A propos de la valeur de l'EEG et des potentiels évoqués dans la pratique clinique

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Federaal Kenniscentrum voor de Gezondheidszorg
Centre fédéral d'expertise des soins de santé
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Centre fédéral d'expertise des soins de santé (KCE).
Cité Administrative Botanique, Doorbuilding (10ème)
Boulevard du Jardin Botanique, 55
B-1000 Bruxelles
Belgium

Tel: +32 [0]2 287 33 88
Fax: +32 [0]2 287 33 85

Email : info@kce.fgov.be
Web : http://www.kce.fgov.be

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ANN VAN DEN BRUEL, JEANNINE GAILLY, FRANK HULSTAERT,
STEPHAN DEVRIESE, MARIJKE EYSSEN

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Auteurs :	Ann Van den Bruel, Jeannine Gailly, Frank Hulstaert, Stephan Devriese, Marijke Eyssen
Experts Externes :	Peter De Deyn (Middelheim, ZNA, Antwerp), Jean-Michel Guérit (Edith Cavell, Brussels), Alain Maertens de Noordhout (Ulg, Liège), Georges Otte (Dr Guislain Instituut, UGent, Ghent), Jozef Peuskens (KUL, Leuven), Jo Ramboer (Vlaamse Vereniging Psychiatrie), Maarten Schrooten (KUL, Leuven), Pierette Seeldrayers (CHU Charleroi), Christian Sindic (UCL, Brussels), Guy Vanderstraeten (UGent, Ghent), Vincent Van Pesch (UCL, Brussels), Kenou Van Rijckevorsel (UCL, Brussels), Michel Van Zandijcke (AZ Brugge, Bruges).
Validateurs Externes :	Dirk Deboutte (UA, Antwerp –Ugent, Ghent), Jacques De Reuck (UGent, Ghent), Hartmut Meierkord (Charité – Universitätsmedizin, Berlin, Germany)
Conflits d'interêt :	Le Dr Van Pesch et le Prof Deboutte ont déclaré avoir reçu des fonds destinés à la recherche académique de la part de sources régionales de financement et d'organisations non gouvernementales. De plus, le Prof Deboutte a déclaré qu'il donnait fréquemment des conférences sur ce sujet, et le Dr Van Pesch a déclaré avoir obtenu de Bayer Schering le paiement de frais de déplacements pour participer à des conférences.
Disclaimer:	Les experts externes ont collaboré au rapport scientifique qui a ensuite été soumis aux validateurs. La validation du rapport résulte d'un consensus ou d'un vote majoritaire entre les validateurs. Le KCE reste seul responsable des erreurs ou omissions qui pourraient subsister de même que des recommandations faites aux autorités publiques.
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AVANT-PROPOS

Le premier rapport d'un enregistrement des courants électriques du cerveau remonte au début du vingtième siècle et l'auteur en était le psychiatre allemand Hans Berger, en 1929. Avec ce rapport, Berger a jeté les bases d'un domaine totalement neuf, la neurophysiologie clinique. En 1936, W. Gray Walter a prouvé qu'il était possible d'identifier une activité électrique anormale dans les zones cérébrales limitrophes d'une tumeur et une activité limitée à l'intérieur de celle-ci. Il fut aussi le premier à établir que le rythme alpha (présent à l'état de repos) disparaît de pratiquement l'ensemble du cerveau durant une tâche mentale exigeant une certaine vigilance, pour être remplacé par un rythme plus rapide, les ondes beta. Plus récemment, le système 10-20 a standardisé le positionnement des électrodes de l'électroencéphalogramme (EEG), tandis que les EEG numériques ont permis de réaliser des interprétations quantitatives.

Les potentiels évoqués sont des potentiels électriques enregistrés suite à l'application d'un stimulus. Ils sont différents des potentiels spontanés tels que détectés par les électroencéphalogrammes. Historiquement, les potentiels évoqués (EP) sont étudiés chez les patients depuis le début des années 50, en se concentrant dans un premier temps sur les composants de latence longue dotés d'une large amplitude. Les « event-related evoked potentials » ou ERP constituent une catégorie distincte de potentiels évoqués. Les ERP sont également enregistrés suite à des stimuli visuels, auditifs ou somatosensoriels, mais exigent, dans la plupart des cas, que le sujet distingue un stimulus dans un groupe d'autres stimuli.

Les indications cliniques de ces tests ont évolué avec le temps. Dans la pratique clinique actuelle, l'EEG et les EP sont largement utilisés pour gérer certains états cibles. Pour l'heure, le positionnement des ERP est moins clair. Le présent rapport du KCE fournit une orientation pour l'utilisation de l'EEG et des EP ou ERP dans la pratique clinique.

Gert Peeters
Directeur général adjoint a.i.

Jean-Pierre Closon
Directeur général a.i.

Résumé

INTRODUCTION

Un électroencephalogramme (EEG) reflète la sommation temporelle et spatiale des potentiels corticaux post-synaptiques synchronisés, mesurés en tant que signaux électriques détectés à la surface du cuir chevelu. L'activité EEG détectée au niveau du cuir chevelu est constituée d'oscillations multiples possédant des fréquences caractéristiques et des répartitions spatiales différentes, de même que des associations différentes avec divers états de fonctionnement cérébral (par exemple, l'éveil par rapport au sommeil).

Les potentiels évoqués sont des changements dans l'activité électrique du cerveau, stéréotypés et liés en temps avec un événement (par exemple, un stimulus). Le stimulus est constitué de clics ou de tonalités (Brain-Stem Auditory Evoked Potential, BAEP), de pattern reversal ou de flashes (potentiels évoqués visuels, VEP), d'une stimulation électrique (potentiels évoqués somatosensoriels, SEP) ou encore d'une stimulation du cortex moteur (potentiels évoqués moteurs, MEP). Les potentiels enregistrés se caractérisent par une latence spécifique entre le stimulus et la réponse, et peuvent être regroupés en potentiels de latence courte, moyenne ou longue. En raison de leurs faibles amplitudes et de leur mélange avec les ondes cérébrales normales de fond, la plupart des EP ne sont pas visibles sur les enregistrements EEG de routine. Afin d'augmenter le rapport « signal/bruit », une méthode fréquemment utilisée est celle de la moyenne (averaging), lorsqu'un stimulus identique est appliqué à de multiples reprises.

Les potentiels liés aux événements (ERP) sont des fluctuations de voltage qui affichent des relations temporelles stables par rapport à un événement de référence définissable, d'origine physique ou mentale. Le stimulus est le plus souvent auditif, mais peut être élargi à des paradigmes et modalités de stimulation plus complexes.

CHAMP D'APPLICATION

Le présent rapport se concentre sur l'utilisation des EEG, des EP et des ERP dans la pratique neurologique ou psychiatrique. L'utilisation expérimentale et l'usage intra-opératoire n'appartiennent pas au champ d'application de ce rapport. En outre, les indications traitées dans des cadres hautement spécialisés ont été exclues.

PREMIÈRE QUESTION DE LA RECHERCHE

Quelle est l'utilisation actuelle des EEG et des EP en Belgique, et quel en est le coût pour l'assurance-maladie et les patients ?

SECONDE QUESTION DE LA RECHERCHE

Quelles sont les preuves scientifiques de la valeur diagnostique et/ou pronostique des EEG, EP et ERP ?

LIMITATIONS

Les recommandations se fondent sur les études disponibles et sont susceptibles de changer si de nouvelles études sont publiées. En conséquence, les présentes directives doivent être considérées comme une ligne d'action générale. Loin de nous l'intention que les recommandations publiées dans le présent rapport soient appliquées stricto sensu à chaque patient. Le respect des recommandations n'est pas une garantie de réussite chez chaque patient, pas plus qu'elles ne peuvent être considérées comme la seule approche clinique possible, en excluant de ce fait d'autres approches visant le même résultat. La décision finale du recours à une certaine procédure ou à un certain traitement relève de la responsabilité du médecin traitant qui, ce faisant, prend en considération toutes les informations cliniques sur le patient.

EXACTITUDE TECHNIQUE ET NORMALISATION

L'exactitude et la reproductibilité des tests diagnostiques sont fortement tributaires de leur standardisation. Le respect d'une technique standardisée et validée est dès lors crucial lorsque les potentiels évoqués et les EEG sont utilisés aux fins d'une prise de décision clinique.

Si des normes techniques sont disponibles pour les EEG et les EP, la situation est moins claire pour les ERP. S'agissant des EEG, le système 10-20 garantit un positionnement normalisé des électrodes à la surface du cuir chevelu. En outre, des normes relatives aux instruments, aux protocoles d'induction et à la transmission des résultats sont disponibles et appliquées. Pour les EP, nous avons identifiés des documents qui décrivent le stimulus, le placement des électrodes, la polarité, l'impédance, la bande passante de filtre (filter band-pass), le balayage d'enregistrement (recording sweep), la moyenne des essais (trials averaged), les enregistrements minimum et l'interprétation. Pour les ERP, seule une norme technique a été identifiée, pour le P300.

UTILISATION ACTUELLE DES TESTS EN BELGIQUE

A l'heure actuelle, les EEG et les potentiels évoqués sont remboursés par l'INAMI. Pour les EEG, il existe deux codes dans la nomenclature : l'EEG normal et l'EEG de 24 heures. Pour les BAEP, VEP et SEP, la nomenclature contient trois codes distincts : un test unique ; deux tests d'une modalité différente (par exemple, BAEP + VEP) ; et trois tests dont chacun d'une modalité différente. En outre, les MEP sont remboursés en tant que catégorie séparée. Les ERP sont remboursés en tant que EP, à l'exception d'un test spécifique (la variation contingente négative) pour lequel une règle d'interprétation spécifie qu'il est remboursé comme un EEG.

EEG et EP peuvent être réalisé par les neurologues/ (neuro) psychiatres, et dans certaines circonstances, par les ophtalmologues, les oto-rhino-laryngologistes, les urologues ou les neuro-pédiatres. Les MEP peuvent être pratiqués par des neurologues/ (neuro) psychiatres ou des spécialistes en médecine interne. Des spécialistes en médecine physique réalisent également des SEP.

Au total, en 2006, plus de 24 millions d'euros ont été dépensés pour 420 000 EEG, répartis de manière égale entre les soins en hôpital et en ambulatoire. Au cours de la dernière décennie, l'utilisation des EEG en Belgique a été relativement stable, avec un léger fléchissement du nombre d'EEG réalisés chez les patients hospitalisés.

En 2006, 17 millions d'euros ont également été consacrés à 200 000 tests de potentiels évoqués. Chez les patients hospitalisés, 41 871 EP uniques, 25 858 EP doubles, 12 448 EP triples et 5 448 MEP ont été pratiqués. En ambulatoire, 43 291 EP uniques, 15 001 EP doubles, 10 557 EP triples et 10 665 MEP on été réalisés. A l'inverse des EEG, le recours aux potentiels évoqués a augmenté au cours de la dernière décennie, surtout en ce qui concerne le code de remboursement pour deux potentiels évoqués.

Les ERP n'étant pas codifiés de manière distincte, leur utilisation est inconnue et constitue un sous-groupe des EEG et des EP.

EXAMEN DES DONNEES PROBANTES

L'objectif de la recherche des données probantes était d'évaluer la valeur de l'EEG, des EP et des ERP dans la pratique clinique, chez les patients présentant des plaintes et/ou une pathologie neurologique ou psychiatrique. Ces tests peuvent être utilisés à des fins diagnostiques ou pronostiques ou encore pour orienter la prise en charge clinique ou surveiller le traitement. Chacun de ces aspects a été pris en considération lors de l'étude.

MÉTHODES

D'abord, nous avons effectué une recherche systématique dans les synthèses méthodiques et les rapports HTA au sujet des tests. Dans un deuxième temps, nous avons passé en revue les recommandations cliniques (guidelines) sur les tests et sur les situations cliniques pour lesquels des preuves avaient été identifiées.

Les publications ont été sélectionnées en fonction des critères prédéfinis. Les restantes ont ensuite été évaluées en terme de qualité en utilisant la liste de l'INAHTA, celle des synthèses méthodiques du Centre Cochrane Néerlandais ou la liste d'AGREE. Les études de qualité médiocre ont été écartées.

Les publications ont été réparties en fonction de la pathologie considérée et les résultats des tests en ont été extraits. Il est important de noter que cette répartition en catégories n'implique pas que la pathologie est connue lors de l'exécution du test. Par exemple, lorsque sur la base de la présentation clinique ou d'autres tests éventuels, on soupçonne une schizophrénie chez un patient, les recommandations pour les investigations diagnostiques de la schizophrénie sont appliquées. Toutefois si chez ce même patient, un diagnostic différentiel d'épilepsie temporale est envisagé, les recommandations pour les investigations diagnostiques pour l'épilepsie s'appliquent également. Des patients peuvent également souffrir de manière concomitante de plusieurs pathologies. Dans ce cas, les recommandations pour toutes les pathologies associées pertinentes s'appliquent. En résumé, plusieurs recommandations peuvent être applicables à un seul et même patient.

RÉSULTATS

Les résultats de notre revue de littérature sont résumés dans le tableau 1. Il en ressort que l'EEG est essentiellement recommandé en cas de suspicion de troubles épileptiques. En outre, il peut être utilisé pour le diagnostic de la maladie de Creutzfeldt-Jacob et de l'encéphalite, pour le pronostic en cas d'encéphalopathie anoxique ischémique chez le nourrisson ainsi que pour prédire l'issue chez les patients comateux. Toutefois, dans ce dernier cas, les SEP représentent le test de prédilection en raison de leur meilleure valeur prédictive. De plus, les potentiels évoqués sont recommandés pour prédire l'issue en cas de traumatisme cérébral (SEP), pour le diagnostic du neurinome acoustique lorsque la résonance magnétique nucléaire (IRM) n'est pas possible, pour le diagnostic de la sclérose en plaques en cas d'incertitude diagnostique afin d'établir la dissémination dans l'espace (VEP), le diagnostic de la neuropathie lorsque l'on ne peut pas obtenir de réponses sensorielles périphériques (SEP), chez les patients paraplégiques en cas de suspicion de paralysie hystérique (MEP) et pour prédire la récupération de la marche (SEP). A l'heure actuelle, les potentiels évoqués « event-related » ne sont pas recommandés en routine pour le diagnostic, le pronostic ou le suivi des patients dans la pratique clinique.

Tableau 1: Résumé des recommandations

	Diagnostic	Pronostic	Suivi	Autre
ADHD	/	/	/	EEG en cas de suspicion d'un autre problème
Alcoolisme	/	/	/	/
Anxiété	/	/	/	/
Autisme	/	/	/	EEG en cas de suspicion de trouble épileptique
AVC	/	/	/	L'EEG peut être utile en cas de crise épileptique
Céphalées ou migraine	/	/	/	EEG en cas de suspicion de trouble épileptique
Coma ou état végétatif	/	SEP (ou EEG) pour prédire une issue défavorable		/
Démence	EEG en cas de doute à propos de la maladie d'Alzheimer	/	/	EEG en cas de suspicion de maladie de Creutzfeldt-Jacob ou d'amnésie épileptique passagère
Dépression ou trouble bipolaire	/	/	/	/
Electrochocs	NA	NA	NA	EEG avant le traitement si l'évaluation clinique l'impose
Encéphalite	EEG pour évaluer l'atteinte cérébrale	/	/	/
Encéphalopathie métabolique	/	/	/	/
Epilepsie	EEG constitue l'examen de référence (gold standard) chez les patients cliniquement suspects d'épilepsie	/	/	/
Infirmité motrice cérébrale	/	/	/	EEG en cas de suspicion d'épilepsie
Métastases cérébrales	/	/	/	EEG en cas de crises ne pouvant pas être identifiées comme épileptiques

	Diagnostic	Pronostic	Suivi	Autre
Mort cérébrale	EEG peut être utilisé pour confirmer le diagnostic	/	/	/
Neurinome acoustique	BAEP lorsque l'IRM est contre-indiquée ou n'est pas tolérée	/	/	/
Neuropathie	SEP peut être utile lorsque l'on ne peut pas obtenir de réponses sensorielles périphériques	/	/	/
Nourrissons souffrant d'encéphalopathie hypoxique ischémique	/	EEG à amplitude intégrée pour prédire une issue défavorable	/	/
Paresthésie	/	/	/	/
Radiculopathie	/	/	/	/
Retard global de développement	/	/	/	EEG en cas de suspicion d'épilepsie
Schizophrénie	/	/	/	L'EEG peut être utile s'il existe une indication clinique
Sclérose en plaques	VEP en cas d'incertitude diagnostique, afin de démontrer la dissémination dans l'espace	/	/	/
Spondylose cervicale	/	SEP or MEP pour prédire les signes/symptômes de la myelopathie	/	MEP pour diagnostiquer une compression de la moelle épinière au niveau cervical
Surdité unilatérale	/	/	/	/
Traumatisme crânien/Traumatisme cérébral	/	SEP pour prédire une issue défavorable	/	/
Traumatisme de la moelle épinière ou paraplégie	MEP en cas de suspicion de paralysie hystérique	SEP pour prédire la récupération de la marche	/	
Vertiges	/	/	/	/

SEP : potentiels évoqués somatosensoriels
VEP : potentiels évoqués visuels
MEP : potentiels évoqués moteurs
BAEP : potentiels évoqués auditifs
NA : non applicable

RECOMMANDATIONS

- Compte tenu de la complexité des tests en termes d'instrumentation, d'interprétation et de transmission des résultats, une formation adéquate du personnel qui les pratique est essentielle. Afin de rester à jour par rapport aux avancées techniques et cliniques, une formation intégrée à la formation médicale continue devrait être organisée par les associations professionnelles de façon systématique et sur une base continue.
- Il n'y a aucune justification clinique à l'utilisation de deux ou trois potentiels évoqués d'une modalité différente chez un même patient. Les codes de la nomenclature pour les tests de deux ou trois EP pourraient dès lors être supprimés.
- A l'heure actuelle, les données probantes pour les ERP (« event-related potentials ») sont insuffisantes pour en justifier une utilisation dans la pratique clinique. De surcroît, des normes portant sur l'instrumentation et la transmission des résultats font défaut. Par conséquent, le remboursement de ces tests n'est pas recommandé. Le remboursement des EPR en utilisant les codes des EEG ou des potentiels évoqués devrait être reconsidéré.

Scientific summary

Table of contents

ABBREVIATIONS

Abbreviation	Full name
AAN	American Academy of Neurology
AANEM	American Association of Neuromuscular and Electrodiagnostic Medicine
ACNS	American Clinical Neurophysiology Society
AD	Alzheimer disease
ADHD	Attention deficit hyperactivity disorder
A/D	Analogue to Digital
AHA	American Heart Association
APA	American Psychiatric Association
BAEP	Brainstem auditory evoked potentials
BAER	Brainstem auditory evoked response
CBO	Centraal Begeleidingsorgaan, Kwaliteitsinstituut voor de Gezondheidszorg
CKS	Clinical Knowledge Summaries
CMCT	Central motor conduction time
CN	Cranial nerve
CNV	Contingent negative variation
CRD	Centre for Reviews and Dissemination
CS	Conditioning stimulus
DARE	Database of abstracts of reviews of effects
DGEC	Dienst voor Geneeskundige Evaluatie en Controle
DLB	Dementia with Lewy bodies
EEG	Electroencephalography
ENT	Ear nose throat
EP	Evoked potentials
ERG	Electroretinogram
ERN	Error-related negativity
ERP	Event related potentials
FVEP	Flash evoked potentials
HTA	Health technology assessment
Hz	Hertz
ICSI	Institute for Clinical Systems Improvement
ICU	Intensive care unit
IFCN	International Federation of Clinical Neurophysiology
INAHTA	International network of agencies for health technology assessment
INAMI	Institut National pour Assurance de Maladie et Invalidité
ISCEV	International Society for Clinical Electrophysiology of Vision
KCE	Kenniscentrum/Centre d'expertise

LDAEP	Loudness dependent auditory evoked potentials
LEP	Laser evoked potentials
LTMA	Long-term monitoring for epilepsy
MEP	Motor evoked potentials
MeSH	Medical subject heading
MMN	Mismatch negativity
MRI	Magnetic resonance imaging
Ms	Milliseconds
MT	Motor threshold
NICE	National Institute of Health and Clinical Excellence
NIHDI	National Institute for Health and Disability Insurance
PDD	Parkinsons's disease with dementia
PVEP	Pattern visual evoked potentials
PSW	Periodic sharp wave complexes
qEEG	Quantitative EEG
RANZCP	Royal Australian and New Zealand College of Psychiatrists
RCP	Royal College of Physicians
REG	Electroretinogram
RIZIV	Rijks Instituut voor Ziekte en Invaliditeits Verzekering
SAEP	Short-latency auditory evoked potentials
SBU	Swedish Council on Technology Assessment in Health Care
SEP	Somatosensory evoked potentials
SICI	Short interval intracortical inhibition
SIGN	Scottish Intercollegiate Guidelines Network
SP	Silent period
SSEP	Short-latency somatosensory evoked potentials
TES	Transcranial electrical stimulation
TMS	Transcranial magnetic stimulation
TS	Test stimulus
TST	Triple stimulation technique
VEP	Visual evoked potentials

1 RESEARCH QUESTIONS AND SCOPE

This KCE project offers guidance for the use of electro-encephalogram (EEG) and evoked potentials (EP) or event related potentials (ERP) in clinical practice.

Electroencephalography (EEG) is defined as the recording of electric currents developed in the brain by means of skin electrodes or needle electrodes applied to the scalp.

Evoked potentials (EP), recorded at the scalp, are the electrical responses within the nervous system in response to an external stimulus. The evoked potential can be auditory (BAEP), somatosensory (SEP), or visual (VEP), according to the nature of the given external stimulus.

Another distinct class of evoked potentials are the "event related potentials" or ERPs. ERPs are also recorded after visual, auditory or somatosensory stimuli, but require in most cases that the subject distinguishes one stimulus from a group of other stimuli.

Motor-evoked potentials (produced by transcranial magnetic stimulation or TMS) are measured by electrodes at the level of the muscle, after stimulation of the scalp overlying the motor cortex. TMS is, generally speaking, a technique for noninvasive stimulation of the human brain.

In 2006, over 400,000 EEGs were recorded and reimbursed by the Belgian Health Insurance for a total amount of approximately 24 million Euros, whereas approximately 17 million Euros were spent on evoked potentials. The budget spent on the reimbursement of ERPs is quite high compared to the relative importance of these tests in clinical practice as defined in the literature (RIZIV/INAMI, DGEC). A survey by the RIZIV/INAMI showed that only 25% of neurologists/neuropsychiatrics use ERPs in their practice, for a set of very diverse indications.

Considering the high number of tests performed yearly, and the observed variation in indications, the purpose of this report is to describe good clinical practice for the use of these tests in relation to current practice in Belgium. The purpose of the project was by no means to audit current practice.

1.1 FIRST RESEARCH QUESTION

What is the current use of the EEG and EP in Belgium, and what are the costs for the Health Insurance and the patients?

1.2 SECOND RESEARCH QUESTION

What is the scientific evidence on the diagnostic and/or prognostic value of EEG, EP and event related potentials?

1.3 SCOPE

This report is focused on the use of EEG, evoked potentials and event related potentials for clinical practice in neurology or psychiatry. Experimental use or use for scientific purposes is outside the scope of this report.

Intraoperative use of the tests, for example spinal monitoring, is excluded as well. In addition, indications treated in specialised settings were excluded, for example sleep-related disorders.

1.4 LIMITATIONS

Guidance is based on the available studies, and can change as new studies are published. Consequently, this guidance should be regarded as a general line of action. It is by no means the intention that the guidance issued in this report should be strictly adhered to in every patient. Adherence to the guidance does not guarantee success in every patient, nor can it be regarded as the only possible clinical approach thereby excluding other approaches that aim for the same result. The ultimate decision of using a certain procedure or treatment remains the responsibility of the treating physician, who takes all clinical information on the patient into account by doing so.

In addition, it is desirable that this guidance should be adapted to the local context.

2 STANDARDISATION AND TECHNICAL ACCURACY

2.1 INTRODUCTION

An EEG reflects the temporal and spatial summation of synchronized postsynaptic cortical potentials, measured as electrical signals on the scalp. Scalp EEG activity is comprised of multiple oscillations. These have different characteristic frequencies, spatial distributions and associations with different states of brain functioning (such as awake versus asleep).

