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Medical Policy Manual Radiology, Policy No. 57

Dopamine Transporter Single-Photon Emission Computed Tomography (DAT-SPECT)

Effective: January 1, 2019

Next Review: January 2020
Last Review: December 2018

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Dopamine transporter single-photon emission computed tomography (DAT-SPECT) detects presynaptic dopaminergic deficit by measuring DAT binding. In general, striatal DAT binding is reduced in certain neurological conditions, while striatal DAT binding is in the normal range in others. Therefore, use of DAT-SPECT is being proposed to improve differential diagnosis between certain types of neurological conditions.

MEDICAL POLICY CRITERIA

Note: This policy only addresses SPECT when used with dopamine transporter ligands for diagnosing specific neurological disorders. Use of SPECT that does not incorporate these ligands is currently addressed in another commercial policy (please see Cross References below).

I. Dopamine transporter single-photon emission computed tomography (DAT-SPECT) may be considered **medically necessary** for any of the following:
   A. Suspected diagnosis of Parkinson disease when unable to be confirmed clinically; or

B. Suspected diagnosis of dementia with Lewy bodies when unable to be confirmed clinically.

II. Dopamine transporter single-photon emission computed tomography (DAT-SPECT) is considered **investigational** for all other indications.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

SUBMISSION OF DOCUMENTATION

It is critical that the list of information below is submitted for review to determine whether the policy criteria are met. If these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Diagnosis and indication for testing

CROSS REFERENCES

1. Biochemical Markers of Alzheimer's Disease, Laboratory, Policy No. 22
2. Transcranial Magnetic Stimulation as a Treatment of Depression and Other Disorders, Medicine, Policy No. 148
3. Magnetic Resonance Spectroscopy, Radiology, Policy No. 27
4. Single Photon Emission Computed Tomography (SPECT) for the Diagnosis of ADHD, Dementias and Other Psychiatric Conditions, Radiology, Policy No. 44
5. Deep Brain Stimulation, Surgery, Policy No. 84

BACKGROUND

Parkinsonian syndromes (PS) are a group of diseases that share similar cardinal signs, characterized by bradykinesia, rigidity, resting tremor, and gait disturbance. Parkinson disease (PD) is the most common cause of parkinsonism; however, diagnosing PD in the early stage of the disease can be difficult. In addition, other etiologies such as essential tremor (ET), corticobasal degeneration, multisystem atrophy, progressive supranuclear palsy, vascular parkinsonism, and drug-induced parkinsonism can lead to a similar set of symptoms. Even in specialized movement disorders centers, up to 25% of patients may be misclassified, and some patients, such as those with ET who have been diagnosed with PD, may be erroneously treated.[1] This has led to the development of additional tests to improve the accuracy of clinical diagnosis of PD and other PSs. One recent approach is to evaluate the integrity of dopaminergic pathways in the brain using dopamine transporter single-photon emission computed tomography (DAT-SPECT).

DAT-SPECT detects presynaptic dopaminergic deficit by measuring DAT binding. In general, striatal DAT binding is reduced in PD, genetic parkinsonism, dementia with Lewy bodies (DLB), corticobasal degeneration, progressive supranuclear palsy, and multiple system atrophy, while striatal DAT binding is in the normal range in AD, ET, dystonic tremor, orthostatic tremor, drug-induced parkinsonism, psychogenic parkinsonism, and vascular parkinsonism.[2] It is proposed that an abnormal DAT-SPECT supports the diagnosis of PD or other neurodegenerative PS (multisystem atrophy, progressive supranuclear palsy), while a normal DAT-SPECT in a symptomatic patient increases the likelihood of a disease not affecting the nigrostriatal dopaminergic pathway. There is, however, a significant percentage of

patients with clinically diagnosed PD who do not show reduced DAT-SPECT binding. These are commonly referred to as scans without evidence of dopaminergic deficit. Additional research may shed light on these cases.[3]

Due to the degeneration of nigrostriatal neurons in DLB, DAT-SPECT is also proposed to differentiate DLB from AD. Some note a severe sensitivity to neuroleptics (potentially life-threatening) in patients with DLB. However, newer agents are usually well-tolerated, and patients with DLB may also respond to the cholinesterase inhibitors that are more commonly used to treat AD.

Analysis of DAT-SPECT images can be visual, semiquantitative, or quantitative. Because patients typically do not become symptomatic before a substantial number of striatal synapses have degenerated, visual interpretation of the scan is thought to be sufficient for clinical evaluation. A variety of methods are being tested to improve the validity and reliability of ratings, including commercially available software to define the region of interest (ROI) for analysis and the development of an atlas for visual interpretation. Quantitative interpretation may aid visual interpretation and, if performed rigorously, may increase diagnostic accuracy; however, interobserver variability tends to be high with manual ROI-based semiquantification.[4] Semiquantitative analysis also requires normal control values and varies across imaging systems.

Dopamine transporter ligands include ^{123}I-β-CIT, ^{123}I-FP-CIT, and 99mTc-TRODAT-1.2 ^{123}I-β-CIT requires a delay between injection and scan of about 24 hours. ^{123}I-FP-CIT (DaTscan™) is a fluoropropyl derivate of β-CIT that can be injected three to six hours before the scan.

