

Single Photon Emission Computerized Tomography (SPECT) Use in Clinical Psychiatry — Justified?

By

WorkSafeBC Evidence-Based Practice Group

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About this report

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The Evidence-Based Practice Group was established to address the many medical and policy issues that WorkSafeBC officers deal with on a regular basis. Members apply established techniques of critical appraisal and evidence-based review of topics solicited from both WorkSafeBC staff and other interested parties such as surgeons, medical specialists, and rehabilitation providers.

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Background

Besides its use in nuclear cardiology, neurology, cancer and spine imaging, Single Photon Emission Computerized Tomography (SPECT) – a functional nuclear imaging technique – is becoming used more frequently for diagnosis and pharmaceutical management of patients with a number of clinical psychiatric conditions. The trend would appear to be led by various brain imaging clinics in the United States.

There are innumerable techniques that are employed for brain imaging. Some focus on brain structure (e.g. standard axial Computed Tomography (CT) and Magnetic Resonance Imaging (MRI)), while others focus on the functionality of the brain (e.g. Magnetoencephalography (MEG), Functional Magnetic Resonance Imaging (fMRI), Magnetic Resonance Spectroscopy (MRS), Positron Emission Tomography (PET) and Single Photon Emission Computerized Tomography (SPECT)). Functional neuroimaging techniques, which inform us about brain activity and chemistry, may measure markers such as electrical or magnetic signals, biochemical neural transmissions, and tissue blood flow.^{1,2}

SPECT employs the use of radioactive materials (radiotracers) to assess the physiologic properties of organ systems (e.g. blood flow, glucose metabolism, or protein aggregates). While planar single photon emission displays a single view of radiotracer distribution in patients (thyroid, ventilation/perfusion, or whole-body bone images); SPECT can display slice (2-dimensional) or volume (3-dimensional) images of radiotracer distribution, which is computed from multiple images taken with multiple cameras.³ An overview of the technical aspects of SPECT technology was presented at the TRIUMF Summer Institute (2007).⁴ FDA-approved radiotracers for brain SPECT scan include Tc-99m HMPAO (Hexamethyl propyleneamine oxime), Tc-99m ECD (ethyl cysteinate dimer), I-123 isopropylidoamphetamine (IMP), and thallium-201 diethyldithiocarbamate (Tl-201 DDC).⁵ In recent years, combination (hybrid) technologies using SPECT imaging have been developed; such as SPECT/CT, which superimposes data from the grey CT and colour-coded SPECT images, and can lead to more accurate diagnoses.⁶

SPECT scanning is commonly used for cancer imaging (e.g. breast, prostate cancers), spine imaging (e.g. back pain), nuclear cardiology (e.g. myocardial perfusion imaging), and nuclear neurology (e.g. Alzheimer's and Parkinson's diseases, epilepsy, cerebrovascular diseases, brain tumour diagnosis and assessments). One advantage of brain SPECT may be an increased chance of defining and measuring neural pathology earlier, as "...functional impairment in cerebral diseases often precedes structural changes."⁷ The recent trend in using functional brain imaging (PET, SPECT, fMRI, etc.) in psychiatry may be due to newly emerging treatment modalities, which work only for certain categories and for earlier stages of some psychiatric/neuropsychiatric disorders (e.g. schizophrenia, Alzheimer's disease (AD)). Most functional brain imaging techniques require either hospital or large clinical settings, and the technology is quite expensive; whereas SPECT technology costs may be

more affordable.⁸ “There are no regulations that prohibit individual physicians from installing and using SPECT equipment in their offices, provided they have satisfied regulatory requirements.”⁹

Brain imaging is especially useful when there is a well defined organic basis for disease; such as is the case for brain tumour, stroke, brain injury, encephalitis, Alzheimer’s and Parkinson’s diseases, multiple sclerosis, or temporal lobe epilepsy. Patients with these conditions may present at clinics with some psychiatric symptoms as well (e.g. delusions, hallucinations, illusions, depression, mania, obsessive compulsive symptoms, or aggression).¹⁰ Some authors note that PET or SPECT scans may detect functional alterations in neurodegenerative diseases even if CT or MRI scans show no structural abnormalities.¹¹ On the US National Institute of Neurological Disorders and Stroke website it is stated that brain imaging diagnostic techniques and procedures “will continue to be important clinical research tools for confirming a neurological disorder, charting disease progression, and monitoring therapeutic effect.”¹²

However, as many authors have noted, the diagnostic accuracy of SPECT in identifying various neuropsychiatric disorders is inconsistent. For example, in one study where SPECT was used for the diagnosis of Alzheimer’s disease (AD), the sensitivity was 63% and specificity was 93%;¹³ whereas when Dougall et al. studied the diagnostic accuracy of SPECT for AD (2004), they found the sensitivity to be 74% and specificity 91%.¹⁴ A recent (2009) meta-analysis found the sensitivity and specificity of SPECT in predicting the conversion of mild cognitive impairment to AD to be 83.8% and 70.4%, respectively.¹⁵ Nevertheless, studies suggest that SPECT may be useful in discriminating AD from other types of dementia.¹⁴

A report on traumatic brain injury by the Workplace Safety and Insurance Appeals Tribunal (WSIAT) of Ontario (Canada) states that, “It is inappropriate to use SPECT findings as confirmatory evidence that there is brain damage, or that any abnormal findings are the result of previous trauma, or to use SPECT as evidence to provide support for abnormal psychological findings.”¹⁶

When a radiotracer (e.g. ^{99m}Tc) carried by a chemical such as HMPAO (Hexamethyl propyleneamine oxime) is injected into the blood stream of a patient for SPECT scanning, the distribution of the gamma rays it emits can be detected by a scanner (single photon tomography) and reflect “...the regional blood flow (“perfusion”) and glucose metabolism, and thus can provide some information about the functional integrity (not anatomical integrity) of various brain areas at the time of the scan.” However, “...areas of decreased radio-tracer uptake in a SPECT scan may simply represent temporary metabolic changes, and do not necessarily represent areas of permanent anatomical or cellular damage, nor do they predict clinical outcome.”¹⁶

A National Institute of Mental Health (NIMH) report states that brain scans may be “used with other medical tests to help doctors find the right diagnosis for mood and behavioral problems” and may “help researchers study healthy brain development, effects of mental illnesses or effects of mental

health treatments on the brain”); but cannot be used alone to diagnose a mental disorder (e.g. autism, anxiety, depression, schizophrenia, or bipolar disorder) or to predict the risk of getting a mental illness. The same report also warns about health risks due to the radiation exposure from brain scans.²

Objective

Recently, a WorkSafeBC (Workers' Compensation Board of British Columbia) consultant psychiatrist requested a rapid review on the scientific basis for the utilization of Single Photon Emission Computerized Tomography (SPECT) scans in clinical psychiatry. He inquired if there were any psychiatric conditions for which the information obtained from a SPECT scan would change treatment decisions and management.