Evoked potentials are changes in electrical brain activity stereotyped and time-locked to an event (e.g. stimulus). EPs and ERPs can be distinguished based on the type of stimulus, the polarity, the latency, and the scalp distribution. The stimulus consists of clicks or tones (Brain-Stem Auditory Evoked Potential, BAEP), pattern reversal or flashes (Visual EP, VEP), electrical stimulation (Somatosensory EP, SEP), stimulation of the motor cortex (Motor Evoked Potentials, MEP). The recorded potentials are characterized by a specific latency between the event and the response, and can be grouped into short, middle or long-latency EPs or ERPs. Most EPs cannot be seen in routine EEG recordings. This is because of their low amplitudes and their admixture with normal background brain waves. To increase the signal-to-noise ratio an often-used method is averaging. This can be done when the same stimulus is presented many times. Historically EPs have been studied in patients since the early 1950s, first focusing on long-latency components having a large amplitude. Since the early 1970s short and middle latency potentials with a smaller amplitude were studied, aided by advances in transistor technology and the ability to amplify biological signal of a fraction of a microvolt.[1]

Event-related potentials are voltage fluctuations that display stable time relationships to a definable reference event, some physical or mental occurrence. These (often long-latency) potentials can be recorded from the human scalp and extracted from the ongoing EEG by means of filtering and signal averaging.[2] The stimulus is most often an auditory stimulus, but can be extended to more complex stimulation paradigms and modalities.

Standardisation of tests contributes to the validity of the test. Adherence to a standard validated technique is critical when EEG and evoked potentials are used for clinical decision making. In this chapter, the technical aspects of EEG, evoked potentials and event related potentials are summarized.

2.2 METHODS

English language technical guidelines and standards were searched in Medline, CRD, SumSearch, and general search engines such as Google and Yahoo. In addition, the websites of the medical specialist organisations of the neighbouring countries France, the Netherlands and Germany were identified and searched for technical guidelines and standards. All search terms used are listed in appendix 1.

2.3 RESULTS FOR STANDARDS AND TECHNICAL GUIDELINES

A list of standards and technical/clinical practice guidelines for EEGs and/or EPs were identified:

- the American Clinical Neurophysiology Society (ACNS)[3-10] and available at https://www.acns.org (updated in 2006)
- the International Federation of Clinical Neurophysiology (IFCN) at http://www1.elsevier.com/homepage/sah/ifcn/doc/standard.htm,
- The American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) at http://www.aanem.org/publications/guidelines.cfm

- the International Society for Clinical Electrophysiology of Vision (ISCEV) [11] (http://www.iscev.org/standards/pdfs/vep-standard-2004.pdf)
- the College of Physicians and Surgeons of Alberta, Canada, (http://www.cpsa.ab.ca/facilitiesaccreditation/neurophysiology_standards.asp)
- the Deutschen Gesellschaft für Klinische Neurophysiologie (http://www.dgkn.de/fileadmin/richtlinien_pdf/ep03.pdf)
- Possible quality indicators are presented in an AANEM paper.(http://www.aanem.org/documents/gl_establish_qa_program.PDF)
- Guidance for the qualifications of US physicians performing electrodiagnostic procedures. (http://www.aanem.org/documents/who_is_qualified.PDF), (https://www.acns.org)
- Guidance for the set-up of an ERP lab and performing ERP testing is provided by Otte.[12]

2.4 PATIENT ISSUES

The risks in electrodiagnostic medicine are discussed in a document of the AANEM.[13] (http://www.aanem.org/documents/risksinEDXMed.pdf).

The EEG is painless, with a minimum of discomfort. Precautions should be taken as to avoid transmission of pathogens between patients, staff, and equipment. Breaking the skin when applying scalp EEG electrodes, creates the risk of infection from bloodborn pathogens such as HIV, Hepatitis C, and Creutzfeldt Jacob Disease. Modern engineering principles suggest that excellent EEG signals can be collected without scalp abrasion. (http://www.ccs.fau.edu/eeg/ferree2001.pdf) Subcutaneous needle electrodes should not be used for ERPs because of the risk of infection. The investigator must balance the need for reducing skin potentials with the necessity of preventing any possibility of infection. Impedances of less than 2 kOhm occur only if the skin layer is effectively breached, which clearly increases the risk of infection. (http://www.ccs.fau.edu/eeg/picton2000.pdf)

Some patient categories are at risk for electrodiagnostic procedures.[13] Needle insertion in patients at risk for bleeding complications may induce bleeding. Specific precautions are given for patients with cardiac pacemakers. Expert consultation is required when the use of electrodiagnostics is considered in patients with implanted defibrillators. Expert advice is also needed in case of transmagnetic stimulation (TMS) in patients with a cardiac pacemaker, a deep brain, spinal or bladder stimulator, or intracranial metallic clips. Electric transcranial stimulation may be dangerous in patients with skull discontinuities after craniotomy. Care should be taken in patients with a history of epileptic seizures or taking drugs which might influence the excitability threshold.[14]

Finally, care should be taken as to avoid the occurrence of pneumothorax or peritonitis when needles are inserted in the thoracic and abdominal region.

The AANEM found no contraindications to perform evoked response testing during pregnancy (based on a literature search in 2007). (http://www.aanem.org/documents/EDXPregnantWomen.pdf)

For the conduct of ERPs, the investigator should take into account the nervousness of the patient which can be induced by a patient-unfriendly examination room.[12]

2.5 THE ELECTRO-ENCEPHALOGRAM (EEG)

Scalp EEG activity is comprised of multiple oscillations. These have different characteristic frequencies, spatial distributions and associations with different states of brain functioning.

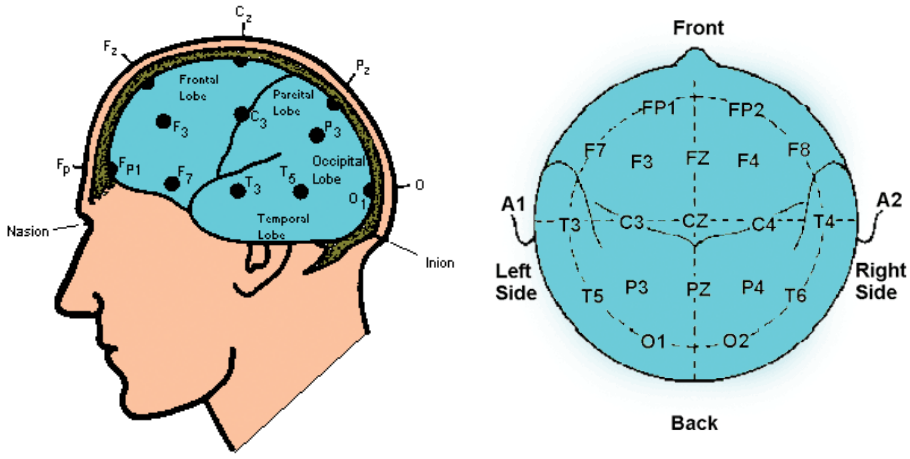
- Alpha waves have a frequency of 8 to 12 cycles per second. Alpha waves are present only in the waking state when the eyes are closed but the subject is mentally alert. Alpha waves go away (desynchronise: "Berger" reaction) when the eyes are open or the subject is concentrating.

- Beta waves have a frequency of 13 to 30 cycles per second. These waves are normally found when the subject is alert or has taken high doses of certain medicines, such as benzodiazepines.
- Delta waves have a frequency of less than 3 cycles per second. These waves are normally found only during sleep or in young children.
- Theta waves have a frequency of 4 to 7 cycles per second. These waves are normally found only during sleep or in young children.
- Sharp waves have a duration of 70-200ms. Spikes are sharp waves with a duration of 20-70ms.

2.5.1 Instrumentation

Electrode locations and names are defined by the international 10–20 system (see Figure 1) for most clinical and research applications. This system ensures that the naming of electrodes is consistent across laboratories.

Figure 1:10-20 system illustration - profile view and top view



Each electrode is connected to one input of a differential amplifier (one amplifier per pair of electrodes); a common system reference electrode is connected to the other input of each differential amplifier. These amplifiers amplify the voltage between the active electrode and the reference. In analog EEG, the signal is then filtered, and the EEG signal is processed as the deflection of pens as paper passes underneath. Appropriate calibration should be made at the beginning and end of every analog EEG recording.[15] The ACNS guideline also states the baseline record should contain at least 20 min of technically satisfactory recording.[9]

Most EEG systems these days, however, are digital, and the amplified signal is digitized via an analog-to-digital converter. Analog-to-digital sampling typically occurs at 256-512 Hz in clinical scalp EEG. The digital EEG signal is stored electronically and can be filtered for display. The high-pass filter (0.5-1 Hz) removes slow artefacts, such as electrogalvanic signals and movement artefacts, whereas the low-pass filter (35–70 Hz) removes high-frequency artefacts, such as electromyographic signals. An additional notch filter is typically used to remove artefacts caused by electrical power lines (50 Hz in Belgium). Recording the EEG in electronic format (digital EEG) has become standard practice: https://www.acns.org//pdfs/QEEG%20Statement.pdf. IFCN standards for the digital recording of clinical EEG are also available.[16]

An extension of the EEG technique, called quantitative EEG (qEEG), involves manipulating the EEG signals with a computer using the fast Fourier, wavelet or other transform algorithm. In addition to the paper EEG, the stored qEEG data allow for:

1. Signal analysis
   - automated event detection, e.g. seizure detection

- monitoring and trending, e.g. intra-operative or in the intensive care unit (ICU)
- source analysis, e.g. help to locate an epilectic focus
- frequency analysis, e.g.. look for excess of slow wave activity
  - subdivision of the EEG into different frequency bands, such as delta, theta, alpha, beta and gamma;
  - estimation of the absolute or relative power in a band;
  - calculating the ratio between bands;
  - investigating left/right symmetry and
  - investigating spectral coherence (i.e., synchronization between channels for evaluation of seizure origin).

2. Topographic displays ("brain maps") and
3. Statistical comparisons versus normative values and diagnostic discriminant analysis (determine with which diagnostic group the patient's EEG is statistically most closely associated)

Dedicated qEEG-software is available. An important critique with regard to qEEG systems is the use of normative databases as most are proprietary and remain a black box for the clinician using the system. In contrast to the routine neurological EEG which uses bipolar montages to detect epileptic foci, qEEG systems will use monopolar montages in order to get a more general idea of the spread of the activity. In fact these are also bipolar montages but they use "linked ears" as reference, average of all points of measurement, or a local average (Laplacian reference).[12]

Standards for EEG instrumentation are available from IFCN.[17] Specific guidance for filter settings and recording is also given by the College of Physicians and Surgeons of Alberta, Canada. (http://www.cpsa.ab.ca/facilitiesaccreditation/attachments/EEG%20Standards.pdf) IFCN guidelines for topographic and frequency analysis of EEGs and EPs have been published.[18]

2.5.2 Procedures

Certain procedures are used to obtain adequate activation of the EEG, e.g. the addition of photic stimulation and hyperventilation. These procedures may trigger seizures in persons with epilepsy and often require increased recording time. Guidelines recommend hyperventilation for a minimum of 3 minutes should be used routinely unless medical or other justifiable reasons contraindicate it. Recording should be continued for at least 1 min after cessation of overbreathing. Recordings with eyes-open should be compared with eyes-closed. At the end of the session the patient may be asked to look at a flashing light to evaluate whether this triggers epileptiform activity.

The recommendations for routine EEG by the International League against Epilepsy were included in the NICE (National Institute of Clinical Excellence) clinical practice guideline for epilepsy (http://www.nice.org.uk/nicemedia/pdf/CG020fullguideline.pdf)

- The 'modified combined nomenclature' derived from the 10-20 system should be used for electrode location
- The minimum number of electrodes should be 21 for adults and 9 for children
- At least bipolar montages with longitudinal and transverse chains should be included
- Artefacts of eye movement should be excluded using eye-opening, eye-closing, and blink procedures
- Activation procedures, such as hyperventilation and photic stimulation, should be used.

Additional minimum technical standards for EEG recordings are available for paediatric use[19], and for the evaluation of suspected brain death.[20]

2.5.2.1 Sleep EEG

A sleep EEG may be carried out in hospital, or at home using an ambulatory EEG. A sleep EEG lasts up to three hours or up to eight or nine hours if it is a night's sleep.

2.5.2.2 Sleep Deprived EEG

Depriving someone of sleep can cause changes in the electrical activity of the brain. Sleep-deprived EEGs can be used when a routine EEG was not informative.

2.5.2.3 The ambulatory EEG

The EEG can be recorded over a period of one or more days, using a small portable EEG recorder which is worn on a waist belt.

2.5.2.4 Long-term EEG monitoring with or without video recording

Long-term monitoring for epilepsy (LTME) refers to the simultaneous recording of EEG and clinical behaviour over extended periods of time to evaluate patients with paroxysmal disturbances of cerebral function. The 1993 IFCN[21] and 1994 ACNS guidelines for LTME[22] have recently been updated and are available at www.acns.org. In case of video-telemetry, a video camera is linked to an EEG machine. The camera will visually record the patient's movements and at the same time the EEG machine will record the brainwave pattern.

2.5.2.5 Comatose and critically ill patients

Standards of clinical practice of EEG and EPs in comatose patients have been proposed by IFCN.[23] Standard terminology for rhythmic and periodic EEG patterns in critically ill patients has been proposed by an ACNS subcommittee.[24]

2.6 EVOKED POTENTIALS

Technical requirements for evoked potentials are listed in Table 1 and are based on published standards. Sources of information used to construct this table can be found below in the text.

Table 1: Characteristics of different types of evoked potentials

Parameter	VEP	(B)AEP	SEP	MEP
Stimulus	Checkerboard Pattern Check size 30s of visual angle Luminance/contrast: documented, constant Time for reversal <20ms Frequency of reversal 0.5-2Hz	Click 100ms square wave, standard audiometric earphones Duration <= 250 microsec Frequency 10-30Hz Intensity: 60-90dB above normal threshold (max 100dB) Contralateral ear receives masking noise of 20-40dB lesser intensity	Square wave constant current, 0.1-0.3ms Frequency (3-)5Hz Intensity 4mA (or 10-20%) above motor threshold, 3-4x sens. threshold N. medianus at wrist N. tibialis post. at knee Point of stimulation close to cathode	Flat round coil Hand: Cortex: flat centrally over Cz Cervical vertebral body 7 Leg: Cortex: flat centrally over Fz Lumbar vertebral body 5 Stimulus: current clockwise for target muscle left, and vise versa Slight tonic contraction of target muscle with cortical stimulation 20% of max Stimulus: 1.5x threshold value
Remarks	Monocular stimulation Fixation at centre Glasses on No sedation	Monoaural stimulation Possible under sedation or general anesthesia	Height and age to be recorded Minimum skin temperature norms	
Electrodes placement	Occipital: Oz, O1, O2 Hemifield study: T5 or PO7, T6 or PO8 versus Fz Reference: vertex Cz	Two channel recordings (both ears) Ear lobe or mastoid versus Cz Reference: mid-frontal Fz	N. medianus Brachial plexus: Erb Spinal: vertebr. body 7 and 2 Cortex: C3' or CP3, C4' or CP4 contralateral versus Fz N. tibialis post. Lumbosacral L1 versus Beckenkamm Cortex: CPz versus Fz	Hand: Inteross. dors. I Abduct.poll.brev. Abduc.dig.min. Leg Tib.ant Abduct.hall Ext.dig.brev. Electrodes at muscle end plate, grounding at distal tendon joining muscle.
Polarity	Negative upwards Reference positive	Positive upwards Reference negative	Negative upwards Reference positive	Negative upwards Reference positive
Impedance	< 5kOhm	<3-5kOhm	< 5kOhm	< 5kOhm
Filter band-pass	0.5-100Hz	30-3000Hz	10-3000Hz or Cortical 5-1000Hz, Spinal 10-1000Hz	1-2000Hz

Parameter	VEP	(B)AEP	SEP	MEP
Recording sweep	250-500ms	10-20ms	50ms (n. medianus) 100ms (n. tibialis post.)	100ms
Trials averaged	50-200	1000-4000	500-2000	
Signal to noise	1/2	1/10	1/4 - 1/10	
Minimum Recordings	Two for each VEP condition	Two for each ear	Two traces should superimpose almost exactly	4-5x
Reproducibility	1ms resolution Latency P100 +/- 20% amplitude P100	0,1ms resolution Latency wave I, II, V +/- 20% amplitudes	N. medianus 0,25ms latency N. tibialis post. 0,5ms latency +/- 20% amplitude	0,5ms latency +/- 20% amplitude
Interpretation	P100 latency P100 amplitude P100 morphology	Wave peak latency: I, III, V Interpeak intervals Amplitude ratio I/V (or V/I)	Latencies arm N9; N13; N14; N20 Leg: N18 lumbar; P40 Amplitude: N20, P40 Interpeak latencies Conduction velocity Side-to-side comparisons Correct for height	Central and peripheral latency Central motor conduction time Arm: cortex-cervical Leg: cortex-lumbar Ratio of amplitudes cortex/peripheral Morphology of potential Correct for height

Note: differences in characteristics or requirements exist between the various sources consulted, the table above should therefore not be used as a standard

2.6.1 Visual Evoked Potentials (VEP) and Electroretinogram (REG)

VEPs are electrophysiologic responses to stimulation by visual stimuli. VEPs test the function of the visual pathway from the retina to the occipital cortex. It measures the conduction of the visual pathways from the optic nerve, optic chiasm, and optic radiations to the occipital cortex. It is important to note that, although the axons from the nasal half of the retina decussate at the optic chiasm, the temporal axons do not. Therefore, retrochiasmatic lesions may not be detected.

An electroretinogram (ERG) is the mass response of the retina to visual stimulation. ERG testing aims to document retinal dysfunction and distinguish whether the abnormality involves the photoreceptors or the ganglion cell layer. In conjunction with VEP testing, the ERG can help clarify whether a VEP abnormality is due to retinal disease or to more central visual pathway disease.[6]

2.6.1.1 Instrumentation

The scalp electrodes should be placed relative to bony landmarks, in proportion to the size of the head, according to the International 10/20 system.[7, 25] Responses are collected over Oz, O1, and O2 and with hemifield studies at T5 and T6 electrodes using the standard EEG electrode placement.

In order to perform a technically adequate clinical electrophysiological procedure it is necessary to calibrate the stimulating and recording equipment.[26]

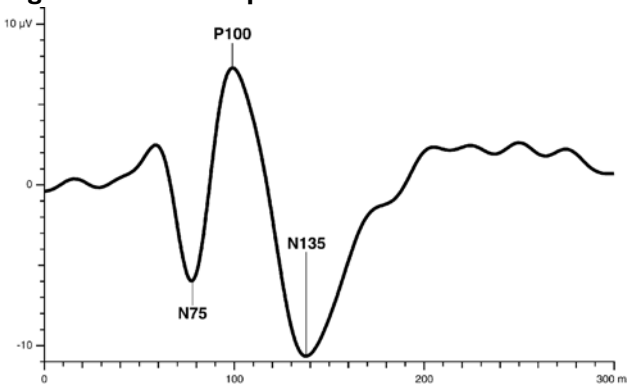
2.6.1.2 Procedures

Stimulation at a relatively low rate (up to 4/s) will produce "transient" VEPs. Stimulation at higher rates (10/s or higher) will produce responses that merge into relatively simple oscillations occurring at the frequency of stimulation. These persist for the duration of the stimulation and are referred to as "steady-state" VEPs. VEP peak latency refers to the time from stimulus onset to the maximum positive or negative deflection or excursion.

Responses evoked by patterned stimuli are "pattern" VEPs or PVEPs. Responses evoked by unpatterned stimuli are "flash" VEPs or FVEPs.[6] The standard pattern reversal stimulus consists of black and white checks that change phase abruptly and repeatedly (i.e., black to white and white to black), at a specified number of reversals per second. Pattern reversal is the preferred technique for most clinical purposes as the results are less variable in waveform and timing than the results elicited by other stimuli. The flash VEP is particularly useful when optical factors or poor cooperation make the use of pattern stimulation inappropriate.

For pattern reversal, the VEP consists of N75, P100 and N135 peaks. The P100 waveform is at its maximum in the midoccipital area. The responses are averaged and the P100 positive polarity waveform that appears in the posterior head region is analyzed.

Figure 2: A normal pattern reversal VEP



Copied from Odom et al.[11] (American standard of reporting)

For standard testing, specifications have been published for the stimulus in terms of the visual angle of each check, the reversal frequency, the number of reversals, the mean luminance, the pattern contrast, and the field size. Testing circumstances should be standardized as well, including seating distance of 70-100 cm from the monitor screen. In order to avoid masking of a unilateral conduction abnormality, monocular stimulation is used by covering the eye not being tested with a patch. The patient focuses on a TV screen which displays the checkerboard pattern. For children or others whose attention may wander, goggles are used which show the pattern to one eye at a time. Flash VEP should be elicited by a well defined flash presented in a dimly illuminated room. Sedation should not be used, and note should be taken of medications that the patient is taking.

A standard for performing VEP is available from the International Society for Clinical Electrophysiology of Vision (ISCEV)[11] (http://www.iscev.org/standards/pdfs/vep-standard-2004.pdf) and from the American Clinical Neurophysiology Society (ACNS)[6] This standard also covers REG. Requirements for VEP using the pattern reversal technique have been published by the College of Physicians and Surgeons of Alberta, Canada (http://www.cpsa.ab.ca/facilitiesaccreditation/neurophysiology_standards.asp). This document provides a number of requirements for VEPs, including the following.

- Time for pattern reversal <20 ms.
- Rate of reversal between 1-2 seconds.
- Stimulus viewed monocularly.
- Patient wears glasses to correct for any refractive error.
- Observe patient during recording to ensure that he/she is fixating at the centre of the stimulus.
- Record visual evoked potentials from the mid-occipital and lateral regions relative to the mid-frontal region.
- Filter band-pass of the amplifier between 1-100 Hz.
- Record response using a sweep of at least 250 ms.
- Averaging carried out over 100-200 trials.

2.6.1.3 Reporting

A minimum of two recordings of each VEP condition should be acquired, measured and displayed. Reports should specify the stimulus parameters; the eye tested and the recording parameters; the filter settings and the locations of the positive (i.e., active) and negative (i.e., reference) and indifferent (i.e., ground) electrodes. In the US, it is recommended that VEP traces be presented as positive upwards, whereas in Europe, the upward presentation of a negative polarity is used. In any case, traces should have a clear indication of polarity, time in milliseconds, and amplitude in microvolts. All VEP reports should include normative values and the limits of normal. Normative data should be assembled on a lab-by-lab basis.[11] The report should also indicate whether the recordings meet the international standard.[11]

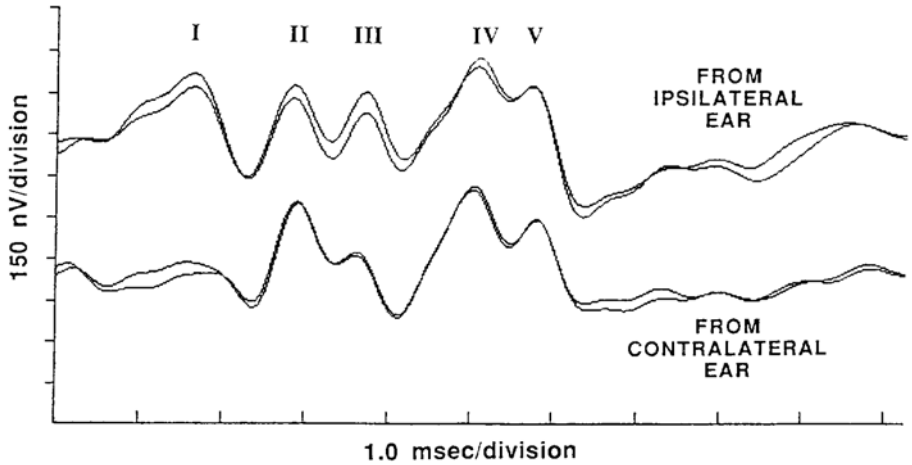
2.6.2 Brain-Stem Auditory Evoked Potential (BAEP) or Brain-Stem Auditory Evoked Response (BAER)

BAEPs are responses of the auditory nerve, brainstem, and, perhaps, higher subcortical structures to acoustic stimulation. Most of its components appear to arise from multiple sources, preventing a simple one-to-one correspondence between potential generators and individual BAEP waves. Generators currently are postulated to be as follows:

- Wave I - Action potential of the cranial nerve (CN) VIII
- Wave II - Cochlear nucleus (and CN VIII)
- Wave III - Ipsilateral superior olivary nucleus
- Wave IV - Nucleus or axons of lateral lemniscus
- Wave V - Inferior colliculus

Short-latency auditory evoked potentials (SAEPs) are electrical responses of the auditory pathways that occur within 10—15 ms of an appropriate acoustic stimulus in normal subjects. This generic term encompasses two categories of events: the "electrocochleogram" and the "brainstem auditory evoked potentials" (BAEP). The electrocochleogram consists of electrical responses of the cochlea and the auditory nerve to acoustic stimulation.[5]

Figure 3: the 5 principal BAEP peaks



The 5 principal BAEP peaks are identified by numerals I-V Peaks shown for a typical adult patient. (Copied from Nuwer et al.[27]).

2.6.2.1 *Instrumentation*

Standards for brain-stem auditory evoked potentials have been published by IFCN[27] and ACNS.[5] These guidelines are limited to the neurological applications of short-latency auditory evoked potentials, i.e., to the use of these responses to detect and approximately localize dysfunctions of the auditory pathways within the auditory nerve and brainstem. The audiologic applications of these potentials, some of which require the utilization of frequency-specific stimuli to assess and quantify hearing function, were not included.