REGULATORY STATUS

DaTscan™ (GE Healthcare) has been in use in Europe since 2000 with a diagnostic indication for use in parkinsonian patients and with expanded use since 2006 in patients suspected of DLB. DaTscan was approved by the U.S. Food Drug Administration (FDA) in 2011 as a new molecular entity (NME) and is “indicated for striatal dopamine transporter visualization using single-photon emission computed tomography (SPECT) brain imaging to assist in the evaluation of adult patients with suspected parkinsonian syndromes (PS). In these patients, DaTscan may be used to help differentiate essential tremor from tremor due to PS (idiopathic Parkinson's disease, multiple system atrophy and progressive supranuclear palsy). DaTscan is an adjunct to other diagnostic evaluations.”

EVIDENCE SUMMARY

Assessment of a diagnostic technology typically focuses on the following three categories of evidence:

1. Analytic validity (technical feasibility) is demonstrated, including reproducibility and precision. For comparison among studies, a common standardized protocol for the new diagnostic technology is established.
2. Clinical validity (diagnostic accuracy) - sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) compared to standards are established in relevant populations of patients, such as those with suspected early Parkinson disease (PD) or inconclusive diagnosis.
3. Clinical utility of a diagnostic technique, i.e., how the results of the study can be used to benefit patient management, is established. The clinical utility of both positive and

negative tests must be established. The effect on patient outcomes (demonstration that the diagnostic information can be used to improve patient outcomes through a randomized controlled trial [RCT] or demonstration of a tightly linked chain of evidence from diagnostic accuracy to outcomes).

The criterion standard for the diagnosis of parkinsonian syndromes (PS) and dementia is postmortem neuropathologic examination. In the absence of comparisons with the criterion standard, long-term clinical follow-up may be used as a surrogate standard to evaluate the ability of dopamine transporter (DAT) imaging with single-photon emission computed tomography (DAT-SPECT) to discriminate degenerative PS from normality or from nondegenerative disorders that present with similar symptoms, and to discriminate dementia with Lewy bodies (DLB) from Alzheimer disease (AD).

The analytic validity of DAT-SPECT is the same, regardless of the indication it is used for, therefore in the evidence summary below, only clinical validity and utility are addressed separately for each indication.

ANALYTIC VALIDITY

DAT-SPECT is based on the selective affinity of ligands for the DAT and the exclusive location of the DAT in dopamine synthesizing neurons.[2] ^{123}I-β-CIT is a cocaine analog that has a high affinity to the DAT and serotonin transporters. ^{123}I-FP-CIT (DaTscan™) is a fluoropropyl derivate of β-CIT that is selective for brain striatal DAT, but it can also bind to the serotonin transporter. Although antiparkinsonian drugs do not interfere with DAT binding, it is unknown if dopamine agonists and levodopa affect DAT expression, which could influence the ability of DAT-SPECT to monitor progression of disease.

In 2014, Seibyl reported intra- and interrater agreement for DAT-SPECT images with data from five multicenter trials (818 patients).[5] DAT binding was classified as “normal” or “abnormal.” Within-reader agreement was assessed in one study, and showed complete (100%) agreement when image evaluation was blinded. In all trials, between-reader agreement was high ($\kappa>0.8$) for PD, but decreased when comparing blinded image evaluation and on-site readers for DLB.

In a 2012 study, Papathanasiou evaluated interobserver variability in the visual interpretation of DAT-SPECT.[6] Eighty-nine previously obtained DAT-SPECT scans were blindly reviewed by three independent observers with different levels of experience (consultant, resident doctor, radiographer), classified as “normal” or “abnormal,” and assigned visual DAT-SPECT uptake scores (2 = normal, 1 = reduced, 0 = no uptake). Results were compared with the diagnosis at last visit to the clinician, divided into PS or no PS. There was good interobserver agreement in 85 of 89 studies for classifying scans as “normal” or “abnormal” (κ range, 0.89-0.93) and moderate agreement in assignment of uptake scores (κ range, 0.71-0.80 for putamina; 0.50-0.79 for caudate nuclei). All three observers achieved a sensitivity of 100%, with specificities of 89-96%.

Section Summary

Preclinical studies to determine the analytical validity of DAT-SPECT report specificity of ligand binding for the striatal DAT. There is limited evidence on the effects of medications on DAT expression. Studies report a high level of interobserver agreement on visual interpretation of images for PD, suggesting that reliability of visual interpretation for this disorder is high. There

was less interobserver agreement on visual interpretation of images for DLB. The analytic validity of DAT-SPECT is the same, regardless of the indication it is used for, therefore in the evidence summary below, only clinical validity and utility are addressed in the following evidence sections.

PARKINSONIAN SYNDROMES

Clinical Validity

The most informative evaluation of clinical validity requires prospective, independent, and blinded assessment of test results compared with a criterion standard in an appropriate population.