“Brain scan clinics” are common in the US. The clinics run by Dr. Amen advocate the use of SPECT scans in brain assessments and in determining treatment for a range of neurologic and psychiatric conditions such as attention-deficit hyperactivity disorder, anxiety and depression, brain trauma, substance abuse, Alzheimer's disease and memory loss, marital problems, aggression, and autism. The Amen Clinic's website states their goal, “To help change your brain so that you may change your life.”¹⁷ On another brain scan clinic's website it is stated that, “Our clinic and other clinics around the country have correlated neurological, psychiatric, and behavioral states with specific brain SPECT patterns. Information from your scan will help your doctor understand your unique brain pattern and treatment needs.”¹⁸

The US National Institute of Mental Health website specifically points out that brain scans cannot “diagnose mental illness when used by themselves” and cannot “predict risk of getting mental illness.”²

According to our consultant psychiatrist, there is a trend of increasing requests for “brain SPECT scan” for psychiatric conditions in British Columbia, Canada, and this therefore may soon become a coverage policy issue for WorkSafeBC. This preliminary review of the topic will provide a baseline resource for any future decision making processes.

Methods

Study selection criteria

We undertook a literature search on SPECT as a diagnostic test and assessment tool. Studies with human subjects, of all possible study designs, were included, with the exception of conference abstracts and single-subject case reports. Only articles published in English from the year 2000 onwards were included. Changes identified by SPECT scans in the brain tissue of patients with various psychiatric/neuropsychiatric conditions and changes in treatment modalities of psychiatric conditions based on SPECT scan findings were the outcomes of interest.

Search strategy

We searched the OVID SP database, including EBM reviews (ACP Journal Club, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, Cochrane Methodology Register, Health Technology Assessment, NHS Economic Evaluation Database), EMBASE, Health and Psychosocial Instruments, International Pharmaceutical Abstracts, Ovid MEDLINE®, Ovid MEDLINE® in Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily, and Ovid OLDMEDLINE®, with the key words [“SPECT”, “SPECT scan”, “Single Photon Emission Computerized Tomography”] AND [“mental disorder”, “mental illness”, “mental condition”, “psychiatric disorder”, “psychiatric illness”, “psychiatric condition”]. We found 104 citations, then limited our search to English language publications of studies on human subjects from the year 2000 onwards, resulting in 26 citations. After discarding duplicates and case reports, we collected the full text of the remaining 7 articles. In addition to OVID SP, we searched the PsycINFO database with the same keywords and strategy, resulting in 653 citations. We then introduced two additional limits to the PsycINFO search (age group: over 13; methodology: brain imaging). This reduced the number of citations to 36. Abstracts were screened for relevance and single case reports were excluded. The full text of 24 articles were collected. Fourteen additional articles were identified and collected through hand searching. In total, we collected 45 full text articles. There were 3 systematic reviews/meta-analyses, 9 clinical trials (1 crossover, 8 before/after designs), 26 observational studies (mostly cross-sectional – either snapshots or repeated over time), and 7 narrative reviews. (Appendix 1)

In addition to database searching, we explored grey literature sources for health technology assessment reports, guidelines, or policies regarding SPECT, and searched the websites of the Agency for Healthcare Research and Quality (AHRQ), the American Academy of Neurology (AAN), the American Psychiatric Association (APA), the National Institute of Mental Health (NIMH), the American College of Radiology (ACR), the Society of Nuclear Medicine, the Canadian Association of Radiologists (CAR), the Canadian Agency for Drugs and Technologies in Health (CADTH), the National Institute for Health Research/Health Technology Assessment (NIHR/HTA), the Instituto de Efectividad Clínica y Sanitaria (IECS), the US Department of Veterans Affairs (VA), and the Cochrane Library HTA database.

We also searched websites of private health insurance companies (Aetna, Regence, Highmark, Anthem, and Empire) for their coverage policies on SPECT scan imaging.^{5,19,20,21,22}

Results

SPECT scan studies

Clinical psychiatric/neuropsychiatric conditions explored by brain SPECT:

- *Pharmaceutical implications*
 - Treatment effects of psychiatric drugs
 - Schizophrenia^{23,24,25,26}
 - Major Depression^{27,28,29}
 - Obsessive-compulsive disorder³⁰
 - Social Anxiety Disorder³¹
 - Social phobia³²
 - Psychiatric illness³³
 - Possibility of predicting treatment responses to psychiatric drugs
 - Major Depression^{34,35}
 - PTSD³⁶
- *Clinical implications*
 - Enlightening physiopathology/causal pathways in psychiatric/neuropsychiatric conditions
 - Schizophrenia^{37,38}
 - Major depression^{39,40,41,42,43,44,45}
 - Addiction^{46,47}
 - Alzheimer's Disease^{48,49,50,51}
 - Bipolar disorder^{52,53}
 - Somatisation disorder⁵⁴
 - Alcoholism⁵⁵
 - Borderline personality disorder⁵⁶
 - Differential diagnosis of neuropsychiatric conditions
 - Alzheimer's and Vascular Dementia¹⁴
 - Dementia with Lewy bodies⁵⁷
 - Alzheimer's and dementia with Lewy bodies⁵⁸
 - Measuring severity/staging of psychiatric/neuropsychiatric conditions; making treatment choices
 - Frontotemporal Dementia (FTD)⁵⁹
 - Frontotemporal lobar dementia (FTLD)⁶⁰
 - Chronic alcoholism⁶¹
 - Alzheimer's disease⁶²
 - Predicting progress of a psychiatric/neuropsychiatric conditions
 - Alzheimer's and Dementia with Lewy bodies⁶³

- *REM sleep behavioural disorder*⁶⁴
 - Predicting risk of developing new conditions in addition to already existing psychiatric conditions
 - *Addiction*⁶⁵
 - A review paper by Camargo (2001) summarizes disorders for which studies with SPECT have been undertaken. The neurologic disorders listed were cerebrovascular diseases, dementias, epilepsy, head trauma, cerebral neoplasms, and movement disorders. Psychiatric disorders listed were obsessive-compulsive disorder, Gilles de la Tourette's Syndrome, schizophrenia, unipolar depression, panic disorder, and psychoactive substance abuse and dependence.⁶⁶
- Out of the 45 full text articles reviewed (obtained from Ovid, PsycINFO, and hand-search of the references of collected articles), 27% were on major depression, 25% were on Alzheimer's disease and other dementia, 14% were on schizophrenia, 11% were on addiction/alcoholism, and 23% were on other disorders (e.g. bipolar disorder, obsessive compulsive disorder, somatisation disorder, social phobia, REM sleep behavioral disorder, or PTSD).

