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GUIDELINES

EANM procedure guidelines for brain neurotransmission SPECT/PET using dopamine D2 receptor ligands, version 2

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Abstract The guidelines summarize the current views of the European Association of Nuclear Medicine Neuroimaging Committee (ENC). The aims of the guidelines are to assist nuclear medicine practitioners in making recommendations, performing, interpreting and reporting the results of clinical dopamine D2 receptor SPECT or PET studies, and to achieve a high quality standard of dopamine D2 receptor imaging, which will increase the impact of this technique in neurological practice.

The present document is an update of the first guidelines for SPECT using D2 receptor ligands labelled with ^{123}I [1] and was guided by the views of the Society of Nuclear Medicine Brain Imaging Council [2], and the individual experience of experts in European countries. The guidelines intend to present information specifically adapted to European practice. The information provided should be taken in the context of local conditions and regulations.

Keywords Brain · Dopamine · D2 receptor · SPECT · PET · Parkinsonism

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Background and definitions

Preclinical studies, clinical investigations and post-mortem evaluations have shown that the dopaminergic neurotransmitter system plays a major role in movement disorders, particularly in parkinsonism. Using SPECT and PET, various functional aspects of dopaminergic neurotransmission can be visualized in vivo.

Since the number of PET devices has rapidly increased, and ^{18}F-labelled radiotracers for the D2-receptor are available [3], e.g. ^{18}F-fallypride [4] or ^{18}F-desmethoxyfallypride (DMFP) [5], in addition to ^{11}C-raclopride [6], PET has evolved from a research tool to a clinical application in several centres with PET capability. Therefore, the guidelines for ^{123}I-labelled SPECT ligands have been extended in this update.

Currently nuclear medicine investigations predominantly assess two aspects of the dopaminergic system: the binding of the presynaptic dopamine transporter and the status of the postsynaptic dopamine D2 receptor [3, 7–10]. Imaging of the dopamine transporter is addressed in separate guidelines. This document deals with the evaluation of the postsynaptic dopaminergic system. Since the vast majority of D2 receptors are located postsynaptically, imaging of D2 receptors is frequently referred to as imaging of the postsynaptic D2 receptors. Numerous investigations have focused on the assessment of the dopamine receptor status. According to their pharmacological response, dopamine receptors are divided into D1-like receptors (D1, D5) and D2-like receptors (D2, D3 and D4). Whereas the assessment of D1-like receptors has not gained any clinical significance, a number of clinical investigations have focused on the D2-like receptor system.

The most widely applied radiotracers for imaging D2-like receptors with SPECT are ^{123}I-labelled IBZM (GE Healthcare, UK) and epidepride (MAP Medical Technologies, Finland) [11]. For PET, ^{11}C-raclopride, ^{18}F-fallypride and DMFP are most commonly used in European centres. These dopamine receptor antagonist derivatives are not selective radiopharmaceuticals for the D2 receptor, since they also bind to the D3 receptor [12]. However, the vast majority of D2-like receptors in the striatum are D2 receptors; therefore, from now on we refer to these radiopharmaceuticals as D2 receptor ligands.

The affinity and the selectivity to the D2 receptors and their pharmacokinetic properties have been shown to vary considerably among available radiotracers resulting in differences with respect to specific binding ratios and the optimal time point for acquisition.

These guidelines deal with the indications, assessment, processing, interpretation and reporting of dopamine D2 receptor SPECT and PET studies using the commercially available radiopharmaceuticals ^{123}I-IBZM and ^{123}I-epidepride, as well as ^{11}C-raclopride, ^{18}F-fallypride and DMFP.

The equipment that is currently used to perform PET or PET/CT for brain imaging has been described in the 2009 EANM procedure guidelines for FDG brain PET.

Indications

A. Common indications

Differential diagnosis of parkinsonian syndromes. The main indication is the differentiation of Parkinson's disease from other neurodegenerative parkinsonian syndromes characterized by loss of D2 receptors (e.g. multiple system atrophy and progressive supranuclear palsy) [5, 13–18]. Several recent reports show that the use of D2 imaging alone may not be highly sensitive; see, for example, reference [19].

