I]) imaging, although to what extent these differences are clinically relevant is unknown. The observed effects should be taken into consideration and allowed for when assessing patients presenting with varying diagnostic states.
Table 13: Logistic regression for ioflupane (123I) sensitivity (PPA) and specificity (NPA) with covariate(s)-PP population.

| Statistics | P-value | Odds ratio (95% CI) | P-value | Odds ratio (95% CI) |
|------------|---------|---------------------|---------|---------------------|
| Sensitivity (PPA) | Number of Observations | 2190 | | |
| | Number of Observations with True Positive | 1855 (84.7%) | | |
| | Disease state (DLB vs. PS) | 0.0090 | 0.674 (0.501, 0.906) | 0.0025 | 0.685 (0.537, 0.875) |
| | Age (yrs) | 0.0646 | 0.987 (0.973, 1.001) | 0.0055 | 0.983 (0.972, 0.995) |
| | Gender (Male vs. Female) | 0.0017 | 1.463 (1.154, 1.856) | 0.0013 | 1.467 (1.161, 1.853) |
| | Reading (Blinded vs. On-site) | 0.0035 | 0.643 (0.478, 0.865) | 0.0081 | 0.673 (0.502, 0.902) |
| | Duration of follow-up (months) | < 0.0001 | 0.973 (0.964, 0.983) | < 0.0001 | 0.977 (0.969, 0.986) |
| Specificity (NPA) | Number of Observations | 1682 | | |
| | Number of Observations with True Negative | 1518 (90.2%) | | |
| | Disease state (DLB vs. PS) | 0.0003 | 0.421 (0.264, 0.671) | 0.0008 | 0.536 (0.373, 0.771) |
| | Age (yrs) | 0.0722 | 1.017 (0.998, 1.036) | 0.3755 | 0.993 (0.979, 1.008) |
| | Gender (Male vs. Female) | 0.0629 | 0.727 (0.520, 1.017) | 0.1782 | 0.799 (0.576, 1.108) |
| | Reading (Blinded vs. On-site) | < 0.0001 | 2.628 (1.884, 3.665) | < 0.0001 | 2.609 (1.876, 3.629) |
| | Duration of follow-up (months) | 0.1181 | 1.016 (0.996, 1.036) | 0.0546 | 1.018 (1.000, 1.036) |

*Age and duration of follow-up are treated as continuous in the logistic regression model.

Conclusion

This subgroup analysis showed that gender and age have some effect on the diagnostic performance of ioflupane (123I) imaging in subjects with movement disorders or dementia when clinical diagnosis is used as the reference standard. Overall, sensitivity and specificity were high. Statistically significant differences were observed in some comparisons. Sensitivity was slightly reduced, though still diagnostically useful, above the age of 75. In subjects with PS, sensitivity was higher in males, whereas specificity was higher in females. Multiple logistic regression model analysis demonstrated that all tested covariates (including age and gender) were significant predictors for sensitivity, but not for specificity, where only disease state and type of reader were significant predictors. To what extent these differences are clinically relevant remains to be elucidated. Additional research may provide further clarification on these issues.

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Conflict of Interest

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