SPECT for specific psychiatric/neuropsychiatric disorders

Canadian researchers Zipursky et al. published a narrative paper in the Canadian Journal of Psychiatry, in 2007. They reviewed findings from recent PET and SPECT studies, which focused on the pathophysiology and treatment of schizophrenia, depression, and dementia. The reviewed studies pointed out that there was a “dopamine system dysregulation” in patients with schizophrenia, and when dopamine D₂ receptors were blocked, an antipsychotic response was observed. Patients with depression showed “loss of monoamines”, and the blockade of serotonin transporter receptors led to an antidepressant response. Cerebral glucose metabolism and perfusion imaging became part of the diagnostic workup for dementia; and discoveries of new radioligands binding to cerebral amyloid deposits were expected to likely help early diagnosis of AD. Although they referred to the clinical limitations of the findings from these PET and SPECT imaging studies (e.g. some schizophrenia patients did not respond to the D₂ receptor blockade and some depression patients did not respond to the serotonin transporter receptor blockade treatments) they concluded that these imaging techniques are likely to become essential tools for the management of psychiatric disorders in the future.⁶⁷

In the guest editorial of the same issue of the Canadian Journal of Psychiatry, Dr. Zipursky wrote: “The magnitude of structural brain abnormalities and the degree to which they change over time may to some degree reflect risk but are likely to be only minor determinants of the variance in outcome.” Regarding structural brain imaging in schizophrenia, he pointed out that the interpretations should be questioned due to the very modest magnitude of findings in treatment outcomes, the massive degree of overlap with the normal population, and the “questionable progression of changes” over time. Although the author noted the role of functional brain imaging with PET and SPECT in the differential diagnosis of dementia, and in exploring the actions of antipsychotic and antidepressant medications, he underlined that we have a very immature understanding of “how receptor binding relates to symptom improvement”. He concluded that even though there had been progress in brain imaging together with molecular genetics, there are great conceptual, technical, and statistical challenges ahead for future psychiatric research.⁶⁸

Alzheimer’s disease (AD)

A 2010 paper by Weih et al. states that the value of brain perfusion SPECT (which shows an altered characteristic temporoparietal pattern) for diagnosis of Alzheimer’s disease (AD) is not as accurate as recently developed techniques using pathophysiology-based biomarkers, such as cerebrospinal fluid (CSF) and Amyloid-PET tracers. The authors state that the value of SPECT in early diagnosis of AD is even less. The authors conclude that the sensitivity of SPECT for AD is “most likely below the desired threshold of a valid biomarker,” but its high specificity makes SPECT “at least a useful diagnostic tool to rule out AD.” They also mention uncertainty about the “AD pattern” captured by a SPECT perfusion scan: whether it “merely reflects cortical neurodegeneration or the secondary cholinergic deficit following degeneration of the basal nucleus of Meynert”.⁵¹

Tartaglia's paper (2011) states that although traditionally the role of brain imaging in dementia has been in ruling out other conditions (treatable and reversible), in the future, it is likely that multiple brain imaging techniques will be used concurrently to identify pathophysiology in the brain and to predict and manage pharmacotherapy of patients.⁶⁹

However, a position paper by Dubois et al. (2007), revising the National Institute of Neurological Disorders and Stroke–Alzheimer's Disease and Related Disorders (NINCDS-ADRDA) criteria, states the core diagnostic criterion to be early episodic memory impairment. If this core criterion is accompanied by one or more supportive features (one of them being PET functional neuroimaging, which shows reduced glucose metabolism in bilateral temporal parietal regions), it is accepted to be "probable AD". If both clinical and histopathological evidence or both clinical and genetic evidence is available, it is accepted to be "definite AD". SPECT findings are not accepted, because estimates of its diagnostic accuracy are below the 80% requirement of the Reagan Biomarker Working Group.⁷⁰

Major Depressive Disorder (MDD)

Fitzgerald et al. undertook a meta-analysis of studies investigating brain regions involved in the pathophysiology of patients with major depressive disorder (MDD). They selected articles which reported on brain imaging techniques (i.e. fMRI, PET and SPECT). The process revealed three potential groups of studies: (1) resting studies (studies conducted at rest); (2) treatment studies (treatment with a selective serotonin reuptake inhibitor (SSRI) antidepressant medication; and (3) emotional activation studies (studies of the brain response to stimuli designed to activate emotion-related brain circuitry). The authors found that there was "limited overlap between the brain regions identified using differing imaging methods." They concluded that "the study has identified a complex network of brain regions involved in the pathophysiology of MDD" and they invited future researchers "in particular to try and delineate the brain areas involved in the primary pathophysiological change and areas in which changes may be secondary."⁴²

Schizophrenia

In a paper published in the *Annals of Nuclear Medicine* (2002), Frankle and Laruelle reviewed literature on molecular imaging in schizophrenia (studying receptors, transporters and enzymes, as well as other cellular processes). They grouped the reviewed papers into two categories: (1) clinical studies (focusing on pathophysiology; comparing PET and SPECT findings from schizophrenia patients and normal controls), and (2) occupancy studies (focusing on the mechanisms of action of different treatment modalities). They characterized the clinical and occupancy studies based on whether the dopamine or serotonin system was investigated. The authors noted that pharmaceutical companies had been highly interested in PET and SPECT studies, both for assessing "in vivo properties of currently marketed drugs as well as to help with the development of new medications

for psychiatric conditions.” The authors pointed out that with the addition of new radiotracers, the application of molecular imaging in psychiatry would further develop.²⁴

One pharmacological study by Stone et al. (2009) pooled original “patient PET and SPECT receptor imaging data” of patients with schizophrenia. They aimed to better understand the mechanisms of action of antipsychotic drugs in vivo in this patient group. They found that “the clinically efficacious dose of antipsychotic drugs is related to dopamine D₂/D₃ receptor occupancy in cortical brain regions” (i.e. temporal cortex); and D₂/D₃ binding in striatal subregions was likely to have a therapeutic role, but was also related with extrapyramidal side effects. They observed no correlation between 5HT_{2A} receptor (a subtype in the serotonin receptor family) occupancy and clinically effective therapeutic doses of the antipsychotic drugs.²⁶