B. Other less-common indications

B.1. Assessment of the extent of D2 receptor blockade during treatment with dopamine D2 antagonists (neuroleptics). D2 receptor imaging provides information about the extent of D2 receptor blockade of patients treated with either typical or atypical neuroleptics [20–22].

B.2. Huntington's disease. In suspected Huntington's disease D2 receptor imaging can confirm degeneration of postsynaptic D2 receptors [23, 24]. However, Huntington's disease diagnosis is now achieved mainly by molecular genetic testing.

B.3. Wilson's disease. D2 receptor imaging findings are related to the severity of neurological symptoms in Wilson's disease and may show the degree of neuronal damage due to cytotoxic copper deposition in the striatum [25].

B.4. Pituitary adenoma. D2 receptor imaging is helpful when assessing the dopamine receptor status/availability of pituitary adenoma, which might have implications for the medical treatment strategy [26].

C. Contraindications

C.1. Pregnancy.

C.2. Breast feeding. Mothers should interrupt breast feeding for 24 h.

C.3. Inability to cooperate with the procedure.

Procedure

A. Patient preparation

A.1. Prearrival

Prior to the investigation patients should, if possible, have drugs known to affect D2 receptor binding withdrawn.

A.2. Preinjection

A.2.1. Check and ensure that the patient is able to cooperate during the investigation.

A.2.2. In case of ^{123}I-ligands, block the thyroid gland with an adequate regimen (e.g. at least 200 mg of sodium perchlorate given at least 5 min prior to injection) to prevent accumulation of free radioactive iodine in the thyroid.

B. Information pertinent to performing D2 receptor imaging studies

- Patient's history with particular focus on neurological and psychiatric disorders, and current neurological and psychiatric status.
- Patient's ability to lie still for 40 to 60 min. If sedation is necessary, it should be given at the earliest 1 h prior to the imaging acquisition. It may be necessary to give conscious sedation (e.g. by a short-acting benzodiazepine, such as intravenous midazolam). The sedative medication should be given shortly before tracer injection, preferably starting only a few minutes before data acquisition. Appropriate monitoring (pulse oximetry) should be performed to detect possible cardiopulmonary depression; appropriate antidote/emergency backup should be available. Doses of sedative medication should be reduced in elderly patients.
- Information about (recent) morphological imaging studies (CT, MRI).
- Current medication, and when last taken. Note that many antiparkinsonian drugs (in particular dopamine agonists), neuroleptics and other medication (e.g. metoclopramide, cinnarizine, flunarizine, amphetamine, methylphenidate etc.) compromise binding of the radioligand to the D2 receptors [20–22, 27]. The period of withdrawal of such drugs prior to the investigation depends on wash-out time and biological half-life of the respective drugs and may range from several hours to months.

L-DOPA therapy may be continued since interaction with D2 receptor ligands is relatively modest. Nevertheless, when possible, patients should preferably be scanned during OFF conditions.

C. Precautions

Continuous supervision of the patient during the whole scanning procedure is necessary.

D. Radiopharmaceuticals

D.1. Radiopharmaceuticals

- [^{123}I]IBZM: [^{123}I](*S*)-2-hydroxy-3-iodo-6-methoxy-(1-ethyl-2-pyrrolidinylmethyl)-benzamide
- [^{123}I]epidepride: [^{123}I](*S*)-*N*-((1-ethyl-2-pyrrolidinyl) methyl)-5-iodo-2,3-dimethoxybenzamide
- [^{18}F]fallypride or [^{18}F]*N*-allyl-5-fluorpropylepidepride
- [^{18}F]desmethoxyfallypride or [^{18}F]DMFP or (*S*)-*N*-((1-allyl-2-pyrrolidinyl)methyl)-5-(3-^{18}F-fluoropropyl)-2-methoxybenzamide
- [^{11}C]raclopride

D.2. Preparation for the radiopharmaceutical

- [^{123}I]IBZM and [^{123}I]epidepride will be delivered ready to use.
- PET ligands are made on-site according to the GMP guidelines. [^{18}F]Fallypride may become commercially available in the future.