In 2015, Jakobson reported a prospective study on the diagnostic accuracy of visual assessment of DAT-SPECT in individuals with early-stage parkinsonian diseases.[7] Strengths of this study include an independent clinical diagnosis made at baseline and follow-up, and blinded reading of the DAT scans. Patients (N=171) were identified incidentally from an ongoing longitudinal population-based research project on parkinsonian disorders. All met criteria for stage one disease on the U.K. Parkinson's Disease Society Brain Bank clinical criteria for PD. Patients with a Mini-Mental State Examination scores less than 24 or evidence of ET or secondary parkinsonism were excluded. The results of DAT-SPECT were compared with criteria-based clinical diagnoses at a mean follow-up of 4.6 years. The clinical diagnoses at baseline and follow-up were performed independently of DAT-SPECT findings. Image analysis was performed by two nuclear medicine specialists who were blinded to the clinical diagnosis. The study also included 37 age-matched healthy controls who underwent DAT-SPECT imaging for evaluation of specificity. There was a discrepancy between the reviewers in 10 cases (9.3%); these were reevaluated to reach a consensus. Visual assessment in this enriched population was found to have a sensitivity of 94% and specificity of 92%, with 3 of 37 controls considered false positives and 10 of 171 patients considered false negatives at baseline. However, at this time, it is not known if the SWEDDs are true false negatives or were misdiagnosed as having a PS.

In 2009 Marshall, reported a prospective, investigator-initiated industry-funded, 36-month European multicenter study with repeat DAT-SPECT and criterion standard clinical diagnosis (video at 36 months by two movement disorders specialists) in 99 diagnostically uncertain cases of PD or essential tremor (ET).[8] Patients with other potential causes of parkinsonism/tremor and patients with major comorbid illness were excluded; three healthy volunteers were included. For analysis, the clinical diagnosis was considered as either PD (including atypical PD) or non-PD (including ET, dystonic tremor, vascular parkinsonism). There was 50% loss to follow-up over the three years of the study (199 enrolled), although patients with PD were not more likely to drop out than patients without PD. DAT-SPECT scans were evaluated by three blinded nuclear physicians using visual criteria, and the inter-reader agreement for rating scans as normal or abnormal was high for scans at baseline, 18 months, and 36 months (κ range, 0.94-0.97).

At 36 months criterion standard diagnosis was degenerative parkinsonism in 71 cases and non-PD in 28 cases. The initial clinical diagnosis had sensitivity of 93% and specificity of 46% compared with diagnosis at follow-up, indicating overdiagnosis of PD. DAT-SPECT at baseline had a sensitivity of 78% and specificity of 97%, with a PPV of 98.2% and an NPV of 66.2%. DAT-SPECT scans were considered normal in 21% of the cases with a criterion standard diagnosis of PD and did not change over the three years of the study. These cases are

referred to as SWEDDS (Subjects with Scans Without Evidence of Dopamine Deficiency). DAT-SPECT did not improve diagnostic accuracy in the SWEDDS patients at the 36-month clinical assessment. Although this study indicates that an abnormal DAT-SPECT scan may help to confirm a clinical diagnosis of PD in the majority of patients, the low NPV suggests that a normal DAT-SPECT scan cannot be used to rule out disease and thus may not be helpful in preventing the potential clinical overdiagnosis of PD.

A number of published studies and meta-analyses have not included an independent reference standard of either blinded clinical diagnosis at follow-up or post mortem analysis of substantia nigra neuron degeneration. When a reference standard is not independent of the diagnostic test, it can result in an apparent increase in the sensitivity and specificity of the test. Therefore, the diagnostic accuracy reported in these studies must be interpreted with caution. These studies are described below.

In 2014 Brigo reported a meta-analysis of DAT-SPECT to differentiate between PD and vascular or drug-induced parkinsonisms.[9] The meta-analysis included five studies that had diagnosis confirmed by imaging. There were a number of study limitations, most notably, in three studies, it was not clear if the diagnosis at follow-up (criterion standard) was made blinded to the results of DAT-SPECT and could thus be considered an independent reference standard. Two studies published in 2014 analyzed data from Kupsch (2012)[10] The studies included 92 patients with clinically uncertain parkinsonian syndromes (CUPS) at baseline who had confirmed clinical diagnosis at one year. Bajaj (2014)assessed the effect of age, disease stage, and other clinical and neurocognitive measures on the diagnostic performance of DAT-SPECT.[11] Hauser (2014) reported that the diagnostic accuracy of DAT-SPECT was higher than clinical diagnosis at baseline.[12] Both studies are limited because clinical diagnosis atone year was influenced by the imaging results and cannot be considered an independent reference standard.

Other studies provide limited information on diagnostic accuracy because they were not conducted in an appropriate population that included patients with clinically uncertain PD or ET. These studies are described below.

In 2014, O'Brien published an industry-funded pooled analysis of four clinical studies that were submitted in support of the new drug application to the U.S. Food and Drug Administration (FDA).[13] All studies assessed the sensitivity and specificity of DAT-SPECT to detect nigrostriatal cell loss in patients with signs and symptoms of movement disorders and/or dementia. The clinical diagnosis, determined at baseline or at 12, 24, or 36 months after imaging, was performed independently of DAT-SPECT results in three of the four studies. The study populations ranged from patients with uncertain clinical diagnosis to patients with established clinical diagnosis. Pooled analysis showed sensitivity of 93.1% (range, 75.0%-96.5%) and specificity of 91.1% (range, 83%-100%) in the intention-to-treat population of 726 patients. Interpretation of this study is limited by heterogeneity in the included studies. Only two studies included a population of patients with an uncertain diagnosis, one of which was an open-label phase VI study where the clinical diagnosis was not independent of DAT-SPECT. Individual studies are described in greater detail in the Clinical Utility section.