In 2009, Howes et al. published a paper outlining findings from PET and SPECT studies that offered insights into the underlying mechanisms of psychosis and treatment response in schizophrenia. The authors focused on studies using PET and SPECT in attempting to identify the pathophysiology of the dopaminergic dysfunction in patients with schizophrenia. They concluded that “schizophrenia is characterised by marked increases in presynaptic dopamine availability and release - which may indeed constitute the primary dopaminergic pathology”; but findings regarding “alterations in the density of post-synaptic D₂/D₃ receptors are less convincing.” They noted that “currently available antipsychotic drugs act downstream at D₂ receptors on postsynaptic terminals” and new therapeutic studies should focus on compounds, which would work upstream and aim to correct “presynaptic hyperdopaminergia”. They anticipated that future PET/SPECT imaging studies would be able to use new radioligands to investigate the role of non-dopaminergic neurotransmitter systems in schizophrenia.²⁵

Major pitfalls of SPECT use in clinical psychiatric research

- Significant levels of radiation (not only for patients; but also for healthy controls)
- Ever-changing imaging techniques (new emerging tracers, etc.) lead to different acquisition and analytic techniques by different study groups, which in return makes study comparisons impossible
- Difficulty in finding/enrolling psychiatric patients to studies with no medical treatment at the baseline
- Failing to distinguish if the observed pathophysiologic finding in SPECT is a trait marker of a psychiatric condition or secondary to an existing situation (starvation, previously used medication, co-existing physical/psychological disorders, etc.)
- Differences in quality of SPECT based on technical factors (i.e. physical performance of the instrument, timing of the tracer injection, duration of scanning, attenuation, patient movement). The quality of the scan images used for the study should be compatible to the current disease-specific SPECT image patterns that construct the norms in the current peer-reviewed literature.
- Expense of the imaging test. The Amen Clinics website states the cost of two SPECT scans as \$1100 and the overall cost of assessment, which includes two SPECT scans doctor evaluations and follow up as \$3,575.⁷¹
- To our knowledge, in British Columbia (BC), Canada, SPECT scanning is not available in private settings and the cost based on the Medical Services Commission fee code (09871) in the provincial healthcare system is \$345.18 (as of April 2011).⁷²

Health insurance companies – SPECT coverage

In private health insurance systems, the member's contract benefits which are in effect at the time of service determine coverage decisions; hence, the following policy examples do not imply coverage or non-coverage of SPECT scan imaging by the noted insurance companies.

Regence considers SPECT as “investigational for evaluation of ADHD, dementias, and all other psychiatric conditions.” They state that currently available studies are preliminary and have not added to the body of knowledge with regards to the clinical utility of SPECT in diagnosis and management of ADHD, dementias or other psychiatric conditions. They refer to the clinical practice guidelines from The American Academy of Child and Adolescent Psychiatry (AACAP) and the American Academy of Neurology (AAN) and conclude that “there is no evidence to support clinical use of neuroimaging in the diagnosis and management of psychiatric conditions.”¹⁹

Aetna considers SPECT use for diagnosis or assessment of the following noncardiac conditions “experimental and investigational”: ADHD, autism, personality disorders (e.g. aggressive and violent behaviors, anti-social personality disorder including psychopathy, schizotypal personality disorder, borderline personality disorder), schizophrenia, stroke, differential diagnosis of Parkinson's disease, initial or differential diagnosis of dementia (e.g. Alzheimer's disease, dementia with Lewy bodies, frontotemporal dementia, and vascular dementia), prosthetic graft infection, scanning of internal carotid artery during temporary balloon occlusion, and vasculitis.⁵

Empire and **Anthem** consider SPECT scans “not medically necessary” for the evaluation or management of cerebrovascular accident (CVA, stroke), subarachnoid hemorrhage, or transient ischemic attack, and “investigational and not medically necessary” for all noncardiovascular indications, including ADHD, chronic fatigue syndrome, and neuropsychiatric disorders without evidence of cerebrovascular disease.^{21,22}

Highmark considers SPECT scans eligible for reimbursement for selected CPT (current procedural terminology) codes related to various liver, bone, brain, and kidney diseases, and tumour and abscess localization. SPECT scans for any conditions other than those listed above are considered “not medically necessary”.²⁰

Institutional guidelines and reports

Canada

Public Health Agency of Canada

The Public Health Agency of Canada has produced a publication entitled “Schizophrenia: A Handbook for Families”. In the section *Research: The Hope For Tomorrow/New Resources*, “imaging facilities” are included amongst the basic science laboratories, brain tissue banks, and genetic laboratories.⁷³ Included in Appendix III of the publication is a list of various brain imaging techniques. In the section *Techniques That Measure Function*, SPECT is mentioned as a promising technique “to monitor the effects of treatment and mechanisms of drug action” as tracers appropriate for imaging entire neurotransmitter systems are being developed. This document also points out the opportunities for the research community as “SPECT and PET have the advantage of being able to evaluate a large group of samples rapidly.”⁸

Canadian Agency for Drugs and Technologies in Health (CADTH)

CADTH has completed two environmental scans as part of the CADTH Medical Isotopes Project.

One of these environmental scans, “Future Alternatives to Molybdenum-99 Production for Medical Imaging” touches upon SPECT. Technetium-99m (^{99m}Tc), one of the most commonly used SPECT radiotracers, is generated from Molybdenum-99 (^{99}Mo). This CADTH report – a response to supply disruption – aims to “identify new and emerging technologies that may play a role in providing either solutions to the supply issue of ^{99}Mo or alternate technologies that circumvent the need for nuclear reactor-based ^{99}Mo over the next five to 15 years.” After reviewing various medical imaging technologies (including hybrid ones) in three categories – available, emerging (“not yet adopted by the health care system, usually in phase 2 or 3 clinical trials or pre-launch”), and investigational (“either at the conceptual stage, anticipated, or in early stages of development, through to a technology that is undergoing bench or laboratory testing”) – the authors suggest three solution options: “(1) Building new, or modifying existing, nuclear reactors and accelerators to produce medical isotopes, (2) Producing new and emerging medical imaging devices that bypass or minimize the need for reactor-produced ^{99m}Tc , (3) Developing alternative isotopes that do not rely on existing nuclear reactor infrastructures.” The authors also underline that even if technologies identified may have a potential for future adoption, there are various factors to determine clinical acceptance, such as cost, reimbursement, and difficulty in replacing established modalities (in terms of capital, infrastructural, and technological investment). In the “Development of Alternative Isotopes” part of the report, another new SPECT tracer agent for imaging of the noradrenaline and peripheral benzodiazepine receptors, being developed by researchers from the University of Glasgow in Scotland, is mentioned.⁷⁴ The authors refer to these researchers, who are “developing radioiodinated compounds for SPECT imaging of neurological receptors that are implicated in a range of