D.3. Quality control check

For SPECT radioligands check for radiochemical purity and other parameters of quality assessment given in the package inserts and follow the instructions of the manufacturer. For PET radioligands refer to the EANM guidelines "Guidelines on Current Good Radiopharmacy Practice (cGRPP) in the Preparation of Radiopharmaceuticals" (https://www.eanm.org/scientific_info/guidelines/gl_radioph_cgrpp.pdf).

D.4. Injection

Inject the radiopharmaceutical intravenously as a slow bolus over approximately 20 s followed by saline to flush the intravenous line.

D.5. Timing of injection

Inject [^{123}I]IBZM and [^{123}I]epidepride within the time frame given by the manufacturer (generally on the day of

delivery). [^{11}C]Raclopride, [^{18}F]desmethoxyfallypride and [^{18}F]fallypride should be injected immediately after production.

D.6. Administered activity

Adults: 150–250 MBq (typically 185 MBq) of either [^{123}I] or [^{18}F] radiopharmaceutical; 220–370 MBq of [^{11}C] raclopride
Children: currently no established clinical indications; if required, dosage according to the recommendations of the EANM Pediatric Task Group.

D.7. Radiation dosimetry

The doses of the various radioligands in adults and children are shown in Table 1.

E. Data acquisition

E.1. Time from injection to start of data acquisition

- [^{123}I]IBZM: 1.5–3 h (preferably 2 h).
- [^{123}I]Epidepride: 2–3 h.
- [^{11}C]Raclopride: 30–60 min (for pseudoequilibrium). If quantification using kinetic analysis and reference tissue methods is of interest, a dynamic PET measurement of 50–60 min should be performed.
- [^{18}F]Desmethoxyfallypride: 1–1.5 h.
- [^{18}F]Fallypride: 2.5–3 h.

A fixed time delay between injection and the start of data acquisition is recommended to ensure that data are comparable between subjects and in intraindividual follow-up studies.

E.2. Set-up for data acquisition

E.2.1. Positioning of the patient

- The patient should be encouraged to void prior to the start of acquisition to ensure maximum comfort during the study. The patient should be advised to void again after the scan session to minimize radiation exposure.
- The patient should be informed about the total acquisition time and positioned for maximum comfort. Since postprocessing routines allow correction of minor irregularity of head orientation, the patient's comfort (which reduces the likelihood of motion during acquisition) is more important than perfect alignment of the head. The patient should be told of the importance of avoiding (voluntary) movements of the head and asked for her/his active cooperation. If the patient is uncooperative sedation can be used. However, the potential interactions of some sedative drugs if administered during tracer uptake should be born in mind. The patient's head should be only lightly restrained; it is not recommended to fix the head firmly in place.

E.2.2. Imaging devices

E.2.2.1. SPECT

- Multiple detector (triple or dual head) or other dedicated SPECT cameras for brain imaging should be used for data acquisition.
- Single-detector units cannot generally be recommended. They may only be used if the scan time is prolonged appropriately (>3 million total detected events), the injected activity is in the upper permissible

Table 1 Radiation dosimetry of D2 receptor radioligands

Radioligand	Organ receiving the largest absorbed dose		Effective dose (mSv/MBq)
	Dose (mGy/MBq)		
Adults			
[^{123}I]IBZM	Thyroid	0.16	0.033
	Bladder wall	0.07	
[^{123}I]Epidepride	Upper/lower large intestine	0.10	0.024
[^{18}F]Fallypride	Gallbladder wall	0.12	0.021
[^{11}C]Raclopride	Gallbladder wall	0.031	0.063
[^{18}F] Desmethoxyfallypride	Not available		Not available
Children (≥5 years)			
[^{123}I]IBZM	Thyroid (despite blockage)	0.86	0.11

Data are from the literature [35] or have been recalculated to effective dose from the organ doses in the literature (for IBZM [36] and epidepride [37]). ICRP report 106 also presents a generic model for brain receptor substances.