Vlaar reported a retrospective study of the diagnostic value of DAT and postsynaptic dopamine receptor binding in 248 patients with unclassified PS in 2008.[14] Two investigators established a clinical diagnosis according to generally accepted clinical criteria and were certain enough to make a final diagnosis from the clinical records or after follow-up in all but 25 of the cases. Of

the 248 patients, 80 underwent DAT-SPECT alone, 38 underwent dopamine receptor SPECT, and 130 underwent both scans. Scans were analyzed by a nuclear medicine specialist blinded to the clinical diagnosis, with ligand binding of two standard deviations above or below healthy controls considered abnormal. Using clinical diagnosis as the comparator, DAT-SPECT was able to distinguish between PD and ET (odds ratio [OR] = 82); between PD and vascular parkinsonism (OR=61); between PD and drug-induced parkinsonism (OR=36); and between PD and atypical PS (OR=1).

In 2000, Benamer conducted a multicenter study that included 158 patients with an established clinical diagnosis of parkinsonism, 27 cases of definite ET, and 35 healthy volunteers.[15] Striatal uptake of the ligand was graded visually as normal or abnormal by an institutional reader who was blinded to the clinical data and a blinded consensus panel of five readers. The institutional reader scored 154 of 158 cases of parkinsonism as abnormal, all 27 cases of ET as normal, and 34 of 35 healthy volunteers as normal, resulting in sensitivity of 97% and specificity (for ET) of 100%. For the consensus blinded read, sensitivity and specificity were 95% and 93%, respectively. A limitation of this study is the population, which was not comprised of patients with atypical or clinically uncertain parkinsonism or ET.

Diagnostic accuracy of DAT-SPECT can be compared with the diagnostic accuracy of clinical diagnosis.

A longitudinal study by Adler (2014) found that, compared with neuropathologic findings of PD as the criterion standard, clinical diagnosis by a movement disorder specialist of possible PD (n=34) had only 26% accuracy.[16] Clinical diagnosis by a movement disorder specialist of probable PD (n=97) on the first visit had 53% PPV in cases with a disease duration less than five years and 88% PPV in patients with disease duration of five years or more.

Joutsa (2014) reported a retrospective study of the diagnostic accuracy of PD by general neurologists.[17] Of 1362 individuals who had been examined post mortem, 122 cases were identified with a clinical and/or neuropathologic diagnosis of PD. The sensitivity of clinical diagnosis of PD was 89.2% and the specificity was 57.8% compared with post mortem neuropathologic diagnosis, indicating that 25% of diagnoses by general neurologists were incorrect.

One study addressed the use of DAT-SPECT in asymptomatic LRRK2 G2019S carriers for predicting conversion to PD.[18] In this prospective study by Sierra (2017), 32 asymptomatic carriers of LRRK2 G2019S were evaluated at baseline and four years later, including clinical examination and DAT-SPECT. Three carriers had converted to PD at the second evaluation, and these participants had a statistically significantly lower striatal DAT binding at baseline than those that did not convert. There was no significant difference between the slope of DAT binding decline between the two scans.

Section Summary

The literature on the clinical validity of DAT-SPECT to diagnose and distinguish Parkinsonian syndromes includes meta-analyses of a number of small studies along with a large and well-conducted industry-sponsored study on the diagnostic accuracy of DAT-SPECT. In general, this evidence supports moderately high sensitivity and high specificity for the test. However, most studies had methodologic limitations, primarily the lack of a true criterion standard for the diagnosis of PS. In the highest quality study, in which the criterion standard was 36-month clinical diagnosis by a panel of independent experts, the sensitivity and specificity of testing

was 78% and 97%, respectively. The PPV was 98.2% and the NPV was 66.2% in a population of patients with a prevalence of underlying PD of approximately 70%. This indicates that, in a population of patients with a high pretest likelihood of PD, a positive test may be useful in confirming PD, while a negative test is less useful in ruling out the disorder.

Clinical Utility

The most rigorous evaluation of the impact of a diagnostic test on clinical outcomes is an RCT that evaluates health outcomes in patients who received the new diagnostic test compared with patients who are evaluated without the new test according to the standard of care.

Bhattacharjee (2017) retrospectively assessed the impact of DAT-SPECT performed for diagnosis and clinical management.[19] Of a total of 48 scans reported, 24 were to confirm early Parkinson's disease, five were to exclude drug-induced parkinsonism, eight were to distinguish essential tremor from parkinsonism, two were to distinguish Lewy body diseases from Alzheimer's dementia, and four were for other indications. There were 26 abnormal scans and 21 scans confirmed a diagnosis of degenerative parkinsonism. In 23% of patients, the scan results altered diagnosis and management.

Oravivattanakul (2015) reported on the concordance between pre-scan diagnosis and scan results in 175 CUPS patients who were seen by movement disorders neurologists.[20] When essential/dystonic tremor was suspected, the scan was normal in 79%. DaTscan influenced medical treatment more when scans were abnormal than when normal. Only 4% of patients with abnormal scans remained off medications, while 24% of patients with normal scans remained on medication.

Sadasivan and Friedman (2015) also reported on the clinical outcome of the change in management.[21] Sixty-five CUPS patients were referred for DAT-SPECT over a 17-month period. Scans were abnormal in 22 patients, leading to a final diagnosis of PD in 22 patients and a change in management in 41 patients (63%). Of the 41 patients with a change in management, 30 (73%) were clinically stable or improved at follow-up. This included 10 patients who were found to have drug-induced PD without any striatal neurodegeneration, leading to discontinuation or reduction in dose of the drug.