An electrode is placed on each ear lobe and at Cz. In order to record a high quality BAEP, it is highly recommended that the impedance of the electrodes is below 3 kOhm.

2.6.2.2 *Procedures*

Standard broadband click stimulation is used on the ear tested, while the contralateral ear receives masking noise. Each ear is usually tested twice. The test can also be performed under sedation or under general anesthesia.

Requirements for Auditory Evoked Potentials have been published by the College of Physicians and Surgeons of Alberta, Canada. (http://www.cpsa.ab.ca/facilitiesaccreditation/neurophysiology_standards.asp). The stimulus used, should be a click obtained by passing a 100 ms square wave through standard audiometric earphones. The intensity of the stimulus has to be between 60-90 dB above normal adult thresholds of this stimulus. For neurological purposes, the clicks shall be presented monaurally at rates between 10 and 30/s. Recordings should also be obtained from the contralateral ear. (i.e. Two channel recordings). The responses shall be recorded between an electrode at the vertex or mid-frontal region and one at the earlobe or mastoid of the ear being stimulated. The filter band pass of the amplifier shall be 30-3000 Hz. The response shall be recorded over a sweep between 10-15 ms. Averaging shall be done using 1000-4000 trials.

2.6.2.3 Reporting

The BAEP measurements must include the following: (1) wave I peak latency; (2) wave III peak latency; (3) wave V peak latency; (4) I-III interpeak interval; (5) III-V interpeak interval; (6) I-V interpeak interval; (7) wave I amplitude; (8) wave V amplitude; and (9) wave IV-V/I amplitude ratio.[5] The I-V interpeak interval, for example, represents the conduction form the proximal eighth nerve through pons and into the midbrain. Factors influencing peak latencies of BAEPs include age, sex, auditory acuity stimulus repetition rate, intensity, and polarity.

A typical upper limit of normal is 4.5 ms, with slightly lower values for young women and slightly higher for older men. Normal right-left asymmetries for the I-V interpeak should be at most 0.5 ms.[27] There is a large variation with age, from a I-V interpeak interval of 5.1-5.2 ms in (a term) neonates to 4.0 ms in children of 2-6 jaar and older. The male-female variation is relatively small compared with variations between subjects. [28]

2.6.3 Somatosensory EP (SEP) and short latency SEP (SSEP)

SEPs may be used to assess the functional integrity of the central and peripheral sensory pathways. SEPs can be recorded after physiological stimuli (eg, muscle stretch). However, electrical stimulation is usually administered to elicit the potential. The usual sites for SEP stimulation are the median nerve at the wrist, the posterior tibial nerve, and the common peroneal nerve at the knee.

2.6.3.1 Instrumentation

For the median nerve response, recordings shall be taken from the brachial plexus, the spinal cord, and the cortex. Brachial plexus responses should be recorded from an electrode on Erb's point (Erb), located within the angle formed by the posterior border of the clavicular head of the sternocleidomastoid muscle and the clavicle, 2-3 cm above the clavicle. The designations EPc and EPi refer to the electrode contralateral or ipsilateral, respectively, to the wrist stimulated. The cortical response should be recorded from a location on the scalp contralateral to the stimulation. The designations Cc and Ci refer to the contralateral or ipsilateral electrode, respectively, to the wrist stimulated.

For recording lower extremity SEPs, electrodes are placed over the lumbosacral spine, placed in the midline and labelled with the name of the vertebral body they are placed on, followed by the letter S, for example T10S. If the lumbar response is not clearly recognizable or not used, the nerve action potential of the posterior tibial nerve at the knee shall be recorded to demonstrate normal or abnormal function in the nerve. The cortical response shall be recorded maximally from an electrode midway between the vertex and the mid-parietal location.

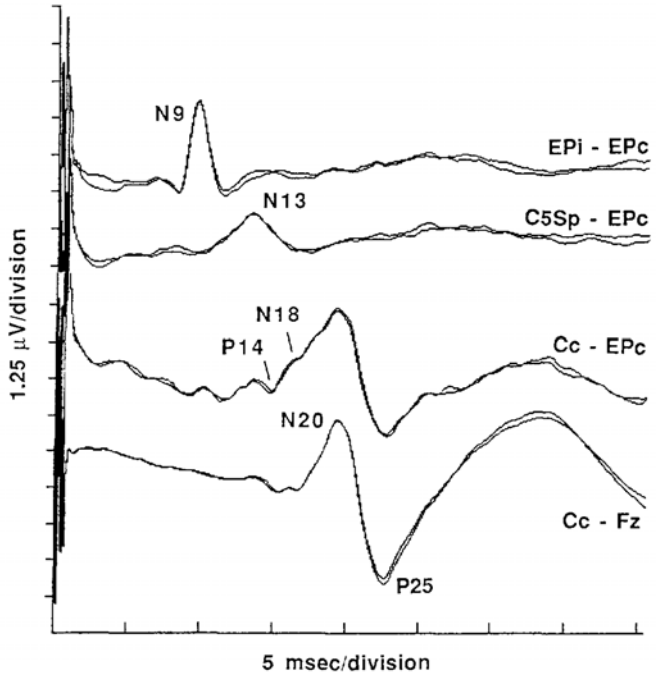
2.6.3.2 Procedures

Standards for short latency SEPs and corresponding reference values have been published by IFCN[29] and ACNS.[4] The scope of the latter guideline is limited to SSEPs following median nerve stimulation at the wrist for the upper extremity, and posterior tibial nerve stimulation at the ankle for the lower extremity.

Requirements for SEPs have been published by the College of Physicians and Surgeons of Alberta, Canada. (http://www.cpsa.ab.ca/facilitiesaccreditation/neurophysiology_standards.asp). These requirements include: "The patient's height should be recorded. The stimulus used should be a constant-current pulse supplied through electrodes located on the skin over the nerves being evaluated. The point of stimulation shall be close to the cathode. The duration of stimuli shall be between 0.1 and 0.3 ms. Stimuli should be presented at rates near 5/s. The intensity of the stimulus shall be adjusted to a level that is 10-20% higher than the threshold for eliciting a visible motor twitch. Somatosensory responses shall be recorded using a filter band-pass of 10-3000 Hz.

Averaging shall be done using 500-2000 trials. The sweep duration shall be 40-50 ms for median nerve responses. The sweep duration shall be 100 ms for tibial nerve responses."

Figure 4: SEP from median nerve stimulation



Typical peaks in each of the 4 recording channels in a normal patient. (Copied from Nuwer et al.[29])

The stimulating current is adjusted to produce a minimal movement of the joint involved. This stimulation intensity may cause some twitching and tingling but is typically well tolerated by patients. Because limb cooling affects peripheral nerve conduction velocity, minimum skin temperature norms should be established for each laboratory. In general, 2-3 separate traces should superimpose almost exactly. Tracings are produced based on the averaging of 500 to 2000 trials. [29]

Amplitude, peak, and interpeak latency measurements with side-to-side comparisons are used to assess abnormalities. Responses recorded are classified according to specific latencies. Short-latency SEPs refer to the portion of the SEP waveform that occurs within 25 milliseconds after stimulation of the upper extremity nerves, 40 milliseconds after stimulation of the peroneal nerve, or 50 milliseconds after stimulation of the tibial nerve. Long-latency refers to the waveforms recorded more than 100 milliseconds following stimulation of these nerves. Middle-latency SEP refers to waveforms that occur between these 2 periods. Middle and long-latency SEPs show more variation making clinical use more difficult. The peripheral conduction velocity is calculated by dividing the arm length by the N9 latency. Similarly, using subtraction of two specific latencies, the conduction time plexus-cord and cord-cortex can be calculated and compared with reference ranges.

2.6.3.3 Reporting

The physician's SEP report should note which nerves were tested, latencies at various testing points, and an evaluation of whether the resulting values are normal or abnormal. Waveforms are described in terms of morphology, amplitude, and dispersion. Each laboratory should establish reference values for latencies and interpeak latencies. Latencies increase with patient's age and height.

2.6.4 Laser-evoked potentials

Laser-evoked potentials (LEPs) are a method of investigating pain using radiant-heat pulse stimuli by laser stimulators, which selectively excite the free nerve endings (A-delta and C) in the superficial skin layers.

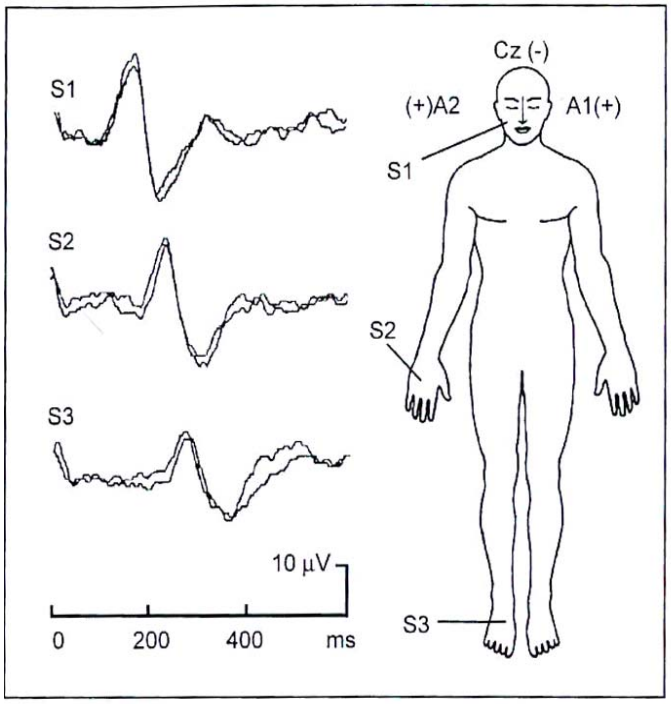
2.6.4.1 Instrumentation

A CO_2 laser stimulator is used to record LEPs after face, hand, and foot stimulation.

2.6.4.2 Procedures

The recordings include the perceptive threshold, latency and amplitude of the main vertex components, and their side-to-side differences. The LEP signals are nociceptive responses. The LEP signal of the A□ nociceptor is a late negative-positive complex (N2-P2) with maximal amplitude at the vertex. The unmyelinated nociceptive pathway related to C-fibre activation produces an ultralate LED, and is technically more difficult to study.[30]

Figure 5: LEP after CO2 stimulation at the cheek (S1), hand (S2) and right foot (S3)



The N2-P2 complex can be seen between 200 and 300 ms. (copied from Nederlandse Vereniging voor Neurofysiologie, http://www.nvknf.nl)

2.6.5 Motor Evoked Potentials (MEP)

MEP can detect disruption on a motor pathway of the brain or spinal cord. The motor cortex can be stimulated using transcranial magnetic stimulation (TMS) or transcranial electrical stimulation (TES). Methods for MEP have been published by the IFCN[14] and have been reviewed by IFCN[31] and Chawla (www.emedicine.com/neuro/topic222.htm).

2.6.5.1 Transcranial magnetic stimulation (TMS)

Magnetic stimulation of the nervous system can occur only in the setting of a rapidly changing magnetic field. Subjects exposed to a constant field, for example in magnetic resonance imaging (MRI), do not experience stimulation of nervous tissue. The intensity of the secondarily produced electrical field in nervous tissue is related to the speed of change in magnetic field strength.

A major advantage of magnetic stimulation over electrical stimulation is its ability to penetrate tissues regardless of electrical resistance. The drop-off is essentially the same for air, bone, fat, muscle, and saline.

2.6.5.2 Instrumentation

In choosing coils, the trade-off is between strength and focality of stimulation. Coil diameter may vary between 5 cm and 15 cm. Large-diameter coils stimulate over a wider area but are less focal than small-diameter coils.

2.6.5.3 Procedures

Several TMS techniques are covered in an IFCN review.[31] Tests used in clinical practice include motor threshold (MT), central motor conduction time (CMCT), the triple stimulation technique (TST), the silent period (SP), and short-interval intracortical inhibition (SICI).

Motor threshold (MT) refers to the lowest TMS intensity capable of eliciting small motor-evoked potentials (MEPs). The recruitment curve, also known as input–output or stimulus–response curves, refers to the increase in MEP amplitude with increasing TMS intensity. Compared to MT, this measure assesses neurons that are intrinsically less excitable or spatially further from the centre of activation by TMS. Recruitment curves are generally steeper in muscles with low MT, such as intrinsic hand muscles.

Central motor conduction time (CMCT) is an estimate of the conduction time of corticospinal fibres between motor cortex and spinal (or bulbar) motor neurons. It includes the times for excitation of cortical cells, conduction via the corticospinal (or corticobulbar) tract and excitation of the motor neuron sufficient to exceed its firing threshold. The estimate is made by subtracting the spinal motor neuron to muscle latency from the cortex to muscle latency.

The triple stimulation technique (TST) is a collision method. Three stimuli are given in sequence with appropriate delays. The first stimulus is TMS. It is followed by two supramaximal stimuli given to the nerve supplying the target muscle, first distally (close to the muscle) and then proximally (as proximally as possible on the nerve). Two collisions of the evoked action potentials occur. If a spinal motor neuron was excited by TMS, its descending action potential collides with the antidromic potential evoked by the distal peripheral stimulus. If a spinal motor neuron was not excited by TMS, the antidromic potential evoked by the distal stimulus does not collide and ascends. After a second delay, the proximal stimulus evokes the response that will be studied. The action potentials evoked by the proximal nerve stimulus will only descend to the target muscle if no antidromic potential is ascending from the peripheral stimulus and they will collide if an action potential ascends. Therefore, only those action potentials will descend on the axons that were excited initially by TMS. In contrast to the original desynchronized action potentials evoked by TMS, the action potentials are now synchronized because they are elicited by a single proximal nerve stimulus. The response is compared to that of a control curve, obtained by a triple stimulation performed on the peripheral nerve.

Besides evoking MEPs in the target muscles, single TMS pulses delivered during voluntary muscle contraction produce a period of EMG suppression known as the silent period (SP). The excitability threshold for MEP elicitation may be lowered by performing a voluntary contraction of the target muscle. TMS may also be used to investigate the facilitatory and inhibitory mechanisms on the corticospinal neurons. Some of these TMS techniques involve paired-stimuli based on a conditioning-test paradigm. Stimulation parameters such as the intensity of the conditioning stimulus (CS) and test stimulus (TS) together with the time between the two stimuli (interstimulus interval, ISI) determine interactions between stimuli. When the CS is below and the TS is above the motor threshold (MT), the CS inhibits the response to TS at ISIs of 1–6 ms. Short-interval intracortical inhibition (SICI) is the ratio of the MEP amplitude produced by CS – TS to that produced by TS alone. Ratios below one represent inhibition and ratios above one represent facilitation.

2.6.5.4 *Transcranial electrical stimulation (TES)*

Electrical stimulators have a simpler design than magnetic stimulators. The stimulation is transmitted through cutaneous electrodes. The main advantage is a better depth of penetration, allowing direct spinal cord stimulation. The main limitation is the local discomfort that is created by the stimulation.

2.6.5.5 *Instrumentation*

Electrical stimulators contain a capacitor that produces constant current, high-voltage pulses of brief duration for percutaneous stimulation. The output current range is 0-1000 milliamperes, from a source voltage as high as 400 V. The pulse width range can be varied from 50 milliseconds to 2 milliseconds. The voltage is kept constant during the stimulation, but the intensity of stimulation depends on the skin impedance. Some electrical stimulators can deliver repetitive (2-9) pulses, which have been shown to facilitate induction of motor responses.

2.7 EVENT-RELATED POTENTIALS

Event-related potentials are (micro)voltage fluctuations that display stable time relationships to a definable reference event, being a physical or mental occurrence. The term "event-related potentials" is used here to include both evoked and emitted potentials. Evoked potentials can be either exogenous, endogenous or both, whereas emitted potentials are always endogenous (mainly the result of mental processing).[2]

These potentials can be recorded from the human scalp and extracted from the ongoing EEG by means of filtering and signal averaging. Mathematical procedures such as Fourier analysis and independent component analysis can be used to analyse the recorded signals. Because the temporal resolution of these measurements is in the order of milliseconds, ERPs can accurately measure when processing activities take place in the human brain. The spatial resolution of ERP measurements is limited both by theory and by present technology, but multichannel recordings allow estimating the intracerebral locations of these cerebral processes.

We were able to identify a standard for the auditory P300 ERP only.[32] More general research guidelines for ERP experiments have been published by Picton[2] (http://www.ccs.fau.edu/eeg/picton2000.pdf) These and other authors[26] insist on the description and calibration of the stimulating and recording equipment, the stimuli used, the recording electrodes (impedance, location, the way electrodes are affixed), the signal amplification (gain and filtering characteristics of the recording system), the A/D conversion rate, the way in which ERPs are time locked to the stimuli or the responses, specifications of any latency-compensation procedures, use of digital filtering for analysis, and procedures used for rejection of artefacts or compensation of artefacts.

The number of responses that need to be averaged will depend on the measurements being taken and the level of background noise present in single-trial recordings. The baseline period should be long enough to average out noise fluctuations in the average waveforms. Averaging may however lead to incorrect conclusions if individual responses are not checked. For example the amplitude of the averaged signal will be lower in case of variable latencies of embedded triggers. Averaging over too long a period may also not be appropriate for some ERP measurements in case the amplitude of the response decreases quickly after the first events.[12]

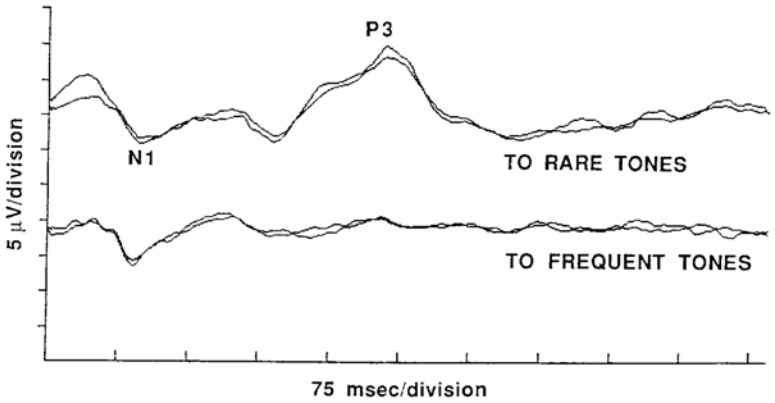
Several ERP labelling systems are currently in use. The two most common approaches are to designate the observed peaks and troughs in the waveform in terms of polarity and order of occurrence in the waveform ~N1, P2, or in terms of polarity and typical peak latency ~N125, P200. A variant of the latter system can be used to describe a mean deflection over a specified time window ~e.g., P20-50, N300-500. Negative latencies may be used to label movement-related potentials that precede response onset. For example, N-90 indicates a negative deflection that peaks 90 ms prior to the response. To emphasize variations among components at different scalp areas, the recording site may at times be usefully incorporated in the label ~e.g., N175/Oz. Observational and theoretical terminology should always be kept distinct.

The presentation of averaged ERP waveforms that illustrate the principal phenomena being reported is mandatory. ERP waveforms can be plotted with upward deflections indicating positive (often used in US) or negative potentials (often used in Europe) at the active electrode relative to the reference. When comparing waveforms and maps to those in the literature, it is essential to consider differences in the reference. For example, the classic adult P300 or P3b wave is usually recorded at Fpz as a negative deflection when using an average reference but as a positive deflection when using an ear or mastoid reference.

2.7.1 P300

The P300 is a positive ERP component recorded widely across the scalp around 300 ms after presentation of an auditory, visual or somatosensory "odd-ball" stimulus.

Figure 6: auditory long-latency event-related potential



Only the Pz channel is shown. The 365 ms P3 latency is within normal limits for this 40-year-old patient (copied from Goodin et al.[32])

2.7.1.1 Procedures

The P300 is typically generated using a binaural auditory 'oddball' protocol in response to low-probability deviant target stimuli requiring an overt response (e.g. the pressing of a button), a covert response or a combination of both. Typically the P300 amplitude in response to the low-probability target stimuli (the rare tone) will be higher than that in response to the standard stimuli (the frequent tone). The response (called "primary task") has an important effect on latency and amplitude of the two components and should be well defined and strictly standardised.

The rate of stimulus presentation is generally less than 1/sec because the ERP becomes attenuated at faster rates. Generally 30-60 rare tones are presented during each repetition of the test. Drowsiness should be avoided as should distracting noises. A filter band of 1Hz-300Hz is typically used.[12]

Standards for long-latency auditory event-related potentials are available from the IFCN.[32]

2.7.1.2 Reporting

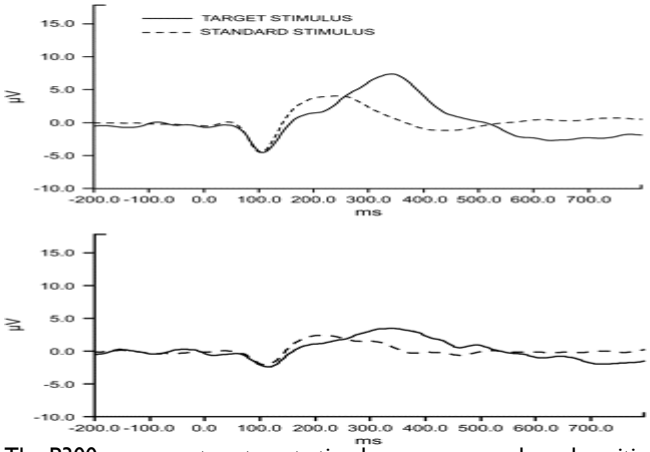
The P300 normally has a latency of about 320 ms at the age of 20. Latency increases with age to a mean of 420 ms at the age of 80. A deviation greater than 2 standard errors from the age-P3 latency regression line is considered as the upper limit of normal.[32] Anticholinergic interventions induce a latency increase and amplitude reduction of P300 whereas the opposite is observed after choline agonists. Care should be taken in scoring the P300 in case of occipito-parietal alpha activity remaining despite averaging, or in case of eye movement.

The P300 wave itself is thought to be comprised of two 'wavelets' known as P3a and P3b signals.

The two wavelets are sometimes referred to as 'non-target' (P3a) and 'target' (P3b) ERPs. The P3a occurs after novel events independently of task relevance and is characterized by a more frontal distribution, a shorter latency and a fast habituation. The P3b corresponds to the classical P300 recorded with an oddball paradigm after rare and task relevant events. P3b originates from temporal–parietal activity associated with attention and appears to be related to subsequent memory and decision processing.

In order to clearly identify the P3a and P3b components it is imperative that a standard task and stimulus paradigm is adhered to. An accepted standard is the "3 way odd ball" paradigm. Three stimuli presented are presented: a standard stimulus, a target stimulus that is not easily differentiated from the standard, and a completely different "novel" stimulus much more salient than standard and target. It is expected that adherence to the 3 way oddball technique as a standard could lead to more robust findings and less between centre variance, allowing multicentre clinical validation studies.

Figure 7: P300 response to an infrequent salient auditory stimulus



The P300 response to a target stimulus appears as a broad positive ERP component between 300 and 400 ms poststimulus, with maximum amplitude at the Pz electrode. (Copied from Turetsky et al.[33])

2.7.2 Loudness dependent AEP (LDAEP)

The 'LDAEP' assesses the auditory evoked N1/P2 response: the increase in amplitude of the N1, a negativity in the EP around 100 ms after stimulus presentation, and the subsequent positivity (P2) elicited by increasing tone loudness/sound level during auditory stimulation.

Figure 8: The N1 amplitudes at several electrode positions (negativity is presented upwards) in response to five different sound levels.

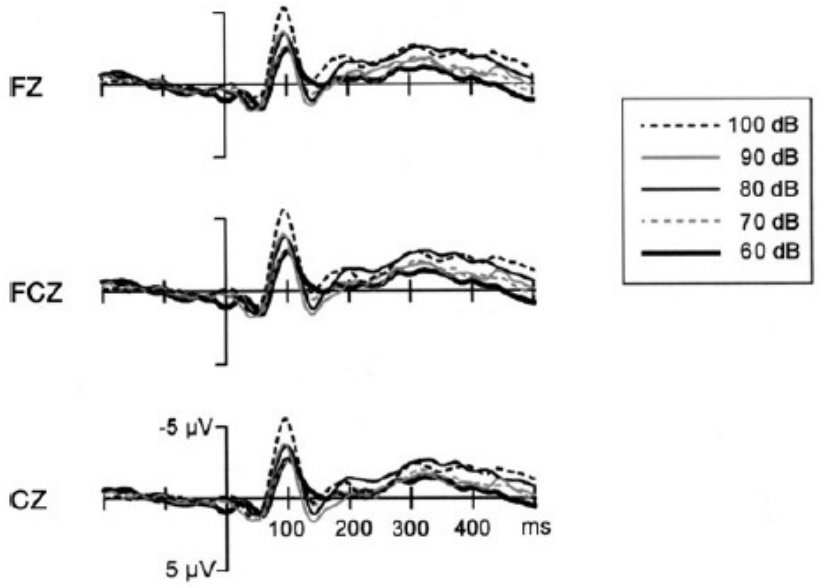


Figure is copied from Linka et al.,[34]

2.7.3 P50 sensory gating

The P50 is used to assess sensory gating.[35] [33] Sensory gating refers to the pre-attentional habituation of responses to repeated exposure to the same sensory stimulus. The inhibition of responsiveness to repetitive stimulation provides humans with the ability to negotiate a sensory-laden environment by blocking out irrelevant, meaningless, or redundant stimuli.