range, and meticulous care is taken to produce high-quality images.
- LEHR or LEUHR parallel-hole collimators are the most frequently available collimator sets for brain imaging. All-purpose collimators are not suitable. The use of medium-energy collimators could be advantageous; however, usually they are hampered by low sensitivity. They may only be used if acceptable event statistics are obtained. If available, collimator sets specifically adapted to the characteristics of ^{123}I may be used. Fanbeam collimators are generally preferred over parallel-hole collimators due to the advantageous trade-off between resolution and sensitivity.
- Acquisition parameters:
  - *Rotational radius*: smallest possible with appropriate patient safeguard.
  - *Matrix*: 128×128 or higher.
  - *Angular sampling*: ≤3° (360° rotation).
  - *Zoom*: acquisition pixel size should be one-third to one-half of the expected resolution; therefore it may be necessary to use a hardware or reconstruction zoom to achieve an appropriate pixel size.
  - *Acquisition mode*: "step and shoot mode" is used predominantly. Continuous mode acquisition may provide shorter total scan times and reduce mechanical wear to the system.
  - *Total detected events*: >3 million.
  - *Total scan time*: depending on the imaging device, typical scan time for a dual head camera is between 40 and 50 min (e.g. 120 projections; 60 projections per head; 40–50 s/projection). The same scan time may be used with triple head cameras, allowing higher detected event statistics.
  - Segmentation of data acquisition into multiple sequential acquisitions may permit exclusion of data with artefacts, e.g. segments of projection data with patient motion can be removed.
  - A transmission scan or CT (SPECT-CT systems) can be used for attenuation correction.

E.2.2.2. PET

- 2-D or 3-D acquisition can be performed.
- Acquisition parameters:
  - *Matrix*: 128×128 or higher.
  - *Zoom*: acquisition pixel size should be one-third to one-half of the expected resolution; therefore it may be necessary to use a reconstruction zoom to achieve an appropriate pixel size.
  - *Total scan time*: 60 min for [^{11}C]raclopride (or static scan between 40and 60 min after injection may suffice) and 20–30 min for [^{18}F]fallypride.
  - Segmentation of data acquisition into multiple sequential acquisitions may permit exclusion of data with artefacts, e.g. segments of projection data with patient motion can be removed. Multiple sequential acquisitions are also needed to extract a proper time–activity curve with sufficient temporal frequency to capture the kinetics of both reference and target regions in case of dynamic quantitative PET studies.
  - Dynamic acquisition over the intended period of time may be preferred to exclude poor quality images, e.g. sinograms with patient motion can be removed.
  - Transmission or CT scan (PET-CT systems) are used for attenuation correction.

F. Interventions

Usually no interventions are performed. In research settings pharmacological challenge may be used to measure acute fluctuations in synaptic dopamine concentration.

G. Image processing

G.1. Review of projection data

Unprocessed projection data should be reviewed in cinematic display (SPECT) prior to filtering to assess the presence and degree of motion artefacts, target-to-background ratios and other potential artefacts. Inspection of projection data in sinogram form (SPECT and PET) may also be useful.

G.2. Reconstruction

G.2.1. SPECT

- Methods: filtered back-projection or iterative reconstruction.
- Make sure that the entire brain volume is reconstructed.
- Reconstruct data at the highest pixel resolution, i.e. maximum one pixel thick.

G.2.2. PET

- Images are reconstructed in the form of transaxial images of at least 128×128 pixels; the usual pixel size is 2–4 mm. Depending on the resolution of the PET system, a final image resolution of 4–6 mm FWHM typically yields images of adequate resolution and noise.

G.3. Filtering

G.3.1. SPECT

- Data should be filtered in all three dimension (x,y,z). This can be achieved either by 2-D prefiltering the projection data or by applying a 3-D postfilter to the reconstructed data.
- Low-pass (e.g. Butterworth) filters should generally be used. Resolution recovery or spatially varying filters have to be used with caution, as they may produce artefacts. Therefore the latter cannot be recommended for general use.

G.3.2. PET

- Commonly used filters are Hanning or Shepp-Logan, but they should be fine-tuned depending on the application, injected activity, camera and acquisition type, and even the physician's preference.

G.4. Attenuation correction

G.4.1. SPECT

- It is mandatory to perform attenuation correction.
- Methods:
  - Use of a calculated homogenous correction matrix according to Chang (linear correction coefficient for ^{123}I: μ=0.10–0.12 cm^{-1} when no scatter correction is applied. A higher value should be used when using scatter correction).