In a retrospective study from a hospital imaging facility in Europe, Thiriez (2015) evaluated whether routine clinical requests for DAT-SPECT were considered appropriate or inappropriate and whether the results led to a change in management.[22] Appropriateness was determined by consensus of two movement disorders specialists, and a request was considered inappropriate if DAT-SPECT was unable to answer the question or if DAT-SPECT results would not change patient care. For example, a differential diagnosis between parkinsonian tremor and ET was considered appropriate, while evaluation of the severity of dopaminergic cell loss in already diagnosed PD was always considered to be inappropriate. Of 516 consecutive requests over an 8-year period, 37% were considered inappropriate. They included requests to assess the degree of dopaminergic denervation in already diagnosed patients (n=40) and confirmation of a clinically evident diagnosis (n=64). Scan requests by movement disorder specialists were considered appropriate more frequently than requests from other physicians (79% vs 57%, $p<0.01$). A change in management was identified in 13% of patients with an inappropriate scan compared with 92% of the patients with an appropriate scan, and a change in management was more frequently observed if the scan was requested by movement disorders specialists than by other physicians (71% vs 56%, $p=0.01$).

Bega (2015) reported a study from a tertiary care center that evaluated 83 scans ordered over a two-year period with specific features that led the physician to question the diagnosis.[23] The greatest impact was to differentiate ET from PD, with a change in diagnosis, management, or both in 72.2% of these patients.

In a retrospective review of the effect of DAT-SPECT on diagnosis by referring physicians, Siefert and Weiner (2013) found that confidence in a diagnosis of PD or non-PD was significantly increased with abnormal scans, but not with normal scans.[24] For many patients, the scan confirmed the diagnosis of PD, despite a poor response to medication and resulted in a change in medication.

In 2012-2013, Kupsch reported an industry-sponsored, open-label, multicenter randomized trial from 19 university hospital centers in Europe and the United State that assessed the impact of DAT-SPECT on diagnosis, confidence of diagnosis, clinical management, health resource use, and safety in 273 patients with CUPS.[10,25] Criteria of uncertainty included at least one of the following: only one of the three cardinal signs of parkinsonism; two signs without bradykinesia; atypical signs; signs of mild intensity; poor response to L-dopa; and lack of disease progression. After the baseline visit and establishment of a clinical management plan, patients were randomized to DAT-SPECT or no imaging controls; the DAT-SPECT scans were visually classified as normal or abnormal by a nuclear medicine physician at each center who was blinded to clinical signs and/or symptoms. Patients were then followed for one year (visits at four weeks, 12 weeks, one year) by neurologists with (n=12) or without (n=7) movement disorder specialization.

The primary outcome was the proportion of patients in the efficacy population (baseline and 12-week visits) who had one or more changes in clinical management. Significantly more patients in the DAT-SPECT group had at least one change in their clinical management plan by 12 weeks than the control group (50% vs 31%, p=0.002). This was due to a greater change in management by movement disorder specialists (51% DAT-SPECT vs 28% controls, p<0.001). Medications were initiated in 29% of patients and withdrawn in 18% of patients after DAT-SPECT (patients could be counted in both categories). Changes included initiation of dopaminergic therapy or more aggressive dopaminergic therapy in patients with an abnormal scan, discontinuation of dopaminergic therapy, or initiation of tremor control drugs in patients with a normal scan, and unplanned diagnostic tests. For the general neurologists, clinical management was not affected by the DAT-SPECT results, with a change in management in 48% of DAT-SPECT patients versus 43% of controls. Changes in diagnosis occurred in 45%, 46%, and 54% of DAT-SPECT patients by four weeks, 12 weeks, and one year, respectively (per protocol population), compared with a change in diagnosis in 9%, 12%, and 23% of control patients at the same time points (p<0.001 for all comparisons). The changes were in the direction of better agreement between the clinical diagnosis and imaging results. Clinicians had increased confidence in diagnosis at four weeks, 12 weeks, and one year in the DAT-SPECT group; the greatest change in confidence in diagnosis was for patients with an initial inconclusive diagnosis (62% vs 22% controls, p<0.001). There were no significant differences in quality of life or health resource utilization during the one-year follow-up period. No serious adverse events occurred during the study.

Bairactaris evaluated the impact of DAT-SPECT on diagnoses of patients with PS in a 2009 report.[26] Sixty-one consecutive patients with an initial diagnosis of parkinsonism (n=40) or uncertain tremor disorder (n=21) by their treating community neurologist were reexamined by two neurologists who were blinded to the original diagnosis (overall agreement between the

two, 75.7%; κ=0.461). Patients then underwent DAT-SPECT imaging, which was evaluated by two masked independent and experienced nuclear medicine physicians using a semiquantitative approach and classified as normal or abnormal (κ=0.855). Based on DAT-SPECT imaging, the initial diagnosis was altered for 21 patients (34.4%) relative to the initial classification from the community neurologist and for six patients (9.8%) diagnosed at their center. All patients were reexamined by two neurologists at the center at one-year follow-up and classified as having neurodegenerative or non-neurodegenerative disorders. With the final diagnosis as the reference standard, DAT-SPECT had a sensitivity of 95%, specificity of 82%, and PPVs and NPVs of 90%. Although this study appears to have been well-conducted, evaluation of DAT-SPECT scans by two experienced nuclear medicine physicians using a semiquantitative approach may not be representative of results obtained outside of the investigational setting. As noted by the authors, DAT-SPECT studies did not appear to add a great deal to the diagnosis made by an expert in movement disorders.