neurological disorders such as clinical depression, Parkinson disease, Alzheimer disease, anxiety, and stroke” and note that “the success of this project may lead to imaging agents with greater selectivity for the peripheral benzodiazepine receptor.” The authors also mentioned Iodine-123 (¹²³I) – an established agent for brain, kidney and thyroid imaging – as now being explored for its diagnostic capacity in myocardial imaging, cerebral blood flow, and neurological diseases (e.g. Parkinson’s disease and dementia). Studies utilizing ¹²³I to image serotonin transporters for various psychiatric disorders were also mentioned.⁷⁵

The other CADTH environmental scan is titled “The Global Impact of Technetium-99M Supply Disruptions”. They report: “Since 2007, there have been a number of medical isotope supply disruptions that have had a severe impact on the delivery of nuclear medicine. To minimize the effect on patient care, the nuclear medicine community has employed a number of mitigation strategies. Common approaches include prioritizing patients, rescheduling non-urgent scans, and referring patients to alternate diagnostic modalities where possible.”⁷⁶

CADTH has also published a health technology assessment report on the clinical- and cost-effectiveness of PET and SPECT for the management of dementia.⁷⁷ This report addresses two research questions: (1) What are the differences in the management of dementia when diagnosed with PET or SPECT? and (2) What is the cost-effectiveness of PET versus SPECT for the diagnosis of dementia? Their literature search was limited to articles in English published between 2004 and May 2009. They identified two health technology assessments, one systematic review, and two cost-effectiveness papers on the topic. One of the HTA reports was on PET services in Belgium (not SPECT).⁷⁸ The other cited HTA report was by the AHRQ and was titled “Positron Emission Tomography, Single Photon Emission Computed Tomography, Computed Tomography, Functional Magnetic Resonance Imaging, and Magnetic Resonance Spectroscopy and for the Diagnosis and Management Of Alzheimer’s Dementia.” The major focus of this report was PET, but it also included annotated bibliographies of identified SPECT studies.⁷⁹ The systematic review was from the Swedish Council on Technology Assessment (report on “Diagnosing Dementia Disorders”)⁸⁰ and the two cost-effectiveness reports were by Moulin-Romsee (2005)⁸¹ and the IECS (report by Ferrante, 2004).^{82,83} The Moulin-Romsee paper is on the cost-effectiveness of F-fluoro-deoxyglucose positron emission tomography (FDG PET), and therefore has not been reviewed; however, the IECS report has been summarized elsewhere in the text.

British Columbia

Aside from “Anxiety and Depression in Children and Youth - Diagnosis and Treatment guideline”, and “Primary Care Management of Sleep Complaints in Adults”, the only other guideline on the BC Ministry of Health Services website relating to a psychiatric disorder is “Depression (MDD) – Diagnosis and Management”(2004).⁸⁴ There is no mention of brain imaging or SPECT in this guideline for the diagnosis and management of major depressive disorder (MDD). MDD diagnosis is based on criteria from the DSM-IV-TR. There is one other BC guideline on dementia, titled

“Cognitive Impairment in the Elderly - Recognition, Diagnosis and Management”. In the neuroimaging section, only “CT or MRI of head” is mentioned; though not for routine use. It is indicated that these imaging tools may be useful when the patient’s age is less than 60, if there is an abrupt onset or rapid progression of the impairment, history of a significant/recent head injury, atypical presentation or uncertain diagnosis, cancer history, new localizing neurological signs or symptoms, suspected vascular dementia, bleeding disorder, use of anticoagulants, urinary incontinence, or early presentation of a gait disorder.⁸⁵

Other jurisdictions

American Psychiatric Association (APA)

The American Psychiatric Association (APA) Practice Guideline for Psychiatric Evaluation of Adults (2006) mentions brain imaging tests “to ascertain the presence of a structural neurological abnormality.” Under Section 4 (Use of diagnostic tests, including psychological and neuropsychological tests), in Table 4 (Tests That May Be Indicated as Part of a Psychiatric Evaluation), the notes regarding imaging studies state that, “Structural (e.g., computed tomography [CT], magnetic resonance imaging [MRI]) and functional (e.g., positron emission tomography [PET], single photon emission computed tomography [SPECT], electroencephalogram [EEG], functional magnetic resonance imaging [fMRI]) studies may indicate regional brain abnormalities related to a psychiatric illness and its management.”⁸⁶

Another APA Practice Guideline for the Treatment of Patients with Major Depressive Disorder, Third Edition (2010), Part C: Future Research Needs section concludes, “In time, brain imaging, genomics, proteomics, and other recent advances in neuroscience should help us ‘carve nature along its joints,’ allowing major depressive disorder to be broken into discrete diseases with defined and personalized treatments. In the meantime, clinical investigation focused on existing and novel treatment strategies remains essential.”⁸⁷

The APA Council on Children, Adolescents, and their Families prepared a resource document in 2005, “Brain Imaging and Child and Adolescent Psychiatry With Special Emphasis on Single Photon Emission Computed Tomography (SPECT)”. They stated that, “Although knowledge is increasing regarding specific pathways and specific brain areas involved in mental disease states, at present the use of brain imaging to study psychiatric disorders is still considered a research tool.” and, “Specifically, no published investigation in the field has determined that any structural or functional brain abnormality is specific to a single psychiatric disorder. Additionally, imaging studies examine groups of patients and groups of healthy controls; therefore, findings may not apply to all individuals with a given disorder.”⁹

American Academy of Neurology (AAN)

The Quality Standards Subcommittee of the American Academy of Neurology (AAN) presented a practice parameter on the diagnosis of dementia (2001). They state that to assess the value of SPECT in the differential diagnosis of dementia, they identified two SPECT studies with autopsy-confirmed diagnoses in a large number of subjects. The figures were encouraging, but not consistently better than those obtained by diagnosis with established clinical criteria. The practice recommendation on SPECT was: “For patients with suspected dementia, SPECT cannot be recommended for routine use in either initial or differential diagnosis as it has not demonstrated superiority to clinical criteria.”⁸⁸

US Agency for Healthcare Research and Quality (AHRQ)

The US Agency for Healthcare Research and Quality (AHRQ) National Guideline Clearinghouse published a technology assessment report (2004) on the utilization of brain imaging techniques in the diagnosis and management of Alzheimer’s dementia.⁷⁹ The report is also available through the Cochrane Health Technology Assessment database as a structured abstract.⁸⁹ While the AHRQ found no evidence for supporting PET use in differential diagnosis for AD, they found FDG-PET likely to be valuable for distinguishing patients with mild cognitive impairment who rapidly convert to frank AD. SPECT was only mentioned in this report in the form of an annotated bibliography of the relevant studies, which did not include any conclusions.