  Shape contouring should be used if available. Contours should include scalp and not just grey matter. Contours should be defined for each individual transversal slice. Correct shape and position of the contours should be reviewed prior to calculation of corrected slices.
  - Use of a measured correction matrix e.g. from a sequentially assessed transmission scan or from a CT scan.

G.4.2. PET

- It is mandatory to perform attenuation correction.
- Methods:
  - Transmission imaging using a ^{68}Ge/^{68}Ga or a ^{137}Cs source.
  - CT scan: PET/CT systems have the capability of using the CT scan for attenuation correction. The advantage of the CT scan is that the detection of X-rays from the CT scan is not affected by the emission photons. Therefore, a CT scan can be performed after the injection of the radiopharmaceutical without affecting the accuracy of the attenuation correction due to emission spill-over.
  - Mathematical attenuation correction: correction procedures estimating the attenuation based on the estimation of organ extent from emission data should only be used when transmission imaging or CT scan are not available. Care should be taken when normalizing to the cerebellum due to systematic bias.

G.5. Reformatting

Transverse slices have to be reformatted into two orthogonal planes. Transverse sections should be generated parallel to a given anatomic orientation (e.g. AC-PC line) ensuring a high degree of standardization in plane orientation. In addition coronal sections should be created orthogonal to the transverse sections and obliquities should be corrected.

G.6. Comparative evaluation

- Region of Interest (ROI) techniques have to be used to assess specific dopamine D2 receptor binding in the striatum and the striatal subregions (head of caudate, putamen). Reference regions with absent (or low) D2 density (e.g. frontal cortex, occipital cortex, cerebellum) are used to assess nonspecific binding.
- It is helpful if ROI size (should be at least twice FWHM) and shape are standardized (e.g. use of templates). If available, ROI definition may be based on individual morphology as obtained by image fusion with MRI, which is particularly important when low specific binding is expected (e.g. in cases of severe loss or blockade of D2 receptor binding).
- Specific binding values [(mean counts of striatal ROI − mean counts of background ROI)/mean counts of background ROI] obtained from the patients are compared with those from normal (preferably age-matched) subjects obtained with the same technique. The striatum may be subdivided into head of the caudate nucleus and anterior/posterior putamen to calculate anteroposterior gradients within the striatum.
- For intraindividual comparison (i.e. baseline vs. follow-up for therapy control or assessment of disease progression), standardized evaluation using approaches based on, for example, stereotactic normalization is most useful. It allows even subtle changes to be detected more reliably.
- If data from age-matched normal controls are available for comparison, the use of analytical approaches based on stereotactic normalisation is

recommended in order to determine abnormalities of D2 receptor binding in an observer-independent way.

H. Interpretation criteria

H.1. Visual interpretation

- Visual assessment should only assist a quantitative evaluation and gives an idea whether D2 receptor binding is normal, elevated or reduced, and, if abnormal, gives an indication of the magnitude of compromised D2 receptor binding. In particular visual assessment may provide information about right to left asymmetry and about the structures (i.e. striatal subregions) most affected.
- Images should be read on the computer screen rather than from hard copies, because this allows the colour table to be varied and the background subtraction or contrast to be adjusted.
- For comparison it is highly desirable to have a normal (preferably age-matched) database available, acquired with the same type of camera and processed in the same way as the patient's studies (reconstruction, filtering, attenuation correction).
- Data evaluation must take into account relevant morphological information (CT, MRI). Specific attention should be paid to known structural lesions in the basal ganglia and in the structures used as reference regions for semiquantitative evaluation.
- Pitfalls/sources of error:
  - Age dependency:
    the known decline of D2 receptor binding with age (6–8% per decade in the striatum) has to be taken into consideration to avoid overinterpretation [28].
  - Level of contrast and background subtraction:
    inappropriate thresholding may result in artefacts. Thresholding, if used, must be based upon knowledge of a normal database for specific radiopharmaceuticals and set-up.
  - Colour table:
    use of noncontinuous colour tables may overestimate findings due to abrupt colour changes.
- Technical artefacts:

the images should be critically examined during interpretation for the presence of head-motion artefacts, attenuation artefacts, or other technical artefacts due to gamma or PET camera problems.