In 2004, Catafau and Tolosa reported a prospective multicenter trial of the impact of DAT-SPECT on diagnosis and clinical management of 118 patients with CUPS, with two-year follow-up reported in 2007.[27,28] Criteria of uncertainty were assessed by referring neurologists and included at least one of the following: only one of the three cardinal signs of parkinsonism, with or without asymmetry; two signs without bradykinesia; atypical signs; signs of mild intensity; poor response to L-dopa; and lack of disease progression. Excluded were patients with an established clinical diagnosis and patients where the uncertainty was between PD, multisystem atrophy, and progressive supranuclear palsy. Following clinical diagnosis into categories (presynaptic or nonpresynaptic PS, or inconclusive diagnosis), all patients underwent DAT-SPECT with visual assessment of images by a trained nuclear medicine physician. After reviewing the DAT-SPECT results, the neurologists again provided a diagnosis and recorded proposed changes in the planned management. At baseline, 67 patients were classified as suspected presynaptic PS, 26 as suspected nonpresynaptic PS, and 25 as inconclusive. DAT-SPECT results were not consistent with the initial diagnosis in 36% of patients with suspected presynaptic PS (normal image) and 54% of patients with nonpresynaptic PS (abnormal image). After imaging, 19 (76%) inconclusive patients were reclassified and 16 of 118 patients (14%) were reclassified as inconclusive. Overall, imaging resulted in a change in the diagnosis in 52% of patients and in a change in management in 72% of cases. All patients with a final diagnosis of presynaptic PS had an abnormal image, whereas 94% of patients with nonpresynaptic PS had a normal scan.

At two years, 85 patients (72%) were available for follow-up.[28] In eight patients (9.4%), the neurologist was unable to provide a definite diagnosis, and in 69 of the remaining 77 patients (90%), the initial DAT-SPECT results agreed with the clinical diagnosis at follow-up. The rate of agreement was higher when the final diagnosis was presynaptic PS (97%) than when it was nonpresynaptic PS (77%). The rate of agreement between clinical diagnosis at baseline (before DAT-SPECT) and follow-up was 56%. This increased to 81% when the diagnosis after DAT-SPECT was compared with the diagnosis at follow-up. If clinical diagnosis at follow-up differed from that suggested by the initial scan (6/8 agreed to a second scan) or was inconclusive (n=8), a second DAT-SPECT scan was performed. There were discrepancies between the first and second scans in 6 of the 14 patients, and in five of these six, the initial scan was considered abnormal. The second DAT-SPECT results helped to establish a diagnosis in seven of eight patients (87.5%) with a previously inconclusive diagnosis.

Additional retrospective studies support a change in diagnosis and increase in confidence in diagnosis following DAT-SPECT. Several tertiary referral centers have reported a change in diagnosis and management for a majority of patients with CUPS.[20,21,23,29]

Other literature indicates that the level of DAT-SPECT binding does not predict disease severity or have prognostic value for the progression of motor symptoms in PD.[30,31]

Section Summary

Evidence on clinical utility of DAT-SPECT includes one well-conducted RCT, a prospective multicenter trial, and several retrospective studies that have evaluated the effect of DAT-SPECT on diagnosis of CUPS and subsequent changes in treatment. These studies report that the use of this technology can result in changes in diagnosis in a minority of patients, greater confidence in the diagnosis by the treating clinician, and changes in treatment (e.g., medication management). However, there is only one retrospective series to indicate that these changes result in improvements in health outcomes. A limitation of this evidence is the lack of a criterion standard diagnosis to evaluate whether the changes were in the direction of more accurate diagnosis and more appropriate management. For example, the RCT showed that more patients evaluated with DAT-SPECT have changes in diagnosis and management than controls without imaging; however, no improvement in quality of life was observed by the one-year follow-up. The evidence is insufficient to determine the effects of the technology on health outcomes.

DEMENTIA WITH LEWY BODIES

Clinical Validity

In a 2017 study by Shimizu, DAT-SPECT was performed in 95 AD patients and 133 DLB patients and the relationship between symptoms and DAT uptake was examined.[32] Patients with parkinsonism had significantly lower DAT uptake than AD patients in the entire striatum, entire putamen, and anterior putamen but there were no differences in any subregion of the striatum. There was a small but statistically significant correlation between severity of parkinsonism and DAT uptake in the entire striatum in patients with DBL. Other symptoms examined did not correlate with DAT uptake in any region of the striatum.

A 2015 meta-analysis by Brigo evaluated the diagnostic accuracy of DAT-SPECT to distinguish between DLB and other dementias.[33] Eight studies were included, of which three studies used histopathology as the reference standard. Studies that used clinical diagnosis as the reference standard showed diagnostic accuracy between 84-86% (ten studies) when using visual or semiquantitative analysis. The two studies using a histopathologic reference standard and visual analysis showed similar sensitivity (87%) and slightly higher specificity (92%) compared with studies that used clinical diagnosis as the reference standard. The single study that used semiquantitative analysis with histopathology as a reference standard correctly identified the 15 patients with DLB (100% sensitivity) and had 90% specificity in the identification of the eight patients with non-DLB dementia. Because only 23 patients enrolled in this study, additional research is needed to corroborate these results.