The AHRQ also presents a guideline synthesis of three guidelines on “Diagnosis and Assessment of Alzheimer's Disease and Related Dementias” (European Federation of Neurologic Studies (EFNS) (2007), Scottish Intercollegiate Guidelines Network (SIGN) (2006), and Singapore Ministry of Health (SMOH) (2007)), on their National Guideline Clearinghouse website. Regarding neuroimaging, the synthesis report states that, “There is overall agreement that imaging can be used to detect reversible causes of dementia (e.g., surgically treatable lesions such as subdural hematomas, cerebral tumors, and normal pressure hydrocephalus), to aid in the differential diagnosis of dementia, and to determine the etiology of the dementia. There is also agreement that functional imaging tests (e.g., SPECT, PET) can be useful in conjunction with structural imaging tests in cases where there is diagnostic uncertainty. With regard to populations in whom neuroimaging should be performed, EFNS and SIGN agree that structural imaging tests (e.g., CT, MRI) should be routinely used in the diagnostic evaluation of all patients with suspected dementia. According to SMOH, there is no consensus regarding whether all patients with dementia require structural imaging. Referring to criteria outlined by the Canadian Consensus Conference on the Assessment of Dementia (CCCAD) for undertaking a CT scan of the head, SMOH recommends an initial CT scan be performed for patients with mild to moderate dementia; but not for patients with advanced dementia of a long duration (>2 years based on CCCAD's recommendations). They add that if the clinician is not inclined to perform a brain scan, there is immense value in discussing the matter with the caregivers and in securing their agreement not to order a neuroimaging procedure.”⁹⁰

American College of Radiology (ACR)

The ACR “Practice Guideline for the performance of SPECT brain perfusion and brain death studies” (2007) lists the clinical indications for SPECT brain perfusion studies as: detection/evaluation of cerebrovascular diseases, differentiation of lacunar/non-lacunar infarctions, prognosis prediction of cerebral accident patients, evaluating patients with ischemic attacks or suspected dementia, preoperative location diagnosis of epileptic foci, evaluating traumatic brain injury, diagnosing encephalitis, follow up of a subarachnoid hemorrhage, mapping of brain perfusion during interventions, and confirming brain death. The document specifically states that for other indications of SPECT, “such as neuropsychiatric disorders and chronic fatigue syndrome, the findings of SPECT brain perfusion imaging have not been fully characterized.”⁹¹

Another guideline (last reviewed in 2007) from the ACR on Appropriateness Criteria for “Dementia and Movement Disorders” (including AD) states that, “Whether brain SPECT contributes substantially to diagnostic accuracy after a careful clinical examination using current diagnostic criteria is controversial.” They also state that even if PET and SPECT can help the differential diagnosis between AD and Frontotemporal dementia (FTD), “they are not recommended for routine use at the present time.” The document includes tables of relative radiation levels of various imaging techniques when used for different disorders. In general, the relative radiation for SPECT appears higher compared to the other techniques.⁹²

US National Institute of Mental Health (NIMH)

The NIMH Division of Neuroscience and Basic Behavioral Science (DNBBS) identifies biological markers (including “imaging”) as areas of high priority to be further validated for “diagnosing and/or detecting risk/vulnerability, onset, progress, and/or severity of mental disorders”,⁹³ and the Brain Imaging Clinical Research Program under the Division of Adult Translational Research and Treatment Development (DATR)/Clinical Neuroscience Research Branch lists the following areas of emphasis:

- “Identification of intermediate phenotypes of adult mental disorders, including imaging and neurocognitive phenotypes that may prove useful for subtyping disorders, elucidating shared and unique neural signatures across disorders, and exploring novel treatment targets.
- Identification and refinement of biomarkers of illness and treatment responses for human applications.
- Establishment of relationships between genetic variations and imaging and cognitive findings and phenotypes (e.g., imaging genetics) in adult mental disorders.
- Development and application of novel imaging approaches and computational methods for elucidating the neural bases of behaviors, symptoms, and cognitive features of adult mental disorders.

- Investigation of potential experimental therapeutic uses of neuroimaging and related techniques (e.g., use of real-time fMRI or other techniques for circuit retraining, such as noninvasive brain stimulation) to treat adult psychopathology.”⁹⁴

Despite this, NIHM Director Dr. Thomas Insel titled his blog post of October 07, 2010, “Brain Scans – Not Quite Ready for Prime Time”. After referring to Dr. Freedman’s editorial notes on the commercialization of diagnostic tests [American Journal of Psychiatry, September, 2010], Dr. Insel briefly mentions SPECT, as a tool now being used as part of diagnostic workup in some clinics. He summarizes the points made by the opponents of this application: SPECT is still premature, patients are exposed to radiation, there is risk of unnecessary treatments based on “shaky interpretations” of SPECT findings, and there are “more powerful, less invasive” [than SPECT] technologies which have been developed in the last decade. Dr. Insel mentions NIMH’s “neuroethics” portfolio which is working towards differentiating between “research opportunities and ready-for-prime-time clinical tools”. He acknowledges recent developments in brain imaging techniques (e.g. new biomarkers) and their possible role in the future clinical care for mental illness; however, he states that “brain imaging is still primarily a research tool when it comes to mental disorders”.⁹⁵

Society of Nuclear Medicine (SNM)

The Procedure Guideline for Brain Perfusion SPECT Using 99mTc Radiopharmaceuticals was published by the SNM in 2009. It includes information to assist nuclear medicine practitioners “in recommending, performing, interpreting, and reporting the results of brain perfusion SPECT studies using 99mTc radiopharmaceuticals”.⁹⁶ This procedure guideline warns practitioners to avoid “implying the existence of cause-and-effect relationships between scan and behavioral or neurologic abnormalities” and encourages them to include a statement of uncertainty whenever interpretation of the SPECT scan is not possible based on well-accepted criteria. Practitioners are also invited to be familiar with the “Ethical Clinical Practice of Functional Brain Imaging”, a document issued by the SNM Brain Imaging Council, in 1996.⁹⁷ This position statement was a product of a multidisciplinary effort of a group of physicians, technologists, neuropsychologists, and neuroscience researchers to promote the ethical use of SPECT and PET imaging in clinical and forensic arenas, and will be discussed elsewhere in this review.