2.7.3.1 Procedures

The P50 is a midlatency auditory event-related potential (ERP) occurring 50 ms after stimulus presentation, elicited in the "paired click" paradigm or the "steady state" paradigm. In the paired click paradigm, the second auditory click is presented 500 ms after an initial click.[33] The first click is commonly referred to as the "conditioning stimulus (C)" or S1, and the second click is called the "testing stimulus (T)" or S2. EEG responses, usually measured at vertex, are averaged for S1 and S2 separately following baseline correction and artefact rejection. A high degree of habituation of every P50 evoked potential both evoked by test (S1) as by conditioning (S2) stimulus may be seen.

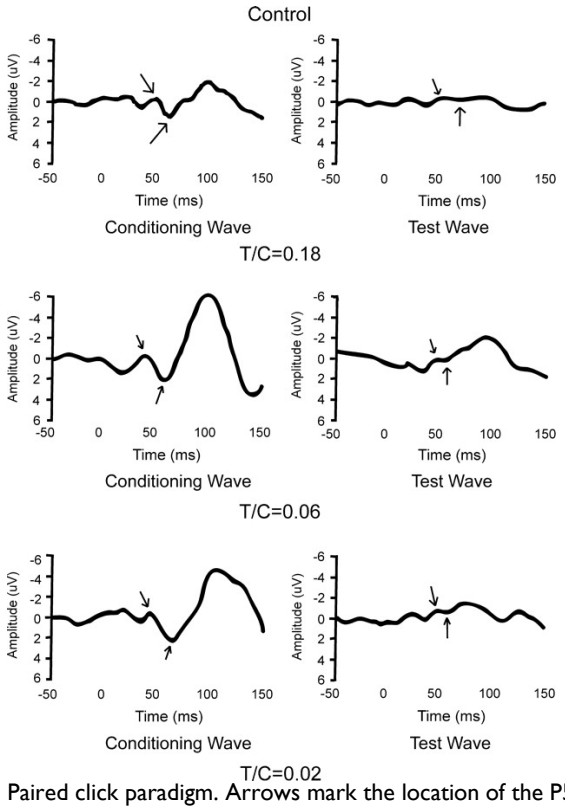
The most commonly used sensory gating index is the T/C ratio, in which the relative average amplitude of the P50 wave generated in response to the T (S2) stimuli is compared to the average amplitude generated in response to the C (S1) stimuli. A T/C ratio below 50% is the usual definition of normal sensory gating.[35] Children of 5-7 years of age have smaller amplitudes to the first response and show less sensory gating compared to the older age groups. There is no need to take gender differences into account.[36]

In the steady state paradigm, auditory clicks are presented at a continuous rate (e.g., 10 clicks/sec). The average P50 amplitude across all trials serves as an indicator of sensory gating, with larger amplitudes suggesting impaired sensory gating.

Data reduction for both paradigms, however, is not completely automated. For example, subjective judgments are required to finalize the selection of trials to be included in the S1 and S2 averages. If subjective inclusion criteria are used by raters who are not blinded with respect to experimental design features, there is a risk for biased results. Test standardization thus remains a priority.

The P50 test is affected by nicotine use. All patients should be warned (and monitored) not to smoke at least one hour before the test.

Figure 9: Auditory evoked responses of 3 control subjects



Paired click paradigm. Arrows mark the location of the P50 wave. Positive polarity is downward. Test-to-conditioning (T/C) ratio is indicated for each subject. (Copied from Turetsky et al.[33])

2.7.4 Error-related negativity (ERN)

The ERN is a large negative polarity peak in the event-related brain potential waveform that occurs when people make errors in reaction time tasks. It begins at the moment of the error and reaches a maximum about 100 ms later. It is largest at fronto-central scalp locations and appears to originate in an area of the brain called the anterior cingulate cortex. Research on ERN is ongoing in the management of depression.

Figure 10: Error-related negativity

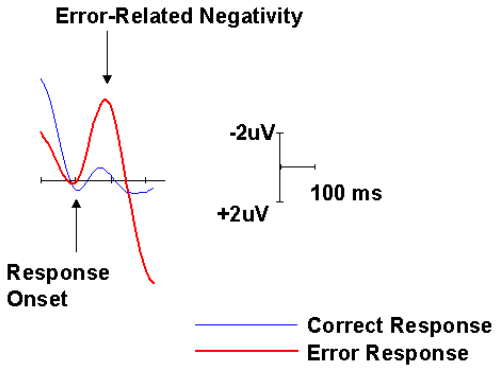


Figure copied from www.gehringlab.org

2.7.5 Mismatch Negativity (MMN)

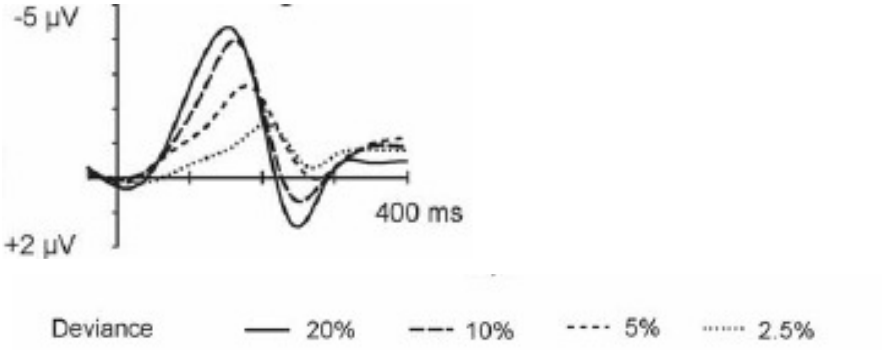
MMN is a negative auditory ERP component that is elicited when a sequence of repetitive standard sounds is interrupted infrequently by "oddball" stimuli. The MMN test does not need specific patient cooperation as it does not involve a specific task, which is considered an advantage in a psychiatric setting.[12] Physiologically, MMN is the first measurable brain response component that differentiates between frequent and deviant auditory stimuli and reflects the properties of an automatic, memory-based comparison of a given stimulus with a previous one. A recent overview on the MMN test has been published by Näätänen.[37]

2.7.5.1 Procedures

A repetitive standard sequence of every 500 ms is interrupted in 10% to 15% of trials by a total of 150 to 250 infrequent stimuli that differ in duration, loudness or pitch from the more frequently presented stimuli. The MMN occurs as early as 50 ms following deviant stimuli, peaks after an additional 100–200 ms.[12, 33, 38] and is recorded over fronto-central brain regions. MMN is mostly shown as the difference wave between the response to the frequent and the deviant stimuli. Recently, it has been demonstrated that not only physical characteristics of the stimulus but also abstract properties can lead to MMN.

In contrast to the habituation seen for the N2b wave (see P300), there is no habituation for the MMN.[12]

Figure 11: MMN elicited by deviances in frequency of various extents

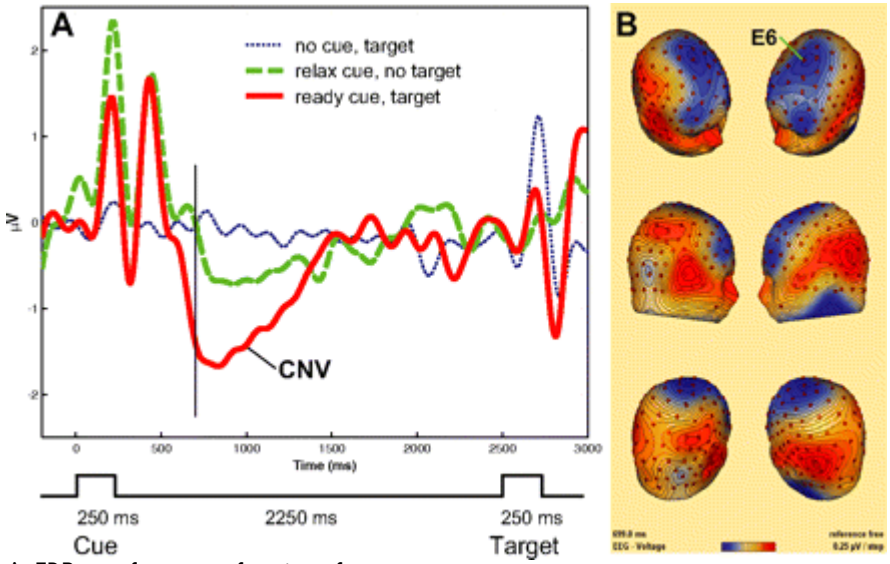


Difference wave containing the MMN elicited by deviances in frequency of various extents is presented. (Figure is copied from Kujala et al.[38]).

2.7.6 Contingent Negative Variation (CNV)

The CNV is a brain potential that develops during a short (~1–5 s) interval between two task-relevant stimuli, with the second "imperative" stimulus typically requiring a motor response. The CNV occurring just before the imperative stimulus, often called the "late CNV" to distinguish it from potentials elicited by the first stimulus, is generated by a network of cortical and subcortical structures that includes prefrontal, posterior parietal, temporal, premotor, primary motor and somatosensory cortex, and the basal ganglia.[39]

Figure 12: Contingent Negative Variation



A. ERP waveforms as a function of cue type.
B. Scalp topography of the voltage difference of ready cue minus relax cue at 699 ms. The time point corresponds to the vertical line in A. E6 indicates the location of the electrode with the maximum CNV amplitude. (Copied from Fan et al.[40])

3 CURRENT USE IN BELGIUM

3.1 REIMBURSEMENT

Currently, the EEG and evoked potentials (auditory, visual and somatosensory) are reimbursed by the Belgian Health Insurance. Event related potentials can be reimbursed by using the nomenclature number of EEG (CNV or Contingent Negative Variation) or EP (other ERP's). TMS (motor-evoked potentials) is also reimbursed; there is no specific nomenclature code for rTMS.EEG/EP can be performed by neurologists/(neuro)psychiatrists, and under certain circumstances by ophthalmologists, ENT-specialists, urologists or neuro-paediatricians. TMS can be performed by neurologists/(neuro)psychiatrists or specialists in physical medicine. Specialists in physical medicine also perform somatosensory evoked potentials (SEP). This KCE report is concerned solely with the performance of EEG, evoked potentials and event related potentials for neurological or psychiatric disorders, thereby excluding ophthalmic, ENT or other indications.

3.2 ANALYSES

All reimbursed tests in the period 1995-2006 (or 2000-2006 depending on availability) were calculated, based on RIZIV/INAMI data. In table 2, all the tests included in the analyses are summarised. For each test, the reimbursement by the NIHDI (National Institute for Health and Disability Insurance, or RIZIV/INAMI) and the co-payment by the patient are given.

Data were analysed separately for tests performed in ambulatory care or in hospital. Data were further stratified according to type of hospital, i.e. general hospital or psychiatric hospital, and according to hospital service.

EP single refers to one evoked potential test, EP double to two evoked potentials of a different modality (e.g. VEP + BAEP) and EP triple to three evoked potentials of a different modality (e.g. VEP + BAEP + SEP).

Table 2: Reimbursement and co-payment amounts in function of preferential status (source NIHDI 2008)

			No preferential status		Preferential status	
	NIHDI code	Ambulatory or in hospital	Reimbursement	Co-payment	Reimbursement	Co-payment
EEG	477131	Ambulatory	54.30 €	8.68 €	62.98 €	0.00 €
	477142	In hospital	62.98 €	0.00 €	62.98 €	0.00 €
EP single	477315	Ambulatory	82.15 €	8.68 €	90.83 €	0.00 €
	477326	In hospital	90.83 €	0.00 €	90.83 €	0.00 €
EP double	477330	Ambulatory	130.59 €	8.68 €	139.27 €	0.00 €
	477341	In hospital	139.27 €	0.00 €	139.27 €	0.00 €
EP triple	477352	Ambulatory	172.98 €	8.68 €	181.66 €	0.00 €
	477363	In hospital	181.66 €	0.00 €	181.66 €	0.00 €
EEG 24h	477411	Ambulatory	152.82 €	8.68 €	161.50 €	0.00 €
	477422	In hospital	161.50 €	0.00 €	161.50 €	0.00 €
MEP neurology/psychiatry	477536	Ambulatory	66.68 €	8.68 €	75.36 €	0.00 €
	477540	In hospital	75.36 €	0.00 €	75.36 €	0.00 €
MEP physical therapy	558655	Ambulatory	66.61 €	8.68 €	75.29 €	0.00 €
	558666	In hospital	75.29 €	0.00 €	75.29 €	0.00 €

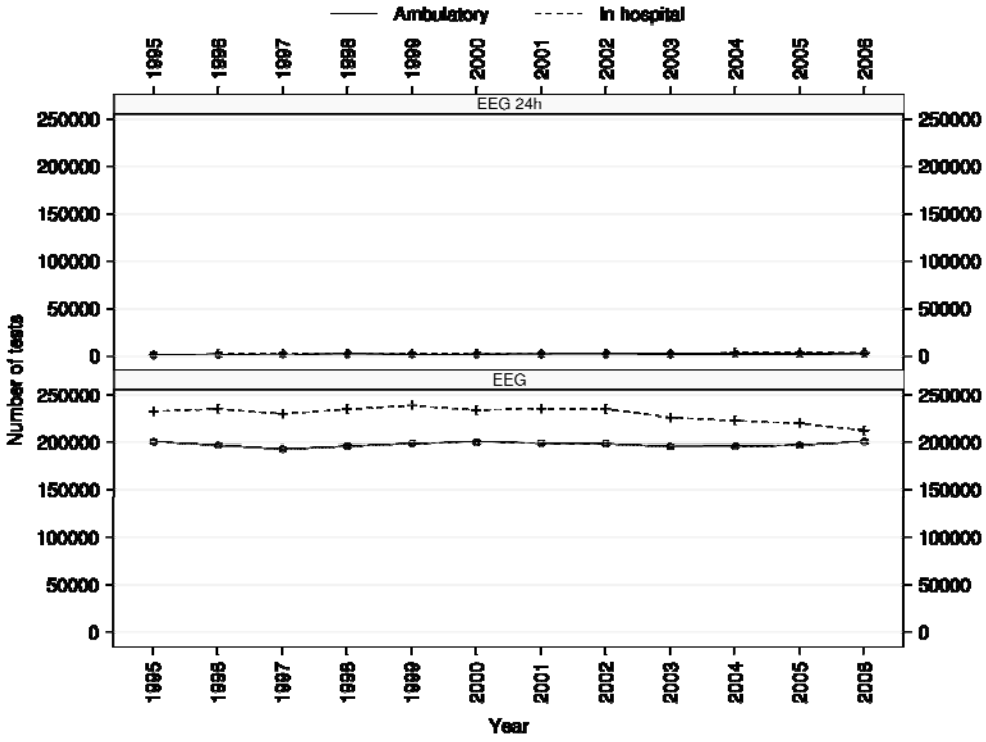
3.3 RESULTS

3.3.1 EEG

The annual number of reimbursed EEGs in ambulatory care or in hospital has remained stable over the last decade.(Figure 13) In 1995, 200,758 tests were reimbursed in ambulatory care and 232,914 tests in hospital, totalling 433,672. In 2006, 200,888 tests were reimbursed in ambulatory care and 212,726 in hospital in 2006, totalling 413,614 tests.

Compared to the standard EEG, the number of annual reimbursed 24h EEG is far less: 1,159 tests in ambulatory care and 1,290 in hospital in 1995, 1,882 tests in ambulatory care and 2.978 in hospital in 2006.

Figure 13: Number of EEG per year in ambulatory care or in hospital.



Likewise, the budget spent on EEGs has remained stable. In 1995, €23,888,093 was spent on EEGs, of which €10,284,200 in ambulatory care and €13,603,893 in hospital care. This has only slightly risen to €24,063,506 in 2006, of which 11,007,625 in ambulatory care and 13,055,880 in hospital.

In contrast, although the absolute number is smaller, the budget spent on 24h EEG has doubled since 1995: from €320,275 in 1995 to €746,625 in 2006. Budget spent in ambulatory care was €146,741 in 1995 and €281,066 in 2006; budget spent in hospital was €173,534 in 1995 and €465,560 in 2006.

Of those performed in hospital, the majority of reimbursed EEGs are performed in general hospitals, only a small number is performed in psychiatric hospitals (Figure 14). Of the 35 different types of hospital service, 26 performed less than 1% of all tests. Of the remaining 9 services, internal medicine performs the highest number of EEGs, followed by services not further specified. Neuropsychiatry is the third most common service performing EEGs

Figure 14: Number of EEG per year in general or psychiatric hospitals.

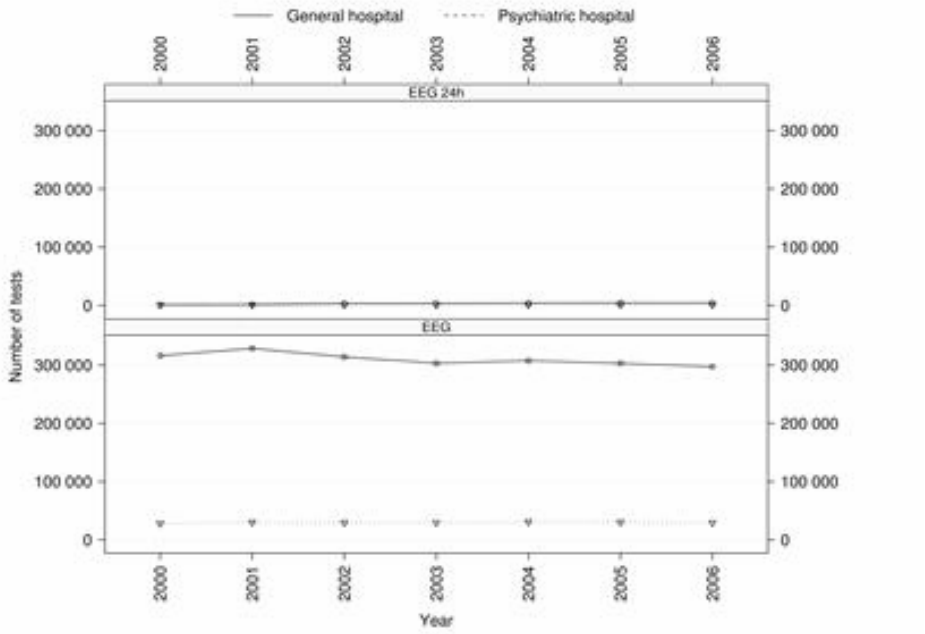
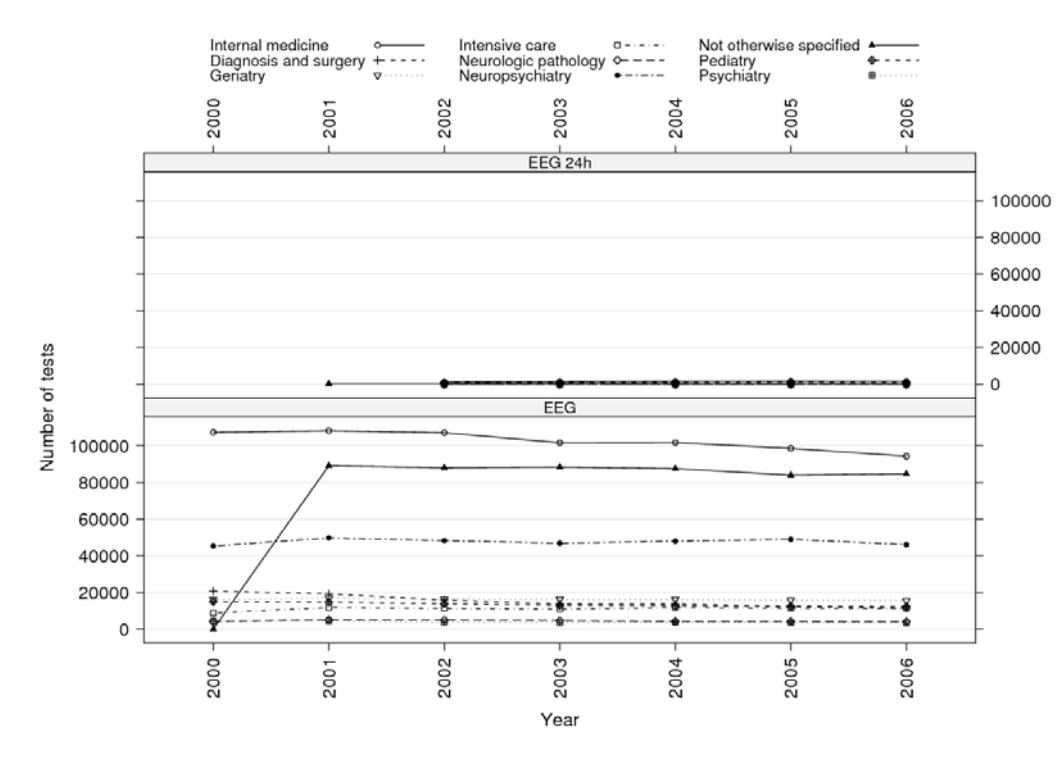


Figure 15: Number of EEG per year in function of hospital service (only services with more than 1% of total volume were included).



3.3.2 Evoked potentials

The number of reimbursed single evoked potentials has increased slightly since 1995: from 73,248 tests to 85,162 in 2006, equally divided over ambulatory care and hospital care. The budget spent on single evoked potentials has risen likewise from €5,308,740 in 1995 to €7,197,180 in 2006.

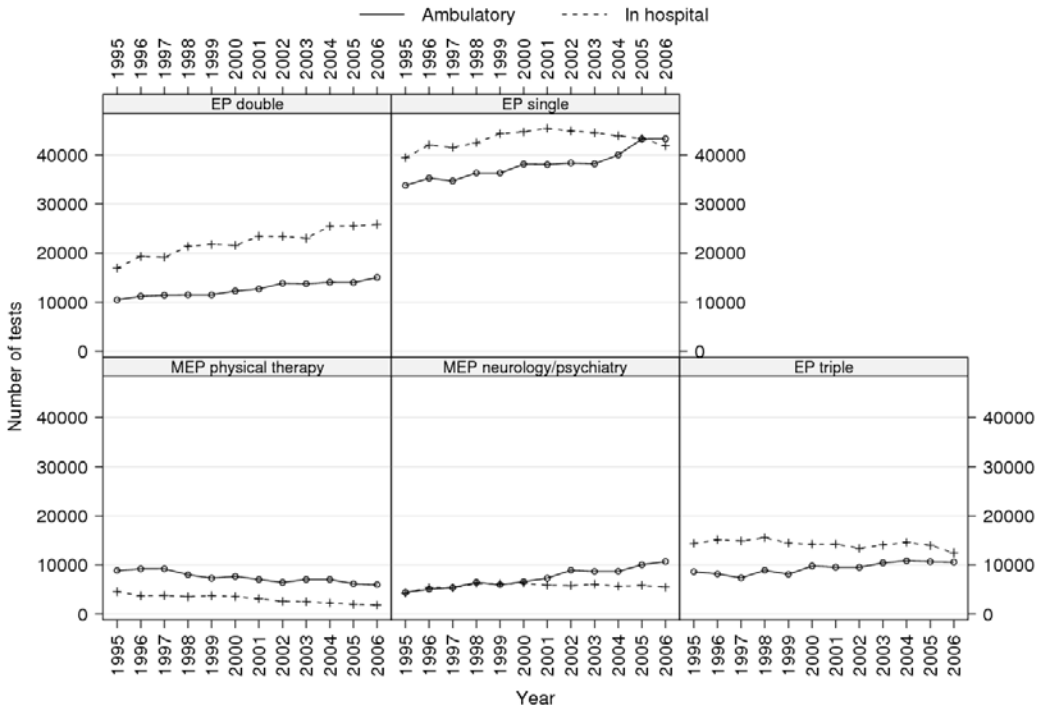
The number of double evoked potentials has increased more than the single evoked potentials: from 27,365 in 1995 to 40,589 in 2006. Likewise, the budget has risen from €3,106,749 in 1995 to €5,406,059 in 2006. Slightly more tests were performed in hospital than in ambulatory care.

As for the number of triple evoked potentials, very little change can be seen between 1995 and 2006. In 1995, 22,965 tests were performed representing €3,419,390; in 2006, 23,005 tests were reimbursed representing €3.974,742. Ambulatory care and hospital care are equally represented.