Papathanasiou reported a meta-analysis of the diagnostic accuracy of DAT-SPECT in DLB in 2012.[34] Four studies with a total of 419 patients were included in the meta-analysis (including the study by McKeith previously described). The studies included both patients with an uncertain diagnosis and patients with a certain diagnosis. Three studies used clinical diagnosis

as the reference standard while one used post mortem histopathology. The estimated pooled sensitivity of DAT-SPECT to differentiate DLB from no DLB was 86.5%, the specificity was 93.6%, and the diagnostic OR was 48.95. Funnel plot analysis showed no significant publication bias. These results might differ if the reference standard (clinical diagnosis) is flawed. The sole study to assess diagnostic accuracy in histologically verified cases (n=23) reported no false negatives and sensitivity of 100%.

The largest study to evaluate the diagnostic accuracy of DAT-SPECT for DLB is a 2007 prospective, investigator-initiated, industry-sponsored, multicenter study by McKeith, who assessed 326 patients with clinical diagnosis of probable (n=94) or possible (n=57) DLB or non-DLB (n=147).[35] In 28 patients, no diagnosis was made. The diagnoses were established by a consensus panel of three clinicians who did not have access to DAT-SPECT results, and DAT-SPECT scans were assessed visually by three nuclear medicine physicians with expertise in DAT-SPECT imaging who were unaware of the clinical diagnosis. DAT-SPECT had a mean sensitivity of 77.7% for detecting clinical probable DLB, a specificity of 90.4% for excluding non-DLB dementia, a PPV of 82.4%, and an NPV of 87.5%. This study did not use long-term clinical follow-up as the standard.

Several studies have followed patients with inconsistent results from DAT-SPECT and clinical diagnosis.

Van der Zande (2016) reported on seven (10.4%) of 67 patients who were clinically diagnosed with DLB but had normal scans.[36] In five of the seven, second DAT-SPECT scans (average 1.5 years later) were abnormal. There were no differences in baseline clinical characteristics, but patients with initially normal scans were less severely affected after one year. This study evaluated small numbers of subjects and lacked autopsy findings to confirm the diagnosis.

In 2013, Siepel reported a longitudinal study of patients who had inconsistent clinical criteria for DLB and DAT-SPECT results at baseline.[37] Fifty patients were evaluated with clinical criteria and DAT-SPECT results and followed for two to five years. Twenty-eight patients met clinical criteria for DLB or non-DLB; the remaining patients were clinically inconclusive and not included in the analysis. For 18 patients the DAT-SPECT scan and clinical criteria were concordant. Blinded analysis showed seven patients who had an abnormal scan but did not initially meet the clinical criteria for DLB developed typical clinical features over follow-up. Three patients who met clinical criteria for DLB but had a normal DAT-SPECT at baseline continued to meet clinical criteria for DLB over follow-up, indicating a false-negative scan (SWEDD) in 6% of patients. The study is limited by the small number of subjects and the lack of autopsy findings to confirm the diagnosis.

Clinical Utility

In 2015, Walker reported an industry-funded RCT to determine whether DAT-SPECT would lead to a change in diagnosis and more confidence in diagnosis in patients with probable DLB or non-DLB dementia.[38] Patients were included in the study if they were diagnosed as possible DLB by local physicians (neurologists or geriatric psychiatrists). Patients were included if they had dementia and either one core feature or one or more suggestive features of DLB. Excluded from the study were patients with: an established clinical diagnosis of probable DLB or non-DLB dementia; Parkinson features for more than one year; significant vascular pathology; severe mental or physical illness that could account for dementia; or a medication known to influence DAT-SPECT binding (including amphetamine, benatropine, bupropion, cocaine, mazindol, methylphenidate, phentermine, and sertraline). A total of 187

patients were randomized in a 2:1 ratio to have DAT-SPECT scans or clinical diagnosis alone. Onsite clinicians recorded DLB features and rated their confidence in diagnosis using a visual analog scale (VAS, 0-100). The readers, who had variable expertise, rated 57% of scans as normal and 43% as abnormal. At both 8- and 24-week follow-ups, the onsite clinicians were more likely to change the diagnosis in patients who had imaging compared with control patients (e.g., 71% revised vs 16%, $p<0.001$) and were more confident in their diagnosis ($p<0.001$). Clinicians were also more likely to change the diagnosis if the scan was abnormal than if it was normal (82% vs 46%).