European Medicines Agency (EMA)

European Medicines Agency (EMA) has a summary report on DaTSCAN (¹²³I), one of the intravenous radiopharmaceuticals used during SPECT brain scanning. DaTSCAN specifically attaches to “the surface of nerve-cell endings in the striatum that are responsible for the transport of dopamine.” Brain SPECT studies employing DaTSCAN are being used for the diagnosis of movement disorders and dementia; enabling differential diagnosis between Parkinson’s disease and essential tremor, or Lewy body dementia from Alzheimer’s disease. EMA has granted marketing authorization for DaTSCAN through a European public assessment report (EPAR).⁹⁸

Another report by EMA is titled “The Guideline on Clinical Evaluation of Diagnostic Agents” and the first appendix of this document is on the topic of imaging agents. After a summary of imaging agents (classification, efficacy, diagnostic performance, and methodological issues), the authors touch upon the “safety issue” as well, and point out that, “Irradiation related to the administration of radiopharmaceuticals is devoid of short-term side effects, but long-term safety is a concern.”⁹⁹

Swedish Council on Technology Assessment in Health Care (SBU)

The SBU report on “Diagnosing Dementia Disorders” (2008) refers to the European Federation of Neurological Societies’ (EFNS) guideline, which states, “Functional imaging should not be used routinely, but may be helpful when there is clinical suspicion of degenerative disorders and structural imaging is normal.” The summary of evidence section of the SBU report states that there is moderately strong evidence for supporting that the “reduction in regional cerebral blood flow or glucose metabolism” as shown by functional imaging (PET, SPECT) contributes to the diagnosis in differentiating AD from other dementias or from controls.⁸⁰

Institute de Efectividad Clinica y Sanitaria (IECS)

There were two health technology assessment reports on SPECT use under the Mental Health category of the Institute de Efectividad Clinica y Sanitaria (IECS). The abstracts of these reports were available in English through the IECS website and the brief records were available from the Cochrane HTA database.

One report was titled “Cerebral SPECT in the assessment of patients with schizophrenia” (2004)^{100,101} In this summary, the authors pointed out the small study samples in the diagnostic studies and the difficulty in finding patients who were off medical treatment. They indicated that often times, major depressive disorder was co-existent. They also mentioned variations in SPECT technique. They concluded that to consider SPECT to assess schizophrenic patients, studies from less specialized centres, from multicentres, with consecutive patient populations, and using standardized analytical methods were needed. They added, “Functional imaging methods do not play an important role in the diagnosis and treatment of schizophrenia and are still considered investigational methods, contributing to the knowledge about the pathophysiological base of this disease.”

The second health technology assessment report was titled “SPECT for the diagnosis and assessment of dementia and Alzheimer's disease” (2004).^{82,83} The authors reviewed thirty-two diagnostic studies which evaluated the precision of SPECT. Most had designs of poor quality. The SPECT diagnostic precision from better quality studies were similar to the precision obtained with clinical assessment by experienced physicians or specialized centres (weighted average 70.4% sensitivity/82.1 % specificity), and was lower than that reported in lower quality studies (weighted average 91.8%

sensitivity/88.3 % specificity). “Clinical diagnosis” was used as the reference test in most of the studies. “SPECT did not give a precise diagnosis, and the correct identification of dementia subtypes did not improve long-term results since there are no clearly effective treatments.” The author concluded that, “...up until now, SPECT has not clearly demonstrated its usefulness in assessing patients with dementia, and it has no precise indications for diagnosis, evaluation of prognosis or monitoring response to treatment.”

Cost-effectiveness

In their article, “Cost-effectiveness of functional imaging tests in the diagnosis of Alzheimer disease”,^{102,103} McMahon et al. calculated the costs and benefits of functional neuroimaging in the diagnostic work-up of patients attending Alzheimer’s disease clinics. They checked the specificity of computed and visual SPECT, and MR plus dynamic susceptibility contrast-enhanced (DSC) MR imaging, for the diagnosis of Alzheimer’s disease (AD). Health effects were measured by quality-adjusted life years (QALYs) gained. They presented their results as incremental cost-effectiveness ratios (ICERs). They used the Markov model to simulate their results. Their base case was defined to be the one with the “best point estimates for data inputs”. Under the base-case results, they found that SPECT (both visual and computed) was “dominated” by standard diagnostic workup; meaning that the standard examination yielded higher effectiveness (QALYs gained) with a lower cost. Although the MR imaging plus DSC MR imaging led to higher QALYs, its cost was also higher. The authors concluded that it was not cost-effective to include functional neuroimaging in the diagnostic workup for AD.

A simulation model was developed to compare cost-effectiveness of different diagnostic scenarios for various stages of Alzheimer’s disease (AD) and described in the article, “Cost-effectiveness of PET in the diagnosis of Alzheimer disease”.^{104,105} The authors assigned quality-adjusted life years (QALYs) for different AD scenarios. They included the sensitivity/specificity of various diagnostic approaches in their model, counting the sensitivity and specificity of SPECT to be 0.90 and 0.87, respectively. When evaluating effects on QALYs they considered five categories: standard examination, DSC MRI, PET, SPECT, and “additional strategies” (“perfect examination” and “treat all dementia”). PET and SPECT showed similar benefit to a standard clinical examination; whereas “perfect examination” showed the highest benefit. When cost was taken into account, standard examination was both less costly and more effective. The authors mentioned that, “In all scenarios modeled, computed SPECT was dominated by either the standard examination or dynamic susceptibility-weighted contrast-enhanced MR imaging” and regarding PET, they concluded that it had a high diagnostic accuracy with a high cost and would add limited benefits to the standard diagnostic regimen at AD clinics.