Motor evoked potentials are reimbursed in physical therapy as well as in neurology/psychiatry. In physical therapy, the absolute number of reimbursed tests has decreased between 1995 and 2006: from 13,360 to 7,753. This decrease can be observed both in ambulatory care and in hospital care. Likewise, the budget spent on motor evoked potentials in physical therapy has decreased from €776,053 to €512,777. In contrast, motor evoked potentials in neurology/psychiatry have doubled since 1995, mostly by an increase in ambulatory care. In 1995, 8,616 were reimbursed in neurology/psychiatry of which 4,377 in ambulatory care and 4,239 in hospital. In 2006, this number has risen to 16,113 in total, of which 10,665 in ambulatory care and 5,448 in hospital. The budget spent has risen from €511,644 to €1,102,279 in 2006.

Evolution of number of reimbursed tests is shown in Figure 16.

Figure 16: Number of evoked potentials (EP) per year in ambulatory care or in hospital.



Of those evoked potentials performed in hospital, the majority of tests are performed in general hospitals rather than in psychiatric hospitals (Figure 17).

Single evoked potentials are most often performed in the following hospital services: not otherwise specified, neuropsychiatry and internal medicine. Double evoked potentials are most often performed in neuropsychiatry, internal medicine and service not otherwise specified. Triple evoked potentials in internal medicine, not otherwise specified and neuropsychatry. MEPs physical therapy are most often performed in services not otherwise specified; MEP neurology/psychiatry in internal medicine and services not otherwise specified. (Figure 18)

Figure 17: Number of EP per year in general or psychiatric hospitals.

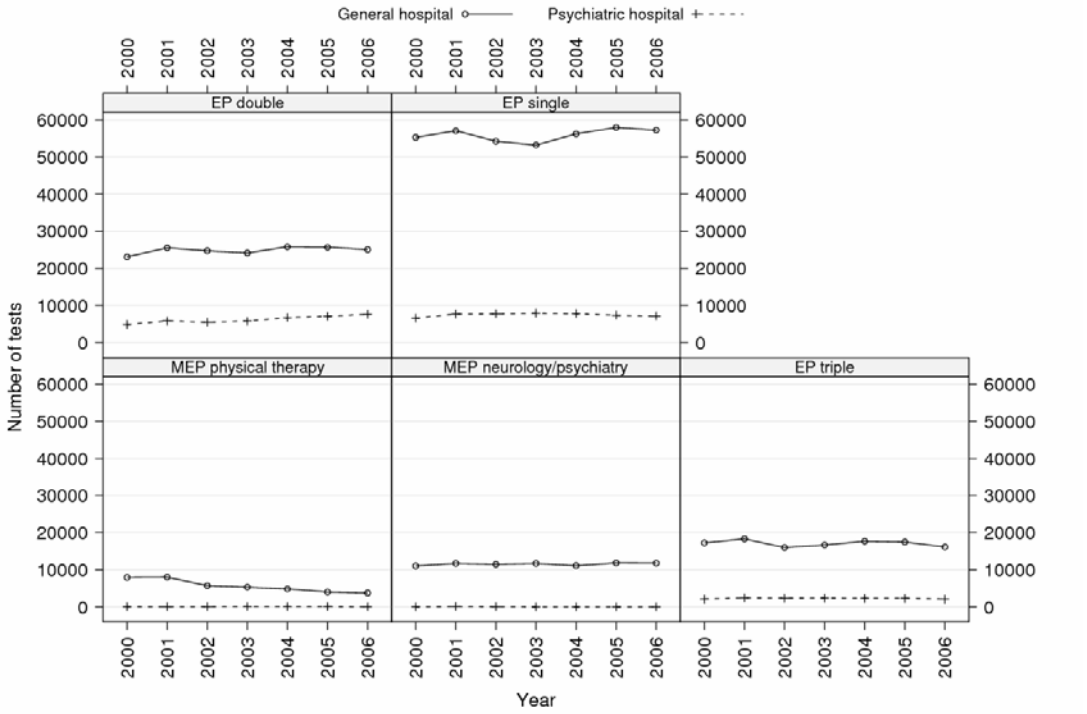
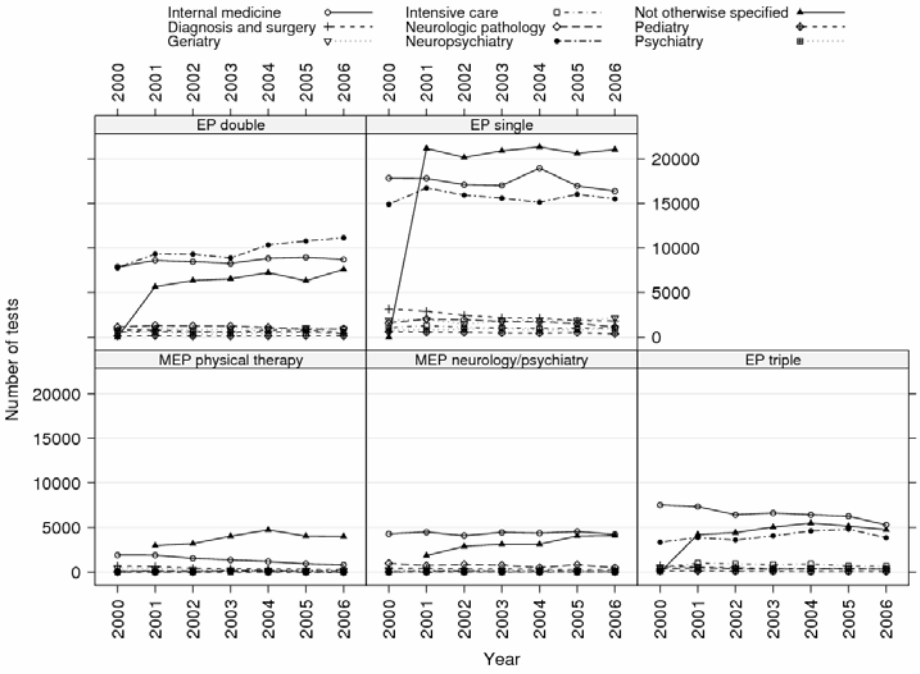


Figure 18: Number of EP per year in function of hospital service (only services with more than 1% of total volume were included).



3.4 DISCUSSION

In 2006, 216,494 EEGs were performed in hospitalised patients, representing 13,570,927 Euros. In ambulatory care, 203,484 EEGs were performed, representing 11,328,921 Euros. Over the last decade, the use of EEG in Belgium has been relatively stable, with a small decline of the number of EEGs performed in hospital.

Also in 2006, 41,871 single evoked potentials, 25,858 double evoked potentials, 12,448 triple evoked potentials, and 5,448 motor evoked potentials were performed in hospitalised patients. Total expenditure was 9,754,169 Euros. In ambulatory care, 43,291 single evoked potentials, 15,001 double evoked potentials, 10,557 triple evoked potentials and 10,665 motor evoked potentials were performed for a total expenditure of 7,926,090 Euros. In contrast to EEG, the use of some evoked potentials has risen over the last decade, especially the reimbursement code for two evoked potentials.

4 LITERATURE REVIEW

4.1 INTRODUCTION

The objective of the literature review was to evaluate the value of EEG, evoked potentials and event related potentials in clinical practice, in patients with neurological or psychiatric complaints and/or conditions. Tests can be used for diagnostic purposes; some tests can be suitable for excluding and others for including a target condition. Tests can be used to predict the prognosis of patients diagnosed with a certain target condition, and tests can be used to guide clinical management or monitor therapy. Each of these different aspects were taken into account in the review, which was divided in two parts: one part on the value of EEG, and one part on the value of evoked potentials and event related potentials.

Similar methods were used for both parts. First, a systematic search was performed on systematic reviews and health technology assessment reports of the tests. Secondly, clinical guidelines were searched on the tests, and on the target conditions for which evidence was identified.

Publications were then selected according to preset criteria, which will be listed in the respective chapters. Subsequently, selected publications were assessed for quality. Health technology assessment reports were assessed using the INAHTA checklist, systematic reviews were assessed using the checklist of the Dutch Cochrane Centre, and guidelines using the AGREE checklist. Low quality studies were excluded from further review.

All publications were then categorised according to target condition, and results on the tests were extracted. It is important to note that this categorisation does not imply that the target condition is assumed to be already known when performing the test. In fact, when the test is used for diagnostic purposes, this is impossible. How then should this categorisation be understood? For example, when a patient is suspected of having schizophrenia, based on clinical presentation and possible other testing, the guidelines for the schizophrenia diagnostic work-up apply. But if, in that same patient, temporal epilepsy is also considered as a differential diagnosis, the guidelines for the epilepsy diagnostic work-up apply as well. In addition to such diagnostic uncertainty by which more than one diagnostic category applies for one patient, patients may also suffer from more than one target condition simultaneously, by which the guidelines for all relevant target conditions apply. In summary, several guidelines may be applicable for one patient.

In case recommendations were supported by levels of evidence or grades of recommendations, these are cited within the text. In appendix 11, the various grading systems are included for consultation.

An important aspect in the assessment of diagnostic tests is whether the test has been evaluated in a patient population that is representative for clinical practice. This is not only a question of external validity, but also a question of avoiding biased results. The optimal design for assessing diagnostic accuracy is a prospective cohort study. As was shown in the study by Lijmer et al. in 1999[41] and confirmed by Rutjes et al. in 2006[42], case-control studies severely bias the results, with a relative diagnostic odds ratio of nearly 5 for studies including severe cases and healthy controls, compared to studies that do not. For this reason, case-control studies are categorised as low level of evidence for diagnostic tests[43]. In fact, the results of case-control studies are to be considered as exploring the possibilities of a diagnostic parameter, but can not determine the true diagnostic accuracy of the test. In this report, which assesses the value of diagnostic tests for every day clinical practice, case-control studies were considered as insufficient to inform clinical practice and were subsequently excluded. Case-referent studies that sample cases and controls from the same clinically relevant population were not excluded[44].

Interested readers are referred to the book edited by Knottnerus and Buntinx, The evidence base of clinical diagnosis' by BMJ Books[45].

Topics are ranked alphabetically.

Key points

- **The value of EEG, evoked potentials and event related potentials was evaluated for the diagnosis, prognosis and follow-up of patients with neurological and/or psychiatric complaints or disorders.**
- **Evidence was searched in two, complementary ways: systematic reviews and clinical practice guidelines.**
- **Evidence is categorised according to target condition.**
- **Several categories may apply for one patient.**

4.2 ELECTROENCEPHALOGRAM

4.2.1 Search for systematic reviews, meta-analyses, and HTA reports

The literature was searched in Medline, Embase, CRD, INAHTA database and NICE in February 2008. All search terms used are listed in the appendix 2, with the number of references that were retrieved. In total, 392 articles were retrieved, discarding duplicates.

Primary selection was done based on title and abstract. Secondary selection of the remaining articles was done based on full text.

Inclusion criteria:

- Design: Systematic reviews or meta-analyses, HTA reports
- Patients: Studies on patients within clinical care, further not specified
- Diagnostic tests: Electroencephalography, electroencephalogram, quantified EEG, sleep EEG, ambulatory EEG, video-telemetry
- Outcome: clinical patient oriented outcomes, for example awakening from coma, diagnose of epilepsy or prognosis impact. Intermediate outcomes are not eligible.

Exclusion criteria:

- Narrative reviews: no details on methods, no systematic and transparent search
- Economic analyses: maybe interesting at a later stage, but not initially
- Studies on animals or in vitro studies

The selection was done independently by two reviewers, discrepancies were resolved by discussion.

4.2.2 Search for guidelines (March 2008)

Guidelines were searched in two ways: by using the search term of the test, in this case EEG, and by using search terms relating to each disease or clinical problem for which systematic reviews or guidelines were selected by the previous search.

Guidelines older than 5 years without revision and guidelines out of the scope (without considering EEG in diagnostic or follow-up) were excluded.

All search terms and references retrieved are listed in appendix 3.

Additional searches, such for mild traumatic brain injury or for death, were done if asked by external experts. These searches are described in the related chapter. Diseases or symptoms, such sleep related disorders, diagnosed in specialized hospital services were not considered in this report.

4.2.3 Quality appraisal

All HTA reports were assessed for quality using the checklist of INAHTA.

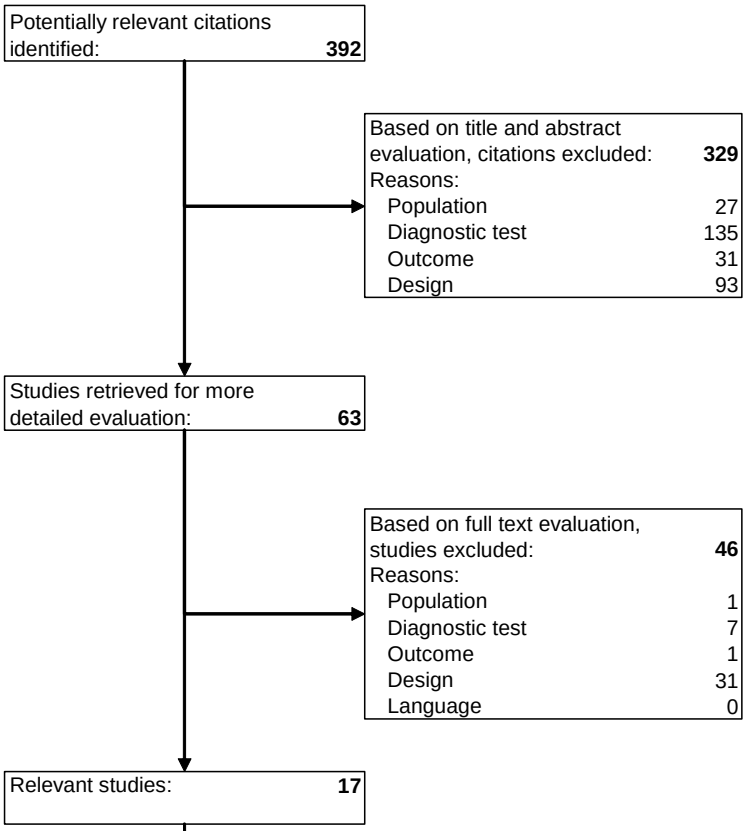
Systematic reviews and meta-analyses were assessed using the checklist of the Dutch Cochrane Centre.

Guidelines were assessed with AGREE. High quality was attributed for a score > 70, good quality for a score 70 - 60, fair quality for a score 59 - 50 and low quality for a score < 50.

4.2.4 Results

After selection, 2 HTA reports and 15 systematic reviews were included in this report. The search and selection process is illustrated in Figure 19. In addition, we included 79 guidelines: 36 were identified in the test-based search, and 43 in the disease-based approach.

Figure 19: Flow chart of the search strategy for systematic reviews and HTA reports on EEG



4.2.5 Patients suspected of or diagnosed with Attention deficit hyperactivity disorder (ADHD)

ADHD affects between 2 and 4 % of school-aged children with a higher prevalence (10 to 16%) in some studies[46]. The prevalence of ADHD in epilepsy is three to five times greater than normal. It has been suggested that methylphenidate lowers the seizure threshold. However, the information to support this possibility is very limited and conflicting[47].

Eight guidelines and two systematic reviews/meta-analyses were identified, of which both systematic reviews included case-control studies only and were subsequently excluded[48, 49] , and two guidelines were of low quality. Finally, six guidelines were included (see Table 3).

All guidelines do not recommend the use of EEG for the diagnosis of ADHD, whereas two guidelines recommend it for the investigation of another underlying medical problem if indicated by elements in the history or physical examination.

In 2008, NICE[50] stated that "The possibility of methylphenidate lowering the seizure threshold for those with epilepsy has been investigated in recent studies in those patients whose seizures were under control. These studies did not find an increase in seizures. It is noted in the literature that patients with seizures are generally excluded from the majority of studies regarding treatment for ADHD."

4.2.5.1 Additional search for original studies

In order to evaluate the value of EEG as a screening test before prescribing a stimulant therapy in patients with ADHD, without clinical signs or history of seizures, an additional literature search was performed (June 2008).

Medline was searched with the following MESH terms: "Seizures"[Mesh] AND "Attention Deficit Disorder with Hyperactivity"[Mesh]) AND "Methylphenidate"[Mesh]. Embase was searched with the terms: 'seizure'/exp/mj AND 'attention deficit disorder'/exp/mj AND 'methylphenidate'/exp. Medline yielded 8 references, Embase 12, and an additional 4 references were identified in the clinical guidelines, totalling 24 references. Six references were duplicates. Eight were excluded being out of the scope. Of the 10 remaining studies, three were narrative reviews, five studies included patients known as having epilepsy, and one studied physiological but no clinical outcomes. Thus, only one study[51] was selected.

The study of Hemmer[51] examined the relationship between EEG findings, stimulant use and seizure occurrence in children with ADHD without known epilepsy. Seizures occurred in 1 of the 175 patients with normal EEG and in 3 of 30 patients with epileptiform EEG ($p < 0.003$). It is, however, a poor quality study with a retrospective design based on record review. No blinding was mentioned. Biased results can not be excluded and good-quality prospective studies are necessary to confirm this result.

4.2.5.2 Conclusion

All recommendations on the use of EEG in children suspected of or diagnosed with ADHD are in agreement, as no guideline recommends it for the diagnosis of ADHD, both in children and adults, nor during management or follow-up of patients with ADHD. EEG is considered only if another underlying medical problem is suspected.

Key points

- **EEG is not useful for the diagnosis of ADHD, both in children and in adults.**
- **EEG is not recommended to exclude epilepsy before prescribing a stimulant treatment.**
- **EEG is not recommended for the management or follow-up of ADHD, except if another medical problem is suspected. Consequently, the recommendations for this other problem apply.**

Table 3: guidelines on ADHD

Institution/authors	Year of publication	AGREE Score	Diagnosis	Prognosis	Follow-up	Methylphenidate chlorhydrate prescription	Other: underlying medical problem
American Academy of Child and Adolescent Psychiatry [52]	2007	60	—	Ø	Ø	Ø	√
SIGN[53]	2005	71	—	Ø	Ø	Ø	√
University of Michigan Health System[54]	2005	62	Ø	Ø	Ø	Ø	Ø
Institute for Clinical Systems Improvement (ICSI)[55]	2007	69	Ø	Ø	Ø	Ø	Ø
Cincinnati Children's Hospital Medical Center[56]	2004	65	—	Ø	Ø	Ø	Ø
British Association of Psychopharmacology[57]	2007	45: excluded					
European clinical guideline[58]	2004	43: excluded					
NICE[50]	2008	72	Ø	Ø	Ø	Ø	Ø

√: recommended; —: not recommended; Ø: not mentioned

4.2.6 Patients suspected of or diagnosed with Autism

Epilepsy is common in patients with autistic disorder. The prevalence of epilepsy in autistic children has been estimated at 7 to 14%, whereas the cumulative prevalence by adulthood is estimated at 20% to 35%[59]. Seizure onset peaks in early childhood and again in adolescence. Mental retardation, with or without motor abnormalities and family history of epilepsy, was a significant risk factor for the development of seizures in autistic individuals. It is unclear whether there is a relationship between autism and an early regressive course (before 36 months), childhood disintegrative disorder ([CDD] after 36 months), Landau–Kleffner syndrome, and electrical status epilepticus during slow wave sleep (ESES)[59].

Three guidelines were identified (see Table 4).

Two of these three guidelines do not recommend universal screening of children with autism with an EEG in the absence of other clinical criteria, the third guideline finds insufficient evidence to recommend for or against screening. All agree on the importance of subtle symptoms of clinical or subclinical seizures, and a history of regression.

Autism with regression and childhood disintegrative disorder have both been associated with seizures or epileptiform sleep-deprived EEG (with adequate sampling of slow wave sleep). A higher incidence of epileptiform EEG abnormalities in autistic children with a history of regression has been reported when compared to autistic children with clinical epilepsy. Seizures or epileptiform discharges were more prevalent in children with regression who demonstrated cognitive deficits. Regression in cognition and language in adolescence associated with seizure onset has also been observed, but little is known about its cause or prevalence. There may be a causal relationship between a subgroup of children with autistic regression and EEG-defined "benign focal epilepsies". The SIGN[60] guideline specified, with a low level of evidence, that when children experience language regression over the age of three, they are more likely to experience seizures and the differential diagnosis should include consideration of an acquired epileptic dysphasia/ Landau Kleffner dysphasia.

Diagnostic properties of EEG in autism spectrum disorder were studied by comparing EEG findings to clinical seizure history[61] . The sensitivity for EEG ranged from 60 to 100% in all but one study. The specificity ranged from 53 to 92%. The positive likelihood ratio ranged from 1.21 to 5.3 in all but two studies (one 0.0 and one 9.6) and the negative likelihood ratio ranged from 0.0 to -0.63. The authors stated that comparing EEG findings to seizure history for specificity and likelihood ratio calculations is not really relevant for screening subclinical epileptiform abnormalities. At this time, little is known about the clinical implications of these abnormalities. There is a lack of evidence about the efficacy of commonly used anticonvulsants to detect changes in language and behaviour. There is no evidence to suggest that anticonvulsants are more or less effective in controlling seizures in autistic patients compared with other patients[61] .

4.2.6.1 Conclusion

All guidelines agree that there is insufficient evidence to recommend EEG in all patients with autism spectrum disorder as a screening test, except in case of associated seizure disorders.

Key points

- **There is insufficient evidence to recommend the performance of an EEG in all patients with autism spectrum disorder, except in case of associated seizure disorders.**
- **EEG is not recommended to screen for subclinical epileptiform abnormalities.**
- **Given the frequency of seizure disorders in patients with autism, a high index of clinical suspicion should be maintained for subtle symptoms of seizures or regression.**

Table 4: guidelines for autism

Institution/Authors	Year of publication	AGREE Score	Diagnosis	Prognosis	Follow-up	Other: Screening for epilepsy
MacMillan Children Center Toronto (Canadian)[61]	2005	51 Good quality systematic review but poor guideline	Ø	Ø	Ø	—
SIGN[60]	2007	78	Ø	Ø	Ø	—
American Academy of Neurology and the Child Neurology Society[59]	2006	63	Ø	Ø	Ø	—

√: recommended; —: not recommended; Ø: not mentioned

4.2.7 Patients suspected of or diagnosed with Brain metastases

Brain metastases represent an important cause of morbidity and mortality for cancer patients. EEG is not used to diagnose brain metastasis, which is done with imaging. The use of EEG is discussed in case of seizures to determine the need of an anticonvulsant therapy.

No HTA reports or systematic reviews were identified; only one guideline by the European Federation of Neurological Societies was found (Table 5). The guideline is based on a systematic literature search; consensus-based recommendations were made when evidence was not available.

The guideline recommends an EEG is indicated in patients who suffer from seizures that cannot be classified as epileptic (good practice point)[62].

None guideline was found about the diagnosis of primary brain tumour.

4.2.7.1 Conclusion

The guideline of the European Federation of Neurological Societies (EFNS) on the diagnosis and treatment of brain metastasis stated as good practice point (consensus of all members of the Task Force) that EEG is indicated in patients who suffer from seizures that cannot be classified as epileptic[62].

Key point

- **EEG is not useful for the diagnosis of brain metastasis, except in case of seizures that cannot be identified as epileptic.**

Table 5: guideline for brain metastases

Institution/Authors	Year of publication	AGREE Score	Diagnosis	Prognosis	Follow-up	Other: Seizures
European federation of neurological Societies[62]	2006	54	—	Ø	Ø	√

√: recommended; —: not recommended; Ø: not mentioned

Table 6: guideline for cerebral palsy

Institution/Authors	Year of publication	AGREE Score	Diagnosis	Prognosis	Follow-up	Other: Seizures
American Academy of Neurology[63]	2004	59	—	Ø	Ø	√

√: recommended; —: not recommended; Ø: not mentioned

4.2.8 Assessment and follow-up of child with Cerebral palsy

The prevalence of epilepsy in children with cerebral palsy ranges from 35 to 62%. The prevalence of EEG varies depending on the type of cerebral palsy that is present. Children with spastic quadriplegia (50 to 94%) or haemiplegia (30%) have a higher incidence of epilepsy than patients with diplegia or ataxic cerebral palsy (16 to 27%). Given the frequency of epilepsy in children with cerebral palsy, EEG is often considered during the initial evaluation[63].

Only one guideline was identified (by the American Academy of Neurology); systematic reviews and HTA reports were not available (Table 6).

The guideline is based on a systematic review of the literature.

Although approximately 45% of children with cerebral palsy develop epilepsy, in none of the retrospective studies involving 2014 children was there evidence that the EEG was useful in determining the aetiology of the child's cerebral palsy. Therefore, an EEG should not be obtained for the purpose of determining the aetiology of cerebral palsy (level A, class I and II evidence). An EEG is not recommended unless there are features suggestive of epilepsy or a specific epileptic syndrome (Level A, class I and II evidence)[63].

4.2.8.1 Conclusion

An EEG should not be obtained for the purpose of determining the aetiology of the cerebral palsy. An EEG is not recommended unless there are features suggestive of epilepsy or a specific epileptic syndrome. Approximately 45% of children with child's palsy develop epilepsy.