Kemp (2011) conducted a retrospective study of the impact of DAT-SPECT on the clinical diagnosis and subsequent management of 80 consecutive patients with possible DLB.[39] The patients had been referred for imaging with suspected DLB by 33 specialists in older-age psychiatry working at 11 memory clinics in the U.K. All DAT-SPECT scans were interpreted visually by a single observer in conjunction with the clinical referral details and any other relevant imaging. DAT-SPECT imaging results were found to be abnormal (indicating DLB) in 20 (25%) and normal in 60 (75%) patients. Of the 20 patients with an abnormal scan, 18 had a postscan working clinical diagnosis of DLB (90%), one had a diagnosis of vascular dementia (5%), and one had no recorded outcome (5%). Fifty-eight of the 60 patients with a normal DAT-SPECT scan had an alternative clinical diagnosis (95%). Subsequent to DAT-SPECT, scan findings and diagnoses were discussed with patients and/or their caregivers in 94% of cases. Pharmacologic management affecting antipsychotic, dopaminergic, or cholinergic medication was changed in about half of the patients after the scan, although many (irrespective of the imaging results) were in the earliest phase of their disease process and did not require immediate treatment for symptoms. In addition, the small numbers did not allow substantive conclusions about changes in specific therapies.

Section Summary

Evidence of clinical utility includes one RCT that evaluated changes in diagnosis and confidence in diagnosis following DAT-SPECT imaging. This study indicates that DAT-SPECT can influence diagnosis of DLB, particularly when the scan is abnormal. It cannot be determined from this study whether the revised diagnosis was more accurate or resulted in a beneficial change in patient management. Longer follow-up of patients in this study may lead to greater certainty regarding the effect of this technology on health outcomes.

PRACTICE GUIDELINE SUMMARY

AMERICAN COLLEGE OF RADIOLOGY

The American College of Radiology (ACR) published appropriateness criteria for dementia and movement disorders in 2015.[40] ACR states that the diagnosis of idiopathic PD is usually based on patient history and physical examination alone and that, when clinical signs and symptoms and response to medication are typical of PD, neuroimaging is not required. In patients with unusual clinical features, incomplete or uncertain medication responsiveness, or clinical diagnostic uncertainty, imaging to exclude alternative pathologies may be indicated. ACR states that positron emission tomography and SPECT tracer studies exploring the presynaptic nigrostriatal terminal function and the postsynaptic dopamine receptors have been unable to reliably classify the various PSs and may not reliably measure disease progression. Use of DAT-SPECT was rated as “may be appropriate” to evaluate suspected DLB or PD with either typical or atypical clinical features.

AMERICAN ACADEMY OF NEUROLOGY

The 2006 practice parameters (reaffirmed in July 2013) from the American Academy of Neurology state that β-CIT and IBZM (iodobenzamide) SPECT are possibly useful in distinguishing PD from essential tremor (ET; five class III studies).[41] There was insufficient evidence to determine if these modalities are useful in distinguishing PD from other forms of Parkinsonism.

MOVEMENT DISORDERS SOCIETY

The Movement Disorder Society's (MDS) diagnostic criteria for PD from 2015 are intended for use in clinical research but may be used to guide clinical diagnosis.[42] MDS considers clinical expert opinion to be the criterion standard to diagnose PD and that diagnoses are usually made clinically without need for ancillary diagnostic testing. Methods that may become available as knowledge advances are diagnostic biochemical markers, anatomical neuroimaging, and methods to detect alpha-synuclein deposition. MDS noted that, although dopaminergic neuroimaging can help to distinguish parkinsonism from PD mimics like ET, "it does not qualify as a criterion for the differentiation of PD from other parkinsonian conditions like atypical parkinsonian syndromes." Normal functional neuroimaging of the presynaptic dopaminergic system is also listed as criteria for exclusion from diagnosis of PD in patients with early/de novo PD.[43]

SOCIETY OF NUCLEAR MEDICINE AND MOLECULAR IMAGING

The Society of Nuclear Medicine and Molecular Imaging (previously known as the International Society of Nuclear Medicine), provided a practice guideline for DAT imaging with SPECT in 2011.[4] The guideline states that the main indication for DAT-SPECT is striatal DAT visualization in the evaluation of adult patients with suspected PS to help differentiate ET from tremor due to presynaptic PS (PD, multiple-system atrophy, progressive supranuclear palsy). However, the pattern of ^{123}I-ioflupane uptake cannot discriminate between the latter disorders with any high degree of accuracy.

Other indications are the early diagnosis of presynaptic PS, differentiation of presynaptic PS from parkinsonism without presynaptic dopaminergic loss (e.g., drug-induced parkinsonism, psychogenic parkinsonism), and differentiation of DLB from AD. The guidance states that visual interpretation of the scan is usually sufficient for clinical evaluation, where the striatal shape, extent, symmetry, and intensity differentiate normal from abnormal. For semiquantitative analysis, each site should establish its own reference range by scanning a population of healthy controls or by calibrating its procedure with another center that has a reference database.

SUMMARY

It appears that dopamine transporter single-photon emission computed tomography (DAT-SPECT) may improve health outcomes for people with a suspected diagnosis of Parkinson disease or dementia with Lewy bodies. Clinical guidelines based on research recommend DAT-SPECT for certain indications. Therefore, DAT-SPECT may be considered medically necessary for a suspected diagnosis of Parkinson disease or dementia with Lewy bodies when policy criteria are met.

In all other situations, there is not enough research to show that dopamine transporter single-photon emission computed tomography (DAT-SPECT) improves health outcomes. Therefore, DAT-SPECT is considered investigational for all other indications.

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CODES

Codes	Number	Description
CPT	78607	Brain imaging, tomographic (SPECT)
HCPCS	A9584	Iodine I-123 ioflupane, diagnostic, per study dose, up to 5 millicuries

Date of Origin: *January 2016*