Ethics

The Society of Nuclear Medicine Brain Imaging Council published the position paper “Ethical Clinical Practice of Functional Brain Imaging” in 1996.⁹⁷ This position document was composed in a manner to be able to respond to the needs of the future, when “the field evolves”. The paper is still valid and currently referred to by the Society of Nuclear Medicine (SNM). The document underlines that the brain’s functional patterns are “highly dependent on a large number of technical, analytical and physiological variables” and points to the subjectivity of the scan interpretations (dependent on interpretive experience, level of expertise, particular clinical bias, etc.) Lack of sufficient studies (with normal controls) to set a clear definition of “normal” in brain scanning practices, is also mentioned. Interpreters are encouraged to include an uncertainty statement whenever “the relation between an observed image pattern and a clinical problem is uncertain”. The statement should make clear that “the ability or inability to assign causation should be made based on peer reviewed, published and generally accepted data.” The SNM position paper also touches upon the use of brain scan images in forensic situations (e.g. criminal, personal injury, product liability, medical malpractice, worker's compensation) and states that this use is “especially controversial”. The paper continues, stating: “When there are few controlled experimental studies and no available sensitivity and specificity rates, the forensic application of nonreplicated, unpublished or anecdotal SPECT or PET observations is inappropriate and has ominous implications. This can lead to unsupportable conclusions if introduced as ‘objective evidence’ linking neurophysiological parameters (such as blood flow or metabolism) to a defendant's judgment, insight or motives associated with the commission of a crime, or as an ‘offer of proof’ of a traumatically caused or substance-induced illness or injury.”

The Society of Nuclear Medicine Brain Imaging Council (SNM) has initiated the development of a “Normal SPECT brain perfusion database”. Today, this database is accessible for educational and research purposes. The database can be searched by entering basic technical (camera, tracer) and demographic (gender, age, and ethnicity) criteria to retrieve the SPECT images of the regional cerebral blood flow studies of healthy human subjects.¹⁰⁶ The output includes downloadable raw data, as well as a four-page demographic form and GIF-format SPECT images.

Call for International Guidelines

Given the upward trend in medical referrals for diagnostic imaging and for interventional radiology procedures, one concern is the unnecessary and perhaps inappropriate use of limited-supply radioisotopes which are vital for imaging techniques used in the diagnosis and management of certain diseases (e.g. metastatic tumors, cardiac ischemia, gastrointestinal bleeding, acute cholecystitis, osteomyelitis, and vascular necrosis). Leading radiology communities all around the world are also concerned that inappropriate use can lead to unnecessary radiation exposures of large populations. Hence, the WHO hosted the consultation “Referral Guidelines for Appropriate Use of Radiation Imaging” in Geneva, March 1-3, 2010. The International Atomic Energy Agency and the European Commission were amongst the agencies/societies represented. The consultation called for development of a global set of referral guidelines with collaboration of relevant international bodies, under WHO leadership, which “would include review, adaptation and expansion, as necessary, of evidence-based guidelines that exist nationally and regionally”.¹⁰⁷

Summary

Key Points

- SPECT is a functional imaging technique using radiotracers, which is able to capture 2-D or 3-D images of brain areas reflecting the physiologic state of blood perfusion, glucose or neurotransmitter (e.g. dopamine, serotonin) metabolism, or protein aggregates.
- Although SPECT was first introduced in the 1980s, attempts for its utilization in clinical psychiatry are fairly new and generally focused on patients with schizophrenia, major depression, and dementia.
- This clinical use in psychiatry is not yet justified, and SPECT should remain as an investigational tool until research evidence from rigorous published studies suggests otherwise.
- Currently available studies differ in sample size (most have small sample sizes), in subject selection protocols, and in imaging and analysis techniques; also, there is difficulty in controlling for confounders, such as other drugs being used, comorbid medical conditions, hormonal changes, physical activity, nutrition, and a myriad of other physiological factors.
- As SPECT demonstrates the state of brain physiology at a point in time, inferences of a causal relationship with a specific psychiatric disorder are likely inappropriate at this stage in its evolving science.
- SPECT poses higher ionizing radiation exposure to the patient when compared to other brain imaging techniques and its long-term effects on the human body are unknown.

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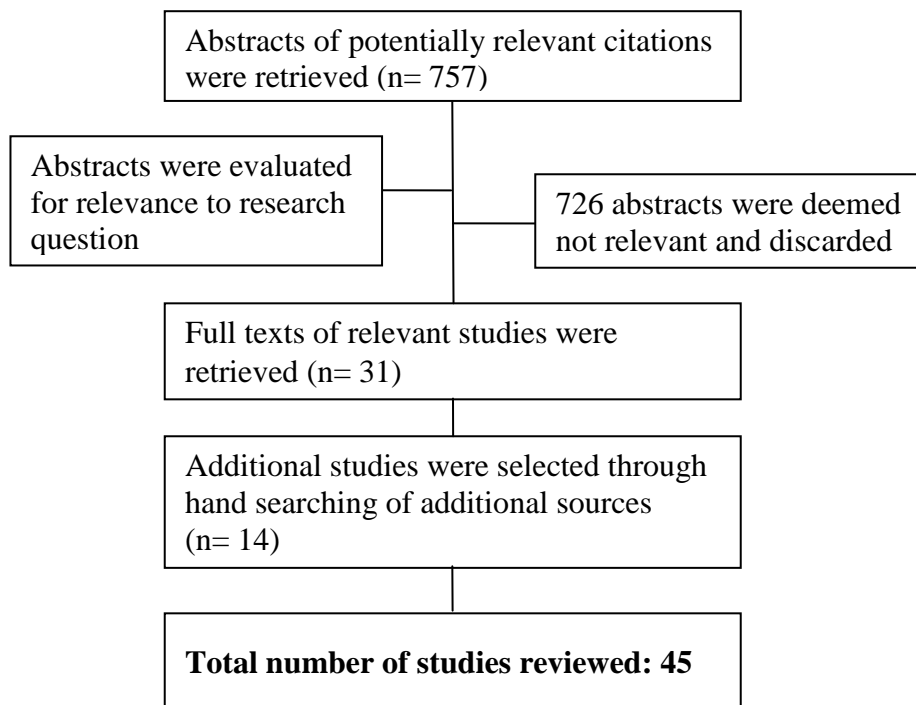
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Appendix 1

Flow diagram (Study selection)



Appendix 2

WorkSafeBC Evidence-Based Practice Group levels of evidence (adapted from 1,2,3,4)

1	Evidence from at least 1 properly randomized controlled trial (RCT) or systematic review of RCTs.
2	Evidence from well-designed controlled trials without randomization or systematic reviews of observational studies.
3	Evidence from well-designed cohort or case-control analytic studies, preferably from more than 1 centre or research group.
4	Evidence from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments could also be included here.
5	Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.

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