Key point

- **EEG is not useful for diagnosing the aetiology of the cerebral palsy.**
- **EEG is recommended in case features suggest epilepsy, which is present in approximately 45% of children with cerebral palsy.**

4.2.9 Prediction of outcome of Comatose patients

In comatose patients, EEG may be performed to predict outcome, i.e. awakening or death. Several types of coma were included in the publications found. This section deals with anoxic or anoxic-ischaemic coma and vegetative state. Traumatic coma is dealt with under the heading of head injury.

The literature search yielded three guidelines and two systematic reviews. One guideline was excluded because of poor quality (AGREE score <50)[64]. (Table 7).

The first systematic review by Zandbergen et al.[65] is of good methodological quality, including both prospective and retrospective studies. In 33 studies on the early neurological examination of patients with anoxic-ischaemic coma, 14 prognostic variables were studied, three of which had a specificity of 100%:

- Absence of pupillary light reflexes on day 3: pooled positive likelihood ratio 10·5 [95% CI 2·1–52·4];
- Absent motor response to pain on day 3: pooled positive likelihood ratio 16·8 [3·4–84·1];
- Bilateral absence of early cortical SSEP within the first week: pooled positive likelihood ratio 12·0 [5·3–27·6].

EEG recordings with an isoelectric or burst-suppression pattern had a specificity of 100% in five of six relevant studies (pooled positive likelihood ratio 9·0 [2·5–33·1]). These characteristics were present in 19%, 31%, 33%, and 33% of pooled patient populations, respectively.

SSEP has the smallest confidence interval of its pooled positive likelihood ratio and its pooled false-positive test rate. Because evoked potentials are also the least susceptible to metabolic changes and drugs, recording of SSEP is the most useful method to predict poor outcome.

The second systematic review[66] is of less quality, with a literature search in Medline only and including poor quality studies as well. In patients with anoxic coma, it appears warranted to delay prognostication until day 3. By that time, approximately half of those patients with no chance of ultimate recovery have died. After day 3, prognosis is made based on clinical signs + EEG + SEP.

Table 7: guidelines on coma

Institution/Authors	Year of publication	AGREE Score	Diagnosis	Prognosis	Follow-up
American Academy of Neurology[67]	2006	64	Ø	√	Ø
Australian Government national Health and medical research Council[68]	2003	73	Ø	√	Ø
Royal College of Physicians[64]	2003	38: excluded			

√: recommended; —: not recommended; Ø: not mentioned

In the guidelines, it is stated that burst suppression or generalized epileptiform discharges on EEG predict poor outcome but with insufficient prognostic accuracy (level C)[67]. In addition, in patients with vegetative state, there is a lack of correlation between EEG recordings and clinical status. Reactivity, if present, suggests a better prognosis, but its absence does not reliably predict post-coma unresponsiveness or death[68].

4.2.9.1 Conclusion

The conclusions for the use of EEG are all in agreement. An EEG recording with an isoelectric or burst-suppression pattern has good specificity for poor outcome in patients with anoxic or anoxic-ischaemic coma and vegetative state. False positives are however possible.

Key points

- **In patients with anoxic coma or vegetative state, an EEG with an isoelectric or burst suppression pattern has good specificity for poor outcome. False positives are however possible.**

4.2.10 Death

Clinical signs (Glasgow score = 3, loss of brainstem reflexes, apnoea) are used to diagnose brain death. EEG is used in some cases to confirm brain death.

A specific search was performed for brain death, as only one systematic review on the subject was identified so far[66]. Search terms used are listed in appendix 4. One guideline[69] was relevant but older than 5 years.

Experts added three consensus documents: Société Française d'anesthésie et de réanimation/Société de reanimation de langue française[70] , European expert consensus[71] and International Federation of Clinical Neurophysiology[72]. These guidelines and consensus documents were considered despite a poor methodological quality as they were the only available.

The systematic review of Attia reports the results of one study on comatose patients, summarizing multiple reports of EEG activity after clinical criteria for brain death had been met (e.g. apnoea test). These results show that the EEG must not be the sole criterion of brain death[66].

The guideline of the American Electroencephalographic Society (1994)[69] published minimum technical standards for EEG recordings in suspected cerebral death. Electrocerebral inactivity (ECI) or electrocerebral silence (ECS) is defined as no EEG activity over 2 µV when recording from scalp electrode pairs 10 or more cm apart with electrode impedances under 10 000 ohms, but over 100 ohms.

An expert consensus conference of the Sfar (Société française d'anesthésie et de reanimation), the SRLF (Société de réanimation de langue française) and the Agence de la Biomédecine about the management of dead patients selected for organ removal concluded encephalic death should be confirmed by an additional test such as silent EEG (no activity >5µV) during 30 minutes and repeated after four hours, or cerebral angiography or Doppler[70].

The guideline of a panel of European experts on the use of neurophysiological tests in the intensive care unit concluded that, even if the EEG is still often recommended, it is technically difficult, often gives rise to ambiguous results, and does not allow the confirmation of breath death in the presence of sedative drugs. The authors stated that there is no single way to confirm brain death, and that lawmakers should adapt their rules[23]. The recommendations of the IFCN (International Federation of Clinical Neurophysiology) confirm the limits of EEG in diagnosing the cerebral death[72].

4.2.10.1 Conclusion

In patients suspected of cerebral death, EEG is used to confirm the clinical diagnose. It is however technically difficult and may give ambiguous results.

Key point

- **In patients suspected of cerebral death, EEG confirms the clinical diagnosis. It is however technically difficult and may give ambiguous results.**

4.2.11 Patients suspected of or diagnosed with Dementia

Dementia is a common disorder in the elderly, involving as many as 10% of those over 65 years of age[73] . Dementia is a generic term indicating a loss of intellectual functions including memory, significant deterioration in the ability to carry out day-to-day activities, and changes in social behaviour. The most common cause of dementia is Alzheimer's disease. Other types of dementia are vascular dementia, dementia with Lewy Bodies, fronto-temporal dementia, mixed dementia and Creutzfeldt-Jacob disease[74] .

Proper diagnosis is essential to the management of patients suffering from mental impairment. The accurate differential diagnosis of dementia subtypes has become increasingly important with the advent of licensed treatments for Alzheimer's disease and the recognition of the potentially serious side effects of antipsychotics in people with Lewy Bodies dementia[74] .

The diagnosis of the different dementia disorders are based on clinical criteria. Definite diagnoses are possible only at histopathology, which should serve as gold standard. Since histopathology is rarely available in the majority of studies, clinical diagnosis in accordance with specific criteria is often used as surrogate gold standard[75] .

The literature search yielded 13 guidelines, one systematic review[76] and one health technology assessment (HTA) report[75].

One guideline was not available in full text[77], one was on radiology only[78] and one was of low quality[79]. In addition, the systematic review[76] was excluded for low quality as well. This leaves 10 guidelines (Table 8) and one HTA report for inclusion in the report.

The HTA report by SBU[75] is of good quality and found there is limited evidence (evidence grade 3) that either visually rated EEG or quantitative EEG helps the diagnostic workup in differentiating Alzheimer disease from controls and other dementia disorders. This conclusion is based on eight publications. However, the majority of the papers presented data on Alzheimer disease (AD) patients versus controls or patients with other dementia disorders versus control, and also AD versus depression.

The EEG is not recommended as a routine investigation for dementia. SIGN recommends an EEG for the diagnosis of sporadic Creutzfeldt-Jacob disease, with reported sensitivity of 65% and specificity of 85%[74]. (level 2+). The Royal College of Psychiatrists recommends an EEG for Creutzfeldt-Jacob and frontal lobe dementia[80]. The CBO[81] states that it is probable that the EEG has low sensitivity (± 45%) and reasonable specificity (± 90%) for the differential diagnosis between patients with Alzheimer disease and healthy patients. In case of doubt about Alzheimer disease, an abnormal EEG background pattern increases the likelihood of Alzheimer disease, while a normal EEG is not very significant (level 2). It is probable that EEG abnormalities, especially slowing down of dominant frequency and decreasing of alpha and beta activity, have an unfavourable prognostic significance for Alzheimer disease (level 2). There are no convincing indications that EEG can discriminate between Alzheimer disease and Lewy bodies' disease, or between healthy subjects and light cognitive disorder. EEG can not predict with reliability which patients with light cognitive disorder will receive a treatment for Alzheimer disease or not (level 2)[81].

The European Federation of neurological Societies[82] recommend that EEG may be a useful adjunct, and should be included in the diagnostic work of patients suspected of having Creutzfeld-Jakob disease or transient epileptic amnesia (level B).

Table 8: guidelines on dementia

Institution/Authors	Year of publication	AGREE Score	Diagnosis	Prognosis	Follow-up	Other: Creutzfeldt-Jacob
SIGN[74]	2006	79	—	Ø	Ø	√
Royal College of Psychiatrists[80]	2005	59	—	Ø	Ø	√
NICE[83]	2006	76	—	Ø	Ø	Ø
Singapore Ministry of Health[84]	2007	62	Ø	Ø	Ø	Ø
US Preventive Services Task Force[85]	2003	61	Ø	Ø	Ø	Ø
Alberta Clinical Practice Guideline Program[79]	2007	48 Excluded				
British Columbia medical association[86]	2007	53	Ø	Ø	Ø	Ø
American Academy of Neurology/ Miyasaki[87]	2006	65	Ø	Ø	Ø	Ø
American Academy of Neurology/ Petersen[88]	2003	58	Ø	Ø	Ø	Ø
American Academy of Neurology/ Knopman[73]	2004	56	Ø	Ø	Ø	Ø
CBO[81]	2005	64	√	√	Ø	√
European federation of Neurological Societies/ Waldemar[82]	2007	59	√	Ø	Ø	√

√: recommended; —: not recommended; Ø: not mentioned

4.2.11.1 *Additional search on suspicion of Creutzfeldt-Jacob disease*

Creutzfeldt-Jakob disease (CJD) is a transmissible, progressive fatal spongiform encephalopathy. The cardinal manifestations for the disease are rapidly progressive dementia, generalized myoclonus and periodic sharp waves complexes on EEG. According to two guidelines[74, 80], EEG may be useful for the diagnostic of sporadic Creutzfeld-Jacob disease, with reported sensitivity of 65% and specificity of 85%.

To complete the clinical value of an EEG to diagnose Creutzfeldt-Jakob disease, an additional search was done in Medline and Embase (July 2008). Search terms are listed in appendix 4. Medline yielded 20 references, Embase 143. Discarding duplicates, 160 references were screened for relevance.

Studies were included if they are prospective diagnostic accuracy studies considering EEG as a test for Creutzfeldt-Jakob disease. Studies were excluded if they included less than 20 patients, covered other diseases, or used other designs (letters, narrative reviews, cases report and case control studies).

Results

Four studies were selected [89-92]. The selection process is illustrated in Figure 20. The main characteristics and critical appraisal (QUADAS score) are available in Table 9.

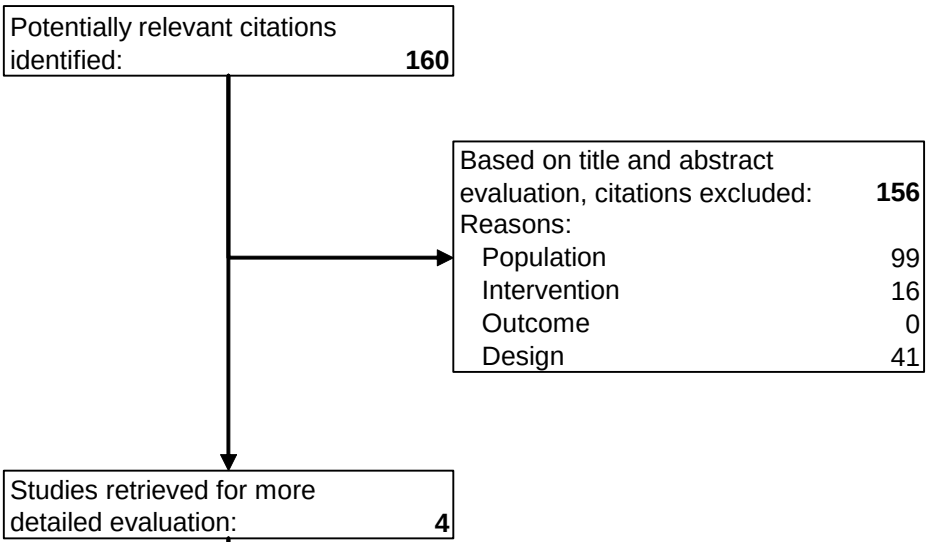


Figure 20: literature search on Creutzfeldt-Jacob disease

In patients with suspicion of Creuztfeldt Jakob disease, the presence of periodic sharp wave complexes (PSWs) in EEG has a sensitivity of 32-67 % and a specificity of 74-98%. The positive predictive value ranges from 83 to 99% and the negative predictive value from 25 to 71%.

4.2.11.2 *Additional search on suspicion of dementia with Lewy bodies*

The prevalence estimates of dementia with Lewy bodies (DLB) vary widely. It is believed to be the second most common cause of dementia, after Alzheimer disease. The clinical diagnostic criteria for DLB have low sensitivity and there are no accepted biomarkers. EEG abnormalities reported in DLB patients are however conflicting, varying from periodic discharge to slowing of the background rhythms with temporal slow-wave transients or findings similar to those of patients with Alzheimer disease or Creutzfeldt-Jakob disease.

Differentiate between these diseases at the early stage may be important because patients with DLB exhibit faster disease progression and different response to acetylcholinesterase inhibitors[93, 94].

To investigate the clinical value of EEG in dementia with Lewy bodies, an additional search was done in Medline and Embase (July 2008). Search terms are listed in appendix 4. Medline yielded 3 publications[93, 95, 96] and Embase 1[97]. External experts provided 2 additional studies[94, 98]. None of these references was cited in guidelines. Two studies were excluded based on design: the first was a letter[97] and the second was a narrative review[95]. A third study[96] was excluded because EEG was not considered as a diagnostic test. Two studies[93, 98] were excluded because they were case control studies. This left one study for inclusion in the report.

The study of Bonanni[94] is a good quality diagnostic accuracy study (QUADAS score: 10Y, 3U, 1N) with a two-gate design. Of consecutive referrals, 140 patients with early stage dementia (MMSE ≥ 20) were selected: 50 with a suspicion of Alzheimer's disease (AD), 50 with a suspicion of dementia with Lewy bodies (DLB) and 40 with a suspicion of Parkinson's disease with dementia (PDD). After 2 years of follow-up, there were 17 drop outs. Clinical diagnosis changed in 12 cases. The EEGs (at the moment of the inclusion) of the 40 clinically confirmed AD, 36 DLB and 35 PDD were analyzed. The most relevant group differences were observed between the AD and DLB patients in EEGs from posterior derivations ($p<0.001$). Dominant frequencies were 8.3 ± 0.6HZ for the AD group and 7.4 ± 1.6HZ for the DLB group, in which most of the patients (88%) exhibited a frequency band of 5.6 ± 7.9Hz. Dominant frequency variability also differed between the AD (1.1 ± 0.4Hz) and DLB groups (1.8 ± 1.2Hz, $P<0.001$).Of note, less than half (46%) of the patients with PDD exhibited the EEG abnormalities seen in those with DLB. At follow-up, EEG abnormalities from posterior leads were seen in all subjects with DLB and in three-quarters of those with PDD.

Table 9: Main characteristics of the studies on Creutzfeldt-Jacob disease

Study	Population	Test	Ref standard	Results	Design
Steinhoff 1996[89]	29 patients with suspected CJD	PSWs in EEG retrospective analysis	15 patients confirmed by autopsy 14 clinical evolution not CJD	Sensitivity: 67 % Specificity: 86 % PPV 83 % NPV 71 %	Diagnostic accuracy study QUADAS score: 6Y, 4U, 4N.
Steinhoff 2004[90]	1001 patients with suspected CJD	PSWs in EEG (Periodic sharp wave complexes)	Autopsy results post mortem diagnosis (available in 330 patients 206 included: 56 CJD excluded and 150 CJD verified)	Sensitivity: 63% Specificity: 98% PPV 99% NPV 49%	Diagnostic accuracy study Two-Gate design QUADAS score: 6Y, 3U, 5N.
Tschampa 2005[91]	193 consecutive patients suspected of CJD 28 patients not included for EEG results	MRI CSF analysis for 14-3-3 protein PSWs in EEG (Periodic sharp wave complexes)	Autopsy results or WHO criteria for CJD (clinically probable and autopsy proven definite case together as CJD)	Sensitivity: 32% Specificity: 94% PPV 95% NPV 25%	Diagnostic accuracy study QUADAS score: 5Y, 6U, 3N.
Zerr 2000[92]	1003 patients suspected of CJD Clinical diagnosis available in 805 cases	PSWs in EEG (Periodic sharp wave complexes) CSF analysis for 14-3-3 protein	Neuropathologic examination/ autopsy (available in 262 patients)	Sensitivity: 66% Specificity: 74% PPV 93% NPV 30%	Diagnostic accuracy study QUADAS score: 6Y, 5U, 3N.

4.2.11.3 Conclusion

EEG is not recommended as routine investigation for dementia diagnosis or follow-up. However, there is limited evidence to sustain the use of EEG in some situations.

- Doubt about the diagnosis of Alzheimer disease
- Suspicion of (temporal) epilepsy or not convulsive status epilepticus, transient epileptic amnesia
- Suspicion of metabolic, toxic or infectious encephalopathy
- Suspicion of Creuzfeldt-Jacob disease

Key points

- **EEG may be a useful adjunct, and should be included in the diagnostic work of patients suspected of having Creutzfeld-Jakob disease or transient epileptic amnesia.**
- **In patients with suspicion of Creuztfeldt Jakob disease, the presence of periodic sharp wave complexes (PSWs) in EEG has high specificity.**
- **In case of doubt about Alzheimer disease, an abnormal EEG background pattern increases the likelihood of Alzheimer disease, while a normal EEG is not very significant.**
- **There is currently no evidence that EEG can discriminate between patients with Alzheimer disease and Lewy bodies' disease, or between healthy subjects and light cognitive disorder.**

4.2.12 Patients suspected of or diagnosed with Depression or bipolar disorders

The prevalence of major depressive and dysthymic disorders is estimated to be approximately 2% in children and 4 to 8% in adolescents[99]. Men experience a life-time risk of 7-12% and women 20-23%[100]. Bipolar affective disorder is relatively common, with a lifetime prevalence of approximately 1.3%[101].

One HTA report[102] was included. The quality of the report is fair: the included studies were of average quality with few patients, the follow-up was short. Several studies were done by the same group of authors and duplicate inclusion of patients was not excluded. Another meta-analysis[103] included experimental instead of clinical studies on resting frontal EEG asymmetry in patients with depression and anxiety. This meta-analysis was consequently excluded.

The Australian HTA report[102] found that qEEG can predict the response to antidepressants. Differences between responders and non-responders to drug treatment of depression are observable by qEEG, despite there being no clinically visible impact of treatment in the patient at this early stage. The main factor consistently linked to response was cordance, which is measured along a continuum of values from negative to positive. Cordance is derived from qEEG data using an algorithm comparing absolute and relative power signals within specific types of frequencies. The evaluation is made at 48 hours and one week after start of treatment. The treatments studied were mainly fluoxetine and venlafaxine.

Eleven guidelines were found. Checked with the AGREE list, three[101, 104, 105] were of high quality, two[106, 107] were of good quality and six[99, 100, 108-111] were of fair quality. (Table 10)

4.2.12.1 Conclusion

All guidelines were in agreement that the EEG is not indicated for the diagnosis and management of patients with depression or bipolar disorders, in adults, adolescents nor children.

The HTA report[102] suggests that "early quantitative EEG (qEEG) cordance" can predict the response to antidepressant therapy. A larger clinical trial is currently underway that may confirm this finding.

Key points

- **EEG is not indicated for the diagnosis and the management of patients with depression or bipolar disorders, in adults, adolescents and children.**
- **The promising findings about « early quantitative EEG cordance » need to be confirmed before utilization in clinical practice.**

Table 10: guidelines on depression or bipolar disorder

Institution/Authors	Year of publication	AGREE Score	Diagnosis	Prognosis	Follow-up
NICE[104]	2005	73	Ø	Ø	Ø
SIGN[101]	2005	75	Ø	Ø	Ø
NICE[105]	2007	76	Ø	Ø	Ø
Institute for Clinical Systems Improvement (ICSI)[106]	2008	62	Ø	Ø	Ø
American Psychiatric Association[108]	2005	57	Ø	Ø	Ø
American Psychiatric Association[107]	2005	60	Ø	Ø	Ø
University of Michigan Health System[100]	2005	56	Ø	Ø	Ø
Amrerican Academy of Child and Adolescent Psychiatry Work Group on Quality Issues/ Birmaher[99]	2007	59	Ø	Ø	Ø
Singapore Ministry of Health[109]	2004	57	Ø	Ø	Ø
Royal Australian and New Zealand college of psychiatrists[110]	2004	54	Ø	Ø	Ø
Royal Australian and New Zealand college of psychiatrists[111]	2004	59	Ø	Ø	Ø

√: recommended; —: not recommended; Ø: not mentioned

4.2.13 Patients scheduled for Electroconvulsive therapy

Electroconvulsive therapy is an effective treatment for some individuals with severe neuropsychiatric illness. EEG is considered for the clinical assessment before elctroconvulsive therapy. This report does not consider the use of ictal EEG during electroconvulsive therapy.

Two guidelines and one systematic review were identified (Table 11). The systematic review included experimental and not clinical studies, and was excluded[112].

One guideline[113] recommends the EEG in adolescents as an option, if dictated by clinical assessment on a case by case basis. Tardive seizures are a rare but potentially serious side effect. These are usually encountered in adolescents who have a normal EEG before treatment and are not receiving seizure lowering medications during treatment. In addition, the EEG is not mentioned in the other guideline.

4.2.13.1 Conclusion

One guideline recommends the EEG as an option if dictated by clinical assessment; the other does not mention the EEG.

Key points

- **EEG is not recommended routinely in patients before electroconvulsive therapy, only if it is dictated by clinical assessment.**

Table 11: guidelines on patients receiving electroconvulsive therapy

Institution/Authors	Year of publication	Score AGREE	Other: assessment before treatment
American Academy of Child and Adolescent Psychiatry [113]	2004	55	√ (optional)
NICE[114]	2003	68	Ø

√: recommended; —: not recommended; Ø: not mentioned

4.2.14 Patients suspected of or diagnosed with Epilepsy

Epilepsy is a frequent neurologic disease. In industrialized countries, about one person on 100 to 150 is diagnosed with epilepsy. The Belgian League against Epilepsy estimates that 70,000 persons are affected in our country.

The diagnosis of epilepsy has important physical, psychosocial and economic implications for the patient. It is therefore important that the diagnosis is correct[115]. EEG results are used for counseling patients with seizures about prognosis and deciding on medications[116].

For the management of patients suspected of epilepsy or diagnosed with epilepsy, 13 guidelines and 7 systematic reviews were identified. One systematic review was in fact a narrative review and was excluded. All other systematic reviews were of good quality One guideline did not describe the methodology used for summarizing the evidence and was consequently excluded; the two CKS guidelines are summaries of the NICE guidelines presenting identical recommendations and thus not included to avoid duplication. (Table 12).

4.2.14.1 Systematic reviews

In the first systematic review, results show there is wide interreader variation in sensitivity and specificity of EEG interpretations. In 25 studies including 4.912 patients, specificity ranges from 13 to 99% and specificity from 20 to 99% for epileptiform EEG interpretations. Diagnostic accuracy of the EEG and the thresholds for classifying EEG as positive varied widely. In the multivariate model, differences in readers' thresholds accounted for 37% of the variance in EEG diagnostic accuracy. This variation influences the ability of the EEG to discriminate between those who will and will not have seizure recurrence[116].

According to the results of the second systematic review, the gold standard to differentiate epileptic and non epileptic seizure is EEG linked to video recording of concurrent behaviour, to register the association of any epileptiform abnormalities with observed behaviour. No procedure (seizure induction, Minnesota multiphasic personality inventory, physiological methods –prolactin levels and SPECT, pre-ictal pseudo sleep and ictal and post ictal symptoms) attains reliability equivalent to EEG video-telemetry[117].

The third systematic review summarised all studies on the predictive value of specific EEG abnormalities in patients with a first unprovoked seizure. Seizure aetiology (known neurological injury, deficit or syndrome) and EEG combined were the strongest predictors: patients with a normal EEG and absence of known neurological aetiology had a recurrence risks of 24% (95% CI 19-29), whereas patients with abnormal EEG and known neurological aetiology had a risk of 65% (95% CI 55-76). In patients with a normal EEG but known neurological aetiology, the recurrence risk was 48% (95% CI 34-62), as well as in patients with an abnormal EEG but no known neurological aetiology (95% CI 40-75)[118]. In children, epileptiform abnormalities significantly increased to risk of a seizure recurrence, compared to children with normal EEGs: pooled relative risk 2.0 (95% CI 1.6-2.6). The relative risk for non-epileptiform abnormalities was not significant for a recurrence compared to a normal EEG, pooled relative risk 1.3 (95% CI 0.9-1.8)[118].