- Differences in performance and accuracy of different scanners (when data cannot be pooled, at least resolution matching should be attempted).
- Medication:

possible interaction of concomitant medication has to be taken into account.

H.2. Quantification

- Semiquantification is *mandatory* to objectively assess striatal D2 receptor binding.
- For PET radioligands and particularly [^{11}C]raclopride, the quantitative outcome measure can be the binding potential estimated using the simplified reference tissue model [29].
- Usually transverse/oblique reformatted slices are picked for ROI definition. For evaluation either only the slices with the highest striatal binding are picked or the entire striatal volume is taken into account.
- Quantification can be performed with anatomically adjusted ROIs (using templates or MRI overlay techniques) or on a pixel-wise basis (see above). Several tools are available, commercially or from academic centres (see for example references [30–34]).
- Interpretation of quantitative results is based on the comparison of specific D2 receptor binding values obtained by ROI techniques with those from age-matched normal controls. In general, D2 receptor binding is assessed for the entire striatum. Additionally the head of the caudate nucleus and the putamen may be assessed separately, or the putamen may be divided into a pre- and postcommissural part.
- Pixel-wise comparisons of a patient study with a normal database.

I. Reporting

I.1. General

Reports should include all pertinent information, including the name of the patient and other identifiers, such as date of birth; the name of the referring physician(s); the type and date of examination; the radiopharmaceutical including the administered activity; the patient's history, including the reason for requesting the study.

I.2. Body of the report

I.2.1. Procedures and materials

- Include in the report a brief description of the imaging procedure and assessment of scan quality (if compromised give the reason, e.g. motion artefacts etc.).

– If sedation is performed, briefly describe the procedure including type and time of medication given in relation to the radiotracer injection.

I.2.2. Findings

– State whether the D2 receptor binding pattern is normal or not. If it is abnormal, describe the location and intensity of abnormal D2 receptor binding. State what criteria were used for interpretation (visual assessment, quantitative or semiquantitative measures, comparison with normal database etc.).

I.2.3. Limitations

– Where appropriate, identify factors that could have limited the sensitivity and specificity of the result of the examination (i.e. movement, concomitant medication).

I.2.4. Clinical issues

– The report should address or answer any pertinent clinical issues raised in the request for the imaging examination.

I.2.5. Comparative data

– Comparisons with previous examinations and reports, if available, have to be part of the report. In particular information about the presynaptic dopamine transporter status (and structural lesions) may be helpful in specific situations.

I.3. Interpretation and conclusions

I.3.1. A precise diagnosis should be given whenever possible. It should be based on generally accepted disease-specific patterns. Any interpretation not based on such criteria has to be explicitly stated as subjective and considered as hypothetical.

I.3.2. Interpretation should be based on the visual evaluation and more importantly on the results of the quantitative evaluation, and should allow a conclusion as to:

– Whether postsynaptic D2 receptor binding is normal, elevated or compromised.
– The extent and the characteristics (e.g. asymmetry, predominantly affected structures) of the compromised D2 receptor binding.

I.3.3. When appropriate, follow-up or additional studies (e.g. presynaptic dopamine transporter studies) should be recommended to clarify or confirm the suspected diagnosis.

J. Quality control

See procedure guidelines of the EANM for quality control.

K. Sources of error

– Artefacts (patient movement, camera-related, introduced by inappropriate processing).
– Interference with drugs possibly acting on the dopamine D2 receptors.
– When the ROI definition is based on segmented and coregistered MRI, errors in segmentation and coregistration may affect the accuracy in defining (reference and target) the ROI/VOI.

Issues requiring further clarification

– Value of iterative reconstruction.
– Added value of PET ligands over SPECT.
– Comparison with FDG PET for differential diagnosis in movement disorders.
– Partial volume effect correction.
– Scatter and attenuation correction, differences between scanners.

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Disclaimer These guidelines summarize the views of the Neuroimaging Committee of the EANM and reflect recommendations for which the EANM cannot be held responsible. The recommendations should be taken in the context of good practice of nuclear medicine and do not substitute for national and international legal or regulatory provisions. The guidelines have been brought to the attention of the National Societies of Nuclear Medicine.

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