The fourth systematic review estimated the risk for relapse in patients with epilepsy who have been seizure free for some time while taking antiepileptic medication and who discontinue epileptic drugs. The overall risk of relapse at 1 year was 0.25 (95% CI 0.21-0.30) and 0.29 (95% CI 0.24-0.34) at 2 years. An abnormal EEG (regardless of degree: mild, moderate or severe) was associated with a relative risk of seizure of 1.45 (95%CI 1.18 to 1.79). Most studies found some increased risk in patients with abnormal compared with normal EEGs, although there was evidence of heterogeneity between the studies (p= 0.0002)[119].

The evidence on risk factors and outcomes for neonatal seizures was summarised by Nunes et al. in the fifth systematic review. The incidence of epilepsy after neonatal seizures varied from 9.4 to 56%; most of the newborns that developed postneonatal epilepsy had epileptic syndromes with unfavourable prognosis. Clinical predictors of outcomes were seizure type, onset, aetiology and duration besides abnormal neonatal examination. EEG predictors of outcome were analyzed in eleven studies; the results showed that abnormal background rhythm, the presence of electrographic seizures and the presence of brief rhythmic discharges were consistently related to unfavourable outcomes[120].

Finally, the last systematic review found that, based on a review of 47 articles, EEG/MRI concordance was a prognostic indicator of seizure remission (positive predictor) after epilepsy surgery (OR 0.52; 95%CI 0.32 – 0.83)[121].

4.2.14.2 Guidelines

NICE[122] states that the standard EEG has variable sensitivity and specificity in determining whether an individual has had an epileptic seizure. In the primary papers reviewed by the authors of NICE guideline, the sensitivity ranged from 26% to 56% and the specificity from 78% to 98%. The likelihood ratio for a positive test ranged from 2.5 to 13 and for a negative test from 0.5 to 0.76 (level of evidence III for adults, IIb for children). The finding of interictal epileptiform activity on EEG can be used to help confirm the clinical diagnosis of an epileptic seizure. A negative EEG cannot be used to rule out the clinical diagnosis of an epileptic seizure (level of evidence III). Individuals with a clinical diagnosis of non-epileptic seizure disorder are unlikely to have, but may occasionally have, epileptiform abnormalities on EEG (level of evidence III). There is insufficient high quality evidence to determine whether performing an EEG within the first 24 hours after a seizure increases the likelihood of obtaining epileptiform activity (level of evidence III).

Great caution is required in performing investigations such as EEG when the clinical history offers limited support for a diagnosis of epilepsy, as the risk of false positive result may lead to misdiagnosis. The misdiagnosed patient may experience social and financial deprivation as a result of having the wrong diagnostic label and from side effects of antiepileptic medication.

4.2.14.3 Children

First, non-febrile seizure

In children experiencing a first, non febrile seizure, the EEG is recommended as part of the standard neuro-diagnostic evaluation by the American Academy of Neurology[123]. The majority of evidence of Class I and II studies confirms that an EEG helps in determination of a seizure type, epilepsy syndrome, and risk of recurrence, and therefore may affect further management decisions.

NICE[122] recommends an EEG should be performed only to support a diagnosis of epilepsy. If an EEG is considered necessary, it should be performed after the second epileptic seizure but it may, in certain circumstances as evaluated by the specialist, be considered after a first epileptic seizure (level of evidence C).

SIGN[124] states that in case of first unprovoked convulsive epileptic seizure, an EEG may offer information regarding recurrence risk (an abnormal EEG doubles recurrence risk), provoking factors (such as photosensitivity) or syndromic epilepsy.

On the other hand, the accuracy of the test is low and the impact of treatment on recurrence risk after the first seizure is small. An EEG should not be used to guide a decision on whether or not to commence antiepileptic drug medication (GCP). It recommends an EEG should only be requested after careful clinical evaluation by someone with expertise in childhood EEG and epilepsy, and particular care is required in interpretation of the paediatric EEG. The sensitivity of interictal EEG recordings is too low to be a reliable diagnostic test for epilepsy. Around 40% of children with seizures will have a normal record on a first standard EEG recording. Even with expert clinical evaluation and repeated recordings, the sensitivity of EEG is only 56% after a single event and 70% after multiple events, with a specificity of 78%. But, the EEG may show paroxysmal activity or background changes in up to 32% of normal children that could be misinterpreted as abnormal. Epileptiform abnormalities are seen in 5% of normal children. These rates are higher where there are pre-existing neurological abnormalities.

Standard EEG with synchronic video is particularly useful in case of juvenile myoclonic epilepsy, infantile spasms and absence seizures[124].

For children with recurrent epileptic seizures and a normal standard EEG, a second EEG recording including sleep should be used to aid identification of a specific epilepsy syndrome, such as benign rolandic epilepsy with centro-temporal spikes, juvenile myoclonic epilepsy and infantile spasms (level of evidence D). Sleep recordings may be difficult to achieve in children; there is no clear evidence that one method of obtaining sleep is significantly more productive than another. The rates of EEG abnormality may be increased during the course of a sleep EEG recording and this may be a pitfall in children who do not have epilepsy. [124]

Recurrent epileptic seizures

SIGN[124] recommends all children with recurrent epileptic seizures should have an EEG. An early recording may avoid the need for repeated EEG investigations (level of evidence C). Where the clinical diagnosis of epilepsy is uncertain and if events are sufficiently frequent, an ictal EEG should be used to make a diagnosis of an epileptic or non epileptic seizure.

Febrile seizures

SIGN[124] states an EEG is not indicated for children with recurrent or complex febrile seizures (GCP). The yield of abnormality of an early post-ictal EEG is low and similar to reported rate of abnormality in children with simple febrile seizures.

Status epilepticus

The American Academy of Neurology[125] states an EEG may be considered in a child presenting with new onset status epilepticus as it may determine whether there are focal or generalized abnormalities that may influence diagnostic and treatment decisions (level C, class evidence III). Data from six class III studies revealed generalized or focal epileptiform activity in 43.1% of the EEGs done for status epilepticus. Abnormalities on EEG occur in 62% of children with status epilepticus compared with 41% of children with a first unprovoked seizure of less than 30 minutes duration.

Although non-convulsive status epilepticus occurs in children who present with status epilepticus, there are insufficient data to support or refute recommendations regarding whether an EEG should be obtained to establish the diagnosis. (level U: unproven)

An EEG may be considered in a child presenting with status epilepticus if the diagnosis of pseudo status epilepticus (non epileptic event that mimics status epilepticus) is suspected (level C, class III evidence). One small class III study reported that 21% of children initially thought to be in convulsive status epilepticus had pseudo status.

4.2.14.4 Adults

First, unprovoked seizure

Three guidelines recommend an EEG only to support a diagnosis of epilepsy in whom the clinical history suggests that the seizure is likely to be epileptic in origin: NICE[122], SIGN[115] and Singapore Ministry of Health[126]. SIGN states the EEG is not routinely indicated and should not be performed to exclude a diagnosis of epilepsy (Grade of recommendation C).

On the other hand, the American Academy of Neurology[127] states that the EEG should be considered as part of the routine neuro-diagnostic evaluation of adults presenting with an apparent unprovoked first seizure (level B), because routine EEGs revealed epileptiform abnormalities in approximately 23% of patients in adults presenting with a first seizure, and these were predictive of seizure recurrence.

The standard EEG can help classify individuals with a clinical diagnosis of an epileptic seizure into different epilepsy seizure types and epilepsy syndromes[122] (level of evidence III) (NICE). In individuals presenting with a first unprovoked seizure, unequivoqual epileptiform activity shown on EEG can be used to assess the risk of seizure recurrence (grade of recommendation B). The specificity of an epileptiform EEG in predicting further seizures ranges from 13% to 99%, and sensitivity from 20% to 91% (level of evidence II). EEG should also be performed in young people with generalized seizures to aid classification and to detect a photo-paroxysmal response (grade of recommendation C), which allows appropriate advice to be given.

Over-interpretation of normal variants as epileptiform abnormalities is a recognized pitfall in adult recordings. Non-specific EEG abnormalities are relatively common, especially in the elderly, patients with migraine, psychotic illness and psychotropic medication. Therefore, non-specific abnormalities should not be interpreted as supporting a diagnosis of epilepsy. In addition, incidental epileptiform abnormalities are found in 0.5% of healthy young adults. On the other hand, a normal EEG does not exclude a diagnosis of epilepsy. A single routine EEG will show definite epileptiform abnormalities in only 29-38% adults who have epilepsy. With recordings, this rises to 69-77%. The sensitivity is improved by performing an EEG soon after a seizure, and by recording with sleep or following sleep deprivation[126].

The diagnostic value of the EEG is influenced by the pre-test probability. In a patient in whom the clinical history suggests an epileptic seizure but is not conclusive, the prevalence of epilepsy will be high. The finding of epileptiform abnormalities is specific, and the diagnostic value of the test is good. In a patient in whom the history is typical of some other disorder, such as syncope, the prevalence of the epilepsy will be low, and any epileptiform abnormalities are more likely to be incidental. The EEG should not be used to exclude a diagnosis of epilepsy in an individual in whom the clinical presentation supports a diagnosis of a non-epileptic event (grade of recommendation C), because of the possibility of a false-positive result (grade of recommendation C)[115, 122].

Repeat EEGs and sleep EEG

Repeating a standard EEG in a selected adult population has been shown to increase the likelihood of obtaining epileptiform activity (level of evidence III), according to NICE[122] and the Singapore Ministry of Health[126]. Repeated standard EEGs may be helpful when the diagnosis of the epilepsy or the syndrome is unclear. However, if the diagnosis has been established, repeat EEGs are not likely to be helpful (grade of recommendation C).

Repeated standard EEGs should not be used in preference to sleep or sleep-deprived EEGs (grade of recommendation C). When a standard EEG has not contributed to diagnosis or classification, a sleep EEG should be performed (grade of recommendation C). Recording of the EEG whilst asleep or after sleep deprivation increases the likelihood of obtaining epileptiform activity (level of evidence III).

Video or ambulatory EEG

Long-term video or ambulatory EEG may be used in the assessment of individuals who present diagnostic difficulties after clinical assessment and standard EEG (grade of recommendation C) (NICE[122] and Singapore Ministry of Health[126]). Long-term video or ambulatory EEG can help differentiate between epileptic and non epileptic seizures in individuals who present diagnostic difficulties after clinical assessment and standard EEG (level of evidence III). Long-term video or ambulatory EEG can help classify seizure type and seizure syndrome in individuals who present diagnostic difficulties after clinical assessment and standard EEG (level of evidence III). SIGN recommends video EEG and other specialist investigations should be available for patients who present diagnostic difficulties (grade of recommendation C). For recording, the attack should usually be occurring at least once a week.

Induction protocols

NICE[122] has found conflicting evidence in adults as to the role of induction protocols; there is no evidence for children (level of evidence III). Provocation by suggestion may be used in the evaluation of non-epileptic attack disorder. However, it has a limited role and may lead to false positive results in some individuals (grade of recommendation C). Photic stimulation is necessary to determine if the individual is photo-sensitive but carries a small risk of inducing a seizure (level of evidence III). Hyperventilation is routinely employed to increase the sensitivity of an interictal EEG (level of evidence IV). Photic stimulation and hyperventilation should remain part of the standard EEG assessment. The individual and family and/or carer should be made aware that such activation procedures may induce a seizure and they have the right to refuse (GCP).

The guideline by the Singapore Ministry of Health considers photic stimulation and hyperventilation a part of standard EEG assessment (grade D level 3).

Alcohol-related seizures

The EFNS[128] states that the incidence of EEG abnormalities is lower amongst patients with alcohol withdrawal seizures than in those with seizures of other aetiology. EEG pathology suggests that the seizure may not have been caused exclusively by alcohol withdrawal. EEG should be recorded after a first seizure. Subsequent to repeat alcohol withdrawals seizures, EEG is considered necessary if an alternative aetiology is suspected (level C: possibly effective).

Status epilepticus

SIGN[115] recommends EEG monitoring within 60 minutes to assess seizure control, if status epilepticus persists for more than 30 minutes (grade of recommendation D). EEG recording may be necessary to confirm the diagnosis and assess control when seizures are clinically subtle (e.g. in partial status or following treatment of tonic-clonic status epilepticus).

The EFNS[129] recommends an EEG for the diagnosis of non-convulsive status epilepticus (GPP). In addition, an EEG is performed in case of refractory general convulsive status epilepticus and subtle status epilepticus to monitor anaesthetic treatment. They recommend the titration of the anaesthetic against an EEG burst suppression pattern. This goal should be maintained for at least 24 hours (GPP).

No clear recommendation for ordering emergency EEG may be made on the basis of available data for adult patients presenting to the emergency department with seizure, according to the American College of Emergency Physicians[130]. Consider an emergent EEG in patients suspected of being in non-convulsive status epilepticus or in subtle convulsive status epilepticus, patients who have received a long-acting paralytic, or in patients who are in a drug-induced coma (level C: inconclusive or conflicting evidence, consensus). The most compelling argument for emergent EEG is for the detection of generalized convulsive status epilepticus that may have evolved into subtle status epilepticus with continuing abnormal EEG discharges.

Table 12: guidelines on epilepsy

Institution/Authors	Year of publication	Score AGREE	Diagnosis	Prognosis	Follow-up
American Academy of Neurology/ Hirtz (children)[123]	2000 (reaffirmed 2006)	63	√	√	Ø
NICE [122]	2004	77	√	√	—
SIGN (children)[124]	2005	77	√	√	—
American College Emergency Physicians[130]	2004	62	√	√	Ø
American Academy of Neurology/ Riviello, (child with status epilepticus)[125]	2006	64	√	√	—
SIGN (adults)[115]	2003	77	√	√	—
European Federation of Neurological Societies/ Brathen[128]	2005	59	√	√	—
Belgian consensus document/ Van Rijckevorsel[131]	2006	Low: excluded			
American Academy of Neurology/ Krumholz[127]	2007	66	√	√	—
Singapore Ministry of Health[126]	2007	63	√	√	—
European Federation of Neurological Societies/ Meierkord[129]	2006	58	√	√	Ø

√: recommended; —: not recommended; Ø: not mentioned

4.2.14.5 Conclusion

Diagnostic value

EEG is the gold standard to diagnose epilepsy. However, all guidelines agree on its limited accuracy. The finding of interictal epileptiform activity on EEG can be used to help confirm the clinical diagnosis of an epileptic seizure. But, a negative EEG cannot be used to rule out the clinical diagnosis of an epileptic seizure.

False positive results are relatively common. Incidental epileptiform abnormalities are found in healthy young adults and non specific EEG abnormalities are found especially in the elderly, patients with migraine, psychotic illness and psychotropic medication. Particular care is required in interpretation of the paediatric EEG. Age specific patterns may be misinterpreted as epileptiform discharges.

Moreover, there is wide interreader variation in sensitivity and specificity of EEG interpretations. Over-interpretation of normal variants as epileptiform abnormalities is a recognized pitfall in adult recordings. This variation influences the ability of EEG to discriminate between those who will and will not have seizure recurrence.

Children

An EEG should be performed only to support, and not to exclude a diagnosis of epilepsy.

Guidelines do not agree on the value of EEG in children with a first non-febrile seizure. The American Academy of Neurology recommends it as part of the routine neuro-diagnostic evaluation after all first non febrile seizures. SIGN recommends an EEG when a first seizure has been diagnosed as epileptic, for the purposes of assessing recurrence risk, making a syndromic diagnosis and identifying precipitating factors. It should not be used to guide a decision on whether or not to start antiepileptic drug medication.

NICE recommends an EEG after the second epileptic seizure if considered necessary, but it may be considered after a first epileptic seizure. In case of a first unprovoked convulsive epileptic seizure, the decision on whether or not to perform an EEG is balanced by the low accuracy of the test and the small impact of treatment on recurrence risk on one hand, and the information regarding recurrence risk, provoking factors or syndromic epilepsy on the other hand.

If a first standard inter-ictal EEG is normal, there is evidence that a second recording increases the yield of diagnostically helpful abnormalities. There is no evidence for children to the role of induction protocols.

All children with recurrent epileptic seizures should have an EEG. Where the clinical diagnosis of epilepsy is uncertain and if events are sufficiently frequent, an ictal EEG should be used to make a diagnosis of an epileptic or non epileptic seizure.

1. When used appropriately, sleep recordings may contribute significantly to epilepsy classification and particularly in syndromes such as benign rolandic epilepsy with centro-temporal spikes, juvenile myoclonic epilepsy and infantile spasms.

Standard EEG with synchronic video is particularly useful in case of juvenile myoclonic epilepsy, infantile spasm and absence seizures.

An EEG is not indicated in case of febrile convulsions, even in case of recurrent or complex febrile seizures.

An EEG may be considered in a child presenting with new onset status epilepticus as it may determine whether there are focal or generalized abnormalities that may influence diagnostic and treatment decisions. An EEG may be considered in a child presenting with status epilepticus if the diagnosis of pseudo status epilepticus is suspected.

Adults

The EEG can be used to support the diagnosis in patients in whom the clinical history indicates a significant probability of an epileptic seizure or epilepsy, and can help classify individuals into different epilepsy seizure types and epilepsy syndromes. In a patient in whom the clinical history suggests an epileptic seizure, the prevalence of epilepsy will be high. The finding of epileptiform abnormalities is specific, and the diagnostic value of the test is good. In a patient in whom the history is typical of some other disorder, such as syncope, the prevalence of the epilepsy will be low, and any epileptiform abnormalities are more likely incidental.

Photic stimulation is necessary to determine if the individual is photo-sensitive but carries a small risk of inducing a seizure. Hyperventilation is routinely employed to increase the sensitivity of an interictal EEG.

An EEG should be performed in young people with generalized seizures to aid classification and to detect a photo-paroxysmal response, which allows appropriate advice to be given.

Repeating a standard EEG in a selected adult population has been shown to increase the likelihood of obtaining epileptiform activity when the diagnosis of the epilepsy or the syndrome in unclear. However, if the diagnosis has been established, repeat EEGs are not likely to be helpful.

Repeated standard EEGs should not be used in preference to sleep or sleep-deprived EEGs. When a standard EEG has not contributed to diagnosis or classification, a sleep EEG should be performed.

Long-term video or ambulatory EEG may be used in the assessment of individuals who present diagnostic difficulties after clinical assessment and standard EEG.

In patients with alcohol withdrawal seizures, EEG pathology suggests that the seizure may not have been caused exclusively by alcohol withdrawal. Subsequent to repeat alcohol withdrawals seizures, EEG is considered necessary only if an alternative aetiology is suspected. This guideline, however, does not consider the risk of false positive result.

In adults with status epilepticus, EEG recording may be necessary to confirm the diagnosis and assess control when seizures are clinically subtle. If status epilepticus persists more than 30 minutes, EEG monitoring within 60 minutes to assess seizure control is recommended.

Prognostic value

Individuals presenting with a first unprovoked seizure who have unequivoqual epileptiform activity on their initial EEG have an increased risk of seizure recurrence.

In patients with epilepsy who have been seizure free for some time while taking antiepileptic medication and who discontinue epileptic drugs, an abnormal EEG is associated with a higher relative risk of seizure.

In neonates with seizures, an EEG showing an abnormal background rhythm, the presence of electrographic seizures and the presence of brief rhythmic discharges were consistently related to unfavourable outcomes.

Based on a review of 47 articles, EEG/MRI concordance was a prognostic indicator of seizure remission (positive predictor) after epilepsy surgery.

Key points

- **EEG is the gold standard to diagnose epilepsy. All guidelines agree however on the limits of EEG accuracy.**
- **EEG is not indicated without clinical suspicion and should not be performed to exclude a diagnosis of epilepsy because of the possibility of a false positive result (level C). A negative EEG cannot be used to rule out the clinical diagnosis of an epileptic seizure (level C).**
- **Standard EEG can be used to support the diagnosis in patients in whom the clinical history indicates a significant probability of an epileptic seizure or epilepsy (level C).**
- **Repeated standard EEGs may be helpful when the diagnosis of the epilepsy or the syndrome in unclear. However, if the diagnosis has been established, repeat EEGs are not likely to be helpful (level C). Repeated standard EEGs should not be used in preference to sleep or sleep-deprived EEGs (level C).**
- **The reliability of EEG video-telemetry to differentiate epileptic and non epileptic seizure is better than other procedures (level B).**
- **In children, an EEG should be performed only to support (and not to exclude) a diagnosis of epilepsy in case of unprovoked non-febrile seizures (level C).**

4.2.15 Evaluation of the child with Global developmental delay

Global development delay encompasses a clinical presentation that has a heterogeneous aetiologic profile and is associated with age-specific deficits in adaptation and learning skills[132]. Significant delay is defined as performance of two standard deviations or more below the mean of age appropriate standardized norm reference testing. The term global development delay is used in children less than 5 years of age whereas mental retardation is used in older children.

One good-quality guideline[132] was identified, by the American Academy of Neurology (Table 13). In this guideline, an EEG is recommended when a child with global developmental delay has a history or examination features suggesting the presence of epilepsy or a specific epileptic syndrome (Level C; class III and IV evidence)

Data are insufficient to permit making a recommendation regarding the role of EEG in a child with global developmental delay in whom there is no clinical evidence of epilepsy (Level U; class III and IV evidence).

4.2.15.1 Conclusion

An EEG can be obtained when a child with global developmental delay has a history or examination features suggesting the presence of epilepsy or a specific epileptic syndrome. (Level C: possibly useful; class III retrospective study).

Key points

- **There is insufficient evidence to recommend the use of EEG in children with global developmental delay, except in case of suspicion of epilepsy.**

Table 13: guideline on children with global developmental delay

Institution/Authors	Year of publication	Score AGREE	Diagnosis	Prognosis	Follow-up	Other: suspicion of epilepsy
American Academy of Neurology [132]	2003	62	Ø	Ø	Ø	√

√: recommended; —: not recommended; Ø: not mentioned

4.2.16 Patients with head injury/ traumatic brain injury

An injury to the brain is identified by confusion or disorientation, loss of consciousness, posttraumatic amnesia and other neurological abnormalities[133].

For traumatic brain injury, three guidelines and one systematic review were identified (Table 14).

A European Federation of Neurological Societies guideline on mild traumatic brain injury was excluded because the publication date was 2002 without revision[134]. For information, EEG was not used for the diagnosis in this guideline. Asked by the external experts of the report, an additional specific search was done with the terms "commotio cerebri" and with "brain concussion" to search additional publications about mild traumatic injury in Sumsearch and Tripdatabase. The search in Medline was done with the terms: ("Brain Concussion"[Mesh] AND "Electroencephalography"[Mesh]) AND systematic[sb]. The search in Embase was done with the terms 'brain concussion'/exp/mj AND 'electroencephalogram'/exp. This search yielded two position statements of the Canadian Paediatric Society were found but excluded because of a lack of methodology description.

The systematic review is of fair quality, with a literature search in Medline only and including studies with both prospective and retrospective design[66]. The review found that in adults with traumatic coma, SSEP and BAEP are more sensitive than EEG (45-60% sensitive versus 35%).

The NICE guideline[135] and the New Zealand guideline[133] do not mention the EEG, the third guideline by the American Academy of Neurology[136] states insufficient data were found on the use of EEG before deciding whether to use antiepileptic drug prophylaxis in patients with severe traumatic brain injury.

4.2.16.1 Conclusion

All guidelines are in agreement that the EEG is not recommended for the diagnosis or the management of patients with severe traumatic brain injury. No data were found upon which to base a recommendation regarding the use of EEG for the use of antiepileptic prophylaxis.

SEP and BAEP are found to be more sensitive than EEG (45-60% sensitive versus 35%) in predicting prognosis of patients with traumatic coma.

No data were found to support the use of EEG in case of mild traumatic brain injury.

Key points

- **EEG is not recommended for the diagnosis or the management of patients with severe traumatic brain injury. No data were found to support the use of EEG in case of mild traumatic injury.**

Table 14: guidelines on head injury and traumatic coma

Institution/Authors	Year of publication	Score AGREE	Diagnosis	Prognosis	Follow-up	Other: antiepileptic prophylaxis
NICE[135]	2007	63	Ø	Ø	Ø	Ø
American Academy of Neurology/ Chang[136]	2003	57	Ø	Ø	Ø	—
New Zealand Guidelines Group[133]	2006	76	Ø	Ø	Ø	Ø

√: recommended; —: not recommended; Ø: not mentioned

4.2.17 Full term infants with Hypoxic-ischaemic encephalopathy

Hypoxic ischemic encephalopathy is diagnosed based on a combination of signs of intrauterine distress and abnormal postnatal findings[137]. Amplitude integrated EEG may be used to monitor infants with severe neurological diseases, as a prognostic tool.

One guideline[138] and one systematic review[137] were identified. The guideline considered only neuroimaging and was subsequently excluded. The systematic review was of high quality. In this systematic review[137], the evidence on amplitude-integrated EEG as a quantitative predictor of neurodevelopmental outcome was summarized. Poor outcomes are defined as cerbral palsy or a developmental quotient ≤85. Eight studies with 31 - 160 infants were included. Both the sensitivities and specificities of severe amplitude-integrated EEG tracings ranged from 73 to 100% with no significant heterogeneity among the studies (p=0.19). Overall, severe amplitude-integrated EEG tracings appeared to be accurate in predicting a poor outcome, with a 91% (95%CI 87-95) pooled sensitivity and a 0.09 (95% CI 0.06-0.15) pooled negative likelihood ratio.

4.2.17.1 Conclusion

In full term infants with hypoxic-ischemic encephalopathy, there was an overall sensitivity of 91% (95% CI 87-95) and a negative likelihood ratio of 0.09 (95% CI 0.06-0.15) for amplitude integrated EEG tracings to accurately predict poor outcome.

Key points

- **Amplitude integrated EEG tracings have high sensitivity to accurately predict poor outcomes in full terms infants with hypoxic-ischemic encephalopathy.**

4.2.18 Patients suspected of or diagnosed with Metabolic encephalopathy

External experts for this report stated that the EEG may be used to diagnose metabolic encephalopathy, specifically hepatic or uraemic encephalopathy.

A search for guidelines on metabolic encephalopathy was done in Sumsearch with the MESH terms "hepatic encephalopathy", "Brain Diseases, Metabolic" AND "EEG" and with "kidney failure" AND "encephalopathy". In Trip database the search for guidelines was done with the terms "metabolic encephalopathy", "Brain Diseases, Metabolic" , "hepatic encephalopathy" and also "kidney failure encephalopathy". Additional publications were also provided by experts[139, 140].

According to the CBO[81], an EEG may be used in case metabolic, toxic or infectious encephalopathy, especially to differentiate delirium with inhibition (slow EEG) from depression (normal EEG). The EEG is sensitive but not specific in case of metabolic encephalopathy with delirium (level C or 3).

In response to the question of the external experts on the use of EEG to grade the severity of metabolic encephalopathy, several guidelines were considered despite a poor methodological quality as they were the only available. One guideline of the American Association for the Study of Liver Diseases[141] covers the evaluation of the patient before liver transplantation. The severity of liver disease is scored with the Child-Turcotte-Pugh Scoring System. In this system, the grade of encephalopathy is based on clinical criteria; the EEG is not mentioned. There is no description of the methodology used for this guideline; quality of evidence is used to base recommendations. One other guideline of the same association [142], with the same remarks on methodology, covers the management of acute liver failure: the EEG is not cited. Grades of encephalopathy are based on clinical criteria. The International society of Hepatic Encephalopathy and Nitrogen Metabolism[140] states that the grading of EEG alterations in hepatic encephalopathy can be obtained by visual pattern recognition, but this approach has limited reliability. Grading based on the simple semi-quantitative evaluation of the frequency of the basic EEG rhythm improves the reliability as well as grading based on quantitative analysis of the EEG (e.g;, spectral analysis) which is proved to provide prognostic information (without reference). Flat EEG is compatible with reversible brain dysfunction in severe hepatic encephalopathy. Drugs affect EEG and their influence should be considered. The recommendations are based on an expert consensus without methodology described. About uraemic encephalopathy, a narrative review about neurological complications in renal failure[139] described that EEG becomes slower with progression of the uraemic state.

4.2.18.1 Conclusion

The use of EEG for patients suspected of metabolic encephalopathy is conflicting and based on poor levels of evidence.

Key points

- **In patients suspected of metabolic encephalopathy, recommendations on the use of EEG are conflicting.**

4.2.19 Patients suspected of or diagnosed with Migraine or headache

Headache and migraine are common diseases. The usefulness of EEG in their diagnosis is debated.

The search identified 9 guidelines. For three guidelines, only summary and recommendations were available[143, 144] (Table 15).

Guidelines agree that the EEG is not useful in routine evaluation of patients with headache. This does not exclude the use of EEG to evaluate headache patients with associated symptoms suggesting a seizure disorder, such as atypical migraine aura or episodic loss of consciousness. Assuming head-imaging capabilities are readily available, EEG is not recommended to exclude a structural cause for headache.

In patients with non acute headache, interictal EEG is not indicated in the diagnostic evaluation of headache patients except if the clinical history suggests a possible diagnosis of epilepsy. Ictal EEG is indicated during episodes suggesting complicated aura and during auras associated with decreased consciousness or confusion. Quantitative EEG methods are not routinely indicated in the diagnostic evaluation of headache patients[145].

An EEG is not recommended in the routine evaluation of a child with recurrent headaches, as it is unlikely to provide aetiology, improve diagnostic yield, or distinguish migraine from other types of headaches (Level C; class II and class III evidence).

Although the risk for future seizures is negligible in children with recurrent headache and paroxysmal EEG, future investigations for epilepsy should be determined by clinical follow up (Level C; class II and class III evidence)[146]

4.2.19.1 Conclusion

The EEG is not indicated in patients with headache, except in those cases where associated symptoms are suggestive of a seizure disorder such as atypical migraine aura or episodic loss of consciousness.

Key points

- **EEG is not useful for routine evaluation in patients with migraine or headache, except in patients with associated symptoms suggesting a seizure disorder (level C).**

Table 15: guidelines on migraine or headache

Institution/Authors	Year of publication	Score AGREE	Diagnosis	Prognosis	Follow-up	Other: suspicion of epilepsy
National Headache Foundation/ Pearlman[144]	2004	Full text not available				
National Headache Foundation/ Martin[147]	2004	Full text not available				
European Federation of Neurological Societies/ Sandrini[145]	2004	51	—	Ø	Ø	√
ICSI[148]	2007	63	Ø	Ø	Ø	Ø
American Academy of Neurology/ Lewis[146]	2005	62	—	—	—	√ determined by clinical follow-up
American Academy of Neurology [143]	1995 reviewed 2006	Summary statement	—	—	—	√
British Association for the Study of the Headache[149]	2007	54	Ø	Ø	Ø	Ø
CKS[150]	2005	52	Ø	Ø	Ø	Ø
CKS[151]	2006	52	Ø	Ø	Ø	Ø

√: recommended; —: not recommended; Ø: not mentioned

4.2.20 Patients suspected of or diagnosed with Schizophrenia

Schizophrenia is a complex and misunderstood illness that affects about 1 in every 100 people at some time in their life. It usually emerges during the critical period of transition to adulthood and occurs in all known cultures.

The search identified 5 guidelines. (Table 16)

Four guidelines[152]; [153]; [154]; [155] do not use an EEG for the diagnosis or the management of schizophrenia. In one guideline [156], EEG is proposed in baseline assessment not routinely, but only if clinically indicated.

Key points

- **EEG is not useful for the diagnosis and management of patients with schizophrenia (level C).**
- **One guideline recommends an EEG at initial diagnosis if clinically indicated.**

Table 16: guidelines on schizophrenia

Institution/Authors	Year of publication	Score AGREE	Diagnosis	Prognosis	Follow-up
Singapore Ministry of Health[152]	2003	57	Ø	Ø	Ø
American Psychiatric Association[156]	2004	60	√	Ø	Ø
CKS [155]	2007	59	Ø	Ø	Ø
Canadian Psychiatric Association[153]	2005	66	Ø	Ø	Ø
RANZCP[154]	2004	54	Ø	Ø	Ø

√: recommended; —: not recommended; Ø: not mentioned

4.2.21 Patients suspected or diagnosed with stroke

Stroke affects between 174 and 216 people per 100,000 population in the UK each year, and accounts for 11% of all deaths in England and Wales[157].

The literature search identified six guidelines (Table 16 bis).

No guideline considers the use of EEG in patients suspected or diagnosed with stroke. One guideline[158]related that electroencephalography may be helpful for evaluating patients with acute ischemic stroke in whom seizures are suspected as the cause of the neurological deficits or in whom seizures could have been a complication of the stroke (without level of evidence).

4.2.21.1 Conclusion

EEG is not useful for the diagnosis, the management or the follow up of patients suspected of or diagnosed with stroke. It may be helpful in patients with associated seizures.

Key points

- **EEG is not useful for the diagnosis or the follow-up of patients suspected of or diagnosed with stroke.**
- **It may be helpful in case of seizures.**

Table16 bis: guidelines on stroke

Institute/Author	Year of publication	AGREE Score	Diagnosis	Prognosis	Follow -up	Other
American Heart Association-American Stroke Association/Adams[158]	2007	63	Ø	Ø	Ø	In case of seizures
Singapore Ministry of Health[159]	2003	63	Ø	Ø	Ø	Ø
NICE / Royal College of Physicians[157]	2008	81	Ø	Ø	Ø	Ø
Australian National Health and Medical Research Council/National Stroke Foundation (1)[160]	2007	84	Ø	Ø	Ø	Ø
Australian National Health and Medical Research Council/National Stroke Foundation (2)[161]	2005	83	Ø	Ø	Ø	Ø
New Zealand Guidelines Group[162]	2003	76	Ø	Ø	Ø	Ø

√: recommended; —: not recommended; Ø: not mentionedPatients suspected of or diagnosed with Viral encephalitis

4.2.22 Patients suspected of or diagnosed with Viral encephalitis

Viral encephalitis is a medical emergency. Correct immediate diagnosis allowing rapid introduction of symptomatic and specific therapy is important for survival and reduction of consequences in survivors.

One guideline[163] was identified (Table 17), in which the EEG is recommended in the diagnostic pathway of patients suspected of encephalitis. EEG is considered as a non specific investigation, although it may still sometimes be useful in certain situations as it may identify focal abnormalities. In acute viral encephalitis, the EEG is an early and sensitive indicator of cerebral involvement, prior to the initial evidence of parenchyma involvement on neuroimaging. During the acute phase, the severity of EEG abnormalities does not correlate with the extent of the disease. (level of recommendation C; class of evidence III).

4.2.22.1 Conclusion

EEG is an early and sensitive indicator of cerebral involvement in case of suspicion of encephalitis. It is a non specific investigation but it may identify focal abnormalities. EEG abnormalities do however not correlate with the extent of the disease.

Key points

- **In case of suspicion of viral encephalitis, EEG is an early and sensitive but non-specific indicator.**

Table 17: guideline on viral encephalitis

Institution/Authors	Year of publication	Score AGREE	Diagnosis	Prognosis	Follow-up	Other: severity
European Federation of Neurological Societies[163]	2005	55	√	Ø	Ø	—

√: recommended; —: not recommended; Ø: not mentioned

4.3 EVOKED POTENTIALS AND EVENT RELATED POTENTIALS

4.3.1 Search for systematic reviews, meta-analyses, and HTA reports

The literature was searched in Medline, Embase, CRD DARE, INAHTA database and NICE. All search terms used are listed in appendix 5, with the number of references that were retrieved.

In total, 227 articles were identified, discarding duplicates.

Primary selection was based on title and abstract, secondary selection of the remaining articles was done based on the full text.

Inclusion criteria:

- Design: Systematic reviews or meta-analyses, HTA reports and guidelines
- Patients: Studies on patients within clinical care, further not specified
- Diagnostic tests: Evoked potentials, including visual, somatosensory, auditory and motor evoked. Event related potentials, such as P300, MMN, CNV, …
- Outcome: clinical patient oriented outcomes, for example awakening from coma, schizophrenia, .. Intermediate outcomes were not eligible.

Exclusion criteria:

- Narrative reviews: no details on methods, no systematic and transparent search
- Economic analyses: maybe interesting at a later stage, but not initially
- Studies on animals or in vitro studies
- Guidelines older than 5 years without revision
- Duplicates

The selection was done independently by two reviewers, discrepancies were resolved by discussion.

4.3.2 Search for guidelines

Guidelines were searched in two ways: by using the search term of the test, in this case evoked potentials and event related potentials, and by using terms relating to each disease or clinical problem for which systematic reviews or HTA reports were selected by the previous search. Sources included the National Guideline Clearinghouse, NICE, SIGN, Trip database, sites of the American Academy of Neurology, the American Psychiatric Association, the Royal Australian and New Zealand College of Psychiatrists, CBO.

Guidelines older than 5 years without revision were excluded.

All search terms and number of publications retrieved are listed in appendix 6.

4.3.3 Quality appraisal

All HTA reports were assessed for quality using the checklist of INAHTA.

Systematic reviews and meta-analyses were assessed using the checklist of the Dutch Cochrane Centre.

Guidelines were assessed with the AGREE checklist, www.agreetrust.org. High quality was attributed for a score >70, good quality for a score between 60-70, fair quality for a score 50-59 and low quality for a score <50.

Publications of low quality were excluded from further review.

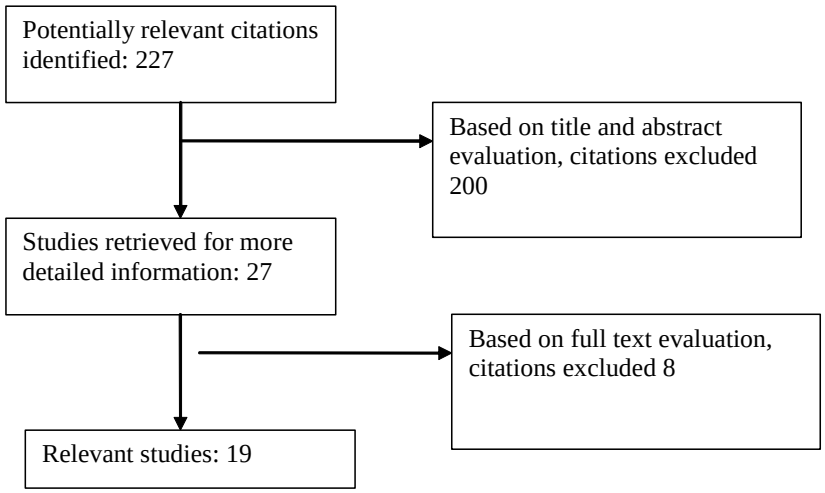
4.3.4 Results

After selection, 19 systematic reviews were included in the report. No HTA reports were identified.

The search and selection process is illustrated in Figure 21.

In addition, 69 guidelines were identified and assessed for quality.

Figure 21: flow chart of the search strategy for systematic reviews and HTA report on evoked and event related potentials



4.3.5 Patients suspected of suffering from Acoustic neuroma

Acoustic neuromas are benign, slow-growing intracranial tumours, which arise from cells in the sheaths that surround the hearing and balance nerves. The neuromas usually manifest themselves as one-sided hearing impairment, which may go ignored by the patient or be dismissed by the doctor. Continued growth of these neuromas ultimately results in compression on the brainstem and raised intracranial pressure. [164]

Magnetic resonance imaging represents the method of choice for identifying the minority of these patients who have an underlying acoustic neuroma. Auditory brainstem responses have been proposed as alternative for MRI imaging.[164]

The search strategy is described in appendix 7. Two guidelines were identified, one of which was of low quality (AGREE score 48) and was subsequently excluded.[165] The other was published in 2002 and was consequently excluded as well. [164]

However, expert opinion states that the brain auditory evoked response can be used in those cases where MRI is contraindicated or not tolerated. This statement is corroborated in the 2002 guideline.

Evidence on vertigo and unilateral deafness was synthesised in paragraph 5.3.20.

Key points

- **Brain auditory evoked response can be used in those cases where MRI is contraindicated or not tolerated.**

4.3.6 Patients suspected of or diagnosed with Alcoholism

Five guidelines and one meta-analysis were identified. The meta-analysis included case-control studies only and was subsequently excluded[166]. In addition, two guidelines were excluded because of low quality(Table 18).

None of the included guidelines mentions evoked or event related potentials for the clinical management of patients suspected of or diagnosed with alcoholism.

4.3.6.1 Conclusion

Evoked or event related potentials are not recommended for the clinical management of patients suspected of or diagnosed with alcoholism, not for diagnosis, prognosis nor follow-up.

Key points

- **Evoked or event related potentials are not recommended for the diagnosis, prognosis or follow-up of alcoholism.**

Table 18: guidelines and reviews on alcoholism

Institute/Author	Year of publication	AGREE Score	Diagnosis	Prognosis	Follow-up
SIGN[167]	2003	80	Ø	Ø	Ø
American Academy of Child and Adolescent Psychiatry[168]	2004	51	Ø	Ø	Ø
American Psychiatric Association[169]	2006	45: excluded			
American Academy of Pediatrics[170]	2005	27: excluded			
US Preventive Services Task Force[171]	2004	65	Ø	Ø	Ø

√: recommended; —: not recommended; Ø: not mentioned

4.3.7 Patients with Anxiety or anxiety disorders

Anxiety was suggested as a potentially interesting topic by the external experts for this report, as a symptom of disorders such as generalised anxiety disorder, phobia, panic disorder or posttraumatic stress disorder.

Five guidelines and one meta-analysis were identified. The meta-analysis summarised case-control studies only, and was therefore excluded[172]. Two guidelines were excluded due to low quality. (Table 19)

Not one of the three remaining guidelines mentions evoked or event related potentials for the clinical management of patients with anxiety or anxiety disorders, not for diagnosis, prognosis nor follow-up.

4.3.7.1 Conclusion

Evoked or event related potentials are not recommended for the clinical management of patients with anxiety or an anxiety disorder.

Key points

- **Evoked or event related potentials are not recommended for the diagnosis, prognosis or follow-up of patients with anxiety or anxiety disorders.**

Table 19: guidelines on anxiety and anxiety disorders

Institute/Authors	Year of publication	Score AGREE	Diagnosis	Prognosis	Follow-up
American Academy of Child and Adolescent Psychiatry[173]	2007	39: excluded			
NICE[174]	2004	76	Ø	Ø	Ø
American Psychiatric Association[175]	2004	42: excluded			
Veterans' Affairs/Department of Defense[176]	2004	63	Ø	Ø	Ø
Canadian Psychiatric Association[177]	2006	50	Ø	Ø	Ø

√: recommended; —: not recommended; Ø: not mentioned

4.3.8 Patients with Cervical spondylosis

"Cervical spondylosis" refers to the degenerative process of the cervical spine, a ubiquitous condition that is, for most part, asymptomatic. When symptoms do arise as a result of degenerative changes, they can be grouped into (axial) pain, radiculopathy, and myelopathy[178]. In patients with cervical spondylosis, SEPs elicited by stimulation of a nerve in the upper or lower extremities may be helpful in indicating which patients are liable to develop a significant cord deficit, so that surgical treatment can be considered at an early stage. The same is true for MEPs, elicited by TMS at the scalp and recorded at the site of the peripheral muscle.

No guidelines specifically on cervical spondylosis were identified, using the search terms: 'cervical spondylosis' OR Spinal Osteophytosis [MeSH]'. One systematic review was found, which was of low quality and was subsequently excluded[179].

At the request of the experts collaborating on this report, an additional search was performed for original studies assessing the value of evoked potentials in patients suspected of or diagnosed with cervical spondylosis. Databases searched were Medline, Embase, Medion and DARE. Search terms are listed in appendix 8.

Discarding duplicates, 175 possibly relevant articles were identified.

Studies were selected for further review if they fulfilled the following criteria:

Inclusion criteria:

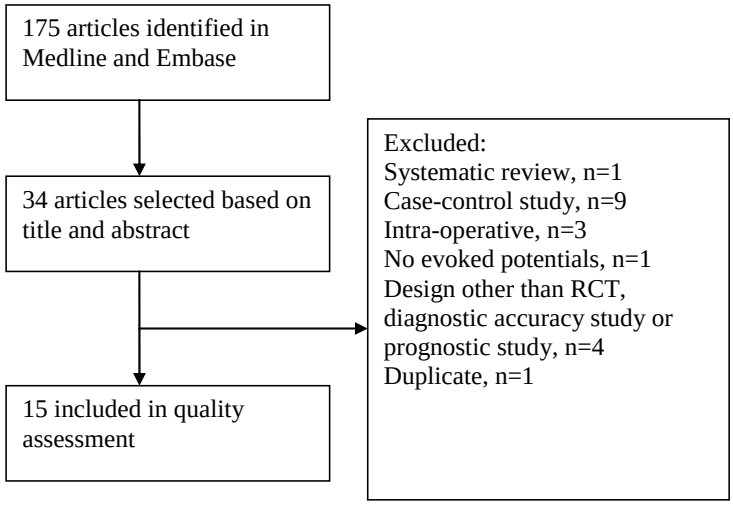
- Diagnostic accuracy study assessing the diagnostic value of evoked potentials or event related potentials
- Prognostic study assessing the prognostic value of evoked potentials or event related potentials
- Randomised controlled trial assessing the impact of using evoked potentials or event related potentials on the patient's outcome
- Patients suspected of or diagnosed with cervical spondylosis

Exclusion criteria:

- Animal studies
- Narrative reviews
- Editorials, letters, commentaries
- Therapeutic studies
- Intra-operative application of the tests
- Case-control studies
- No valid reference standard, or outcome assessment tool
- Sample size of less than 20 patients
- Studies in a language other than English, French, Dutch or German

Based on title and abstract, 34 articles were selected. Of these articles, the full content was first scanned. A further 18 articles could be excluded, using the same in- and exclusion criteria described above. Of the remaining 16 articles one more was excluded because of substantial overlap with another article from the same author. Fifteen publications were read in full, and quality was appraised as defined in the general methodology in chapter 5.1 (flow chart Figure 22) Details can be found in Appendix .

Figure 22: flow chart of selection of studies



4.3.8.1 Diagnostic accuracy studies evaluating the use of EP in cervical spondylotic myelopathy

Seven studies evaluating the diagnostic accuracy were available. Of these, two were of very low quality (positive QUADAS scores 3[180] and 2[181] respectively). In addition, one study did not use a valid reference standard[182]. These three studies were subsequently excluded.

In 1991, Maertens de Noordhout et al. were among the first to describe the use of upper limb motor MEP and SEP in patients diagnosed with cervical cord compression by myelography[183]. Myelography consists of X-ray of the spine, after the injection of contrast medium in the subdural space by lumbar puncture; it allows for evaluation of the spinal cord. The authors found a much higher percentage of abnormal MEP in patients with than in patients without cord compression (84% respectively 22%). MEP of the biceps showed to be less sensitive than MEP of the first dorsal interosseus (FDI); and the central motor conduction time (CMCT) determined by the waveforme latency was more sensitive than the waveforme amplitude or morphology. SEP of the median nerve proved to be abnormal in a much lower percentage (25% of all cases). Although its methodological evaluation highlighted some major methodological flaws, like the lack of blinding of the assessor to the patient's myelography, the purpose of this publication was merely to propose a new evaluation tool that could possibly offer a less invasive alternative to myelography. In 1998, the same authors published a series including 55 patients[184] all with myelographic signs of cord compression and clinical signs/symptoms of cervical myelopathy (e.g. weakness, spasticity, hypaesthesia, sphincter disturbances etc.), in which they confirmed their previous findings, but methodologically this study also had some flaws. They additionally included MEP of lower limb muscles (anterior tibial muscle) and lower limb SEP (posterior tibial nerve) as well as SEP of the ulnar nerve.

Simo M et al[185] also studied lower limb MEP and SEP and evaluated these tests in 51 patients against MRI abnormalities of cervical cord compression, with or without clinical signs/symptoms of myelopathy. They could confirm that abnormalities are more prevalent in MEP than in SEP; however, the methodological strength of this study was not high. Moreover, it is well known that lower limb MEP and SEP are more variable and prone to artefacts[183, 184] and that a rigorous evaluation of their contribution to cervical myelopathic signs and symptoms (e.g. when deciding on cervical surgical decompression or not) might require exclusion of thoracolumbar spondylotic lesions, which none of the included studies did.

Lo YL et al published in 2006 the results of a well-conducted large cross-sectional evaluation including 226 participants with cervical spondylosis, in whom they conducted MEP of upper and lower limbs[186].

They subdivided the patients in 4 groups based on the cervical compressive signs on MRI: group 1 with spondylosis but no cord deformity (N=50), group 2 with mild cord deformity but anterior-posterior cord diameter 2/3 or more of normal (N=77), group 3 with significant deformity, anterior-posterior cord diameter less than 2/3 of normal but no intramedullary hyperintensities (N=40), group 4 with the same characteristics of group 3 but with additional intramedullary hyperintensities (N=59). MEP of the upper limbs (FDI) and of the lower limbs (abductor hallucis) showed a very high sensitivity and specificity (both 98%) when all 4 muscles were taken together to detect any cord abnormality as found on MRI. None of the patients in group 1 had MEP abnormalities (defined as abnormal CMCT, abnormal difference between right and left CMCT or abnormal amplitude); and only 3 patients in group 2 had completely normal MEPs. Physical neurological examination in these patients to reveal cervical cord myelopathic symptoms, correlated with MRI as follows for group 1 to 4: 76%- 73%- 93%- 98%. EMG demonstrated abnormalities suggestive for root pathology in 18%- 77%- 95%- 98%. This study again emphasizes the diagnostic value of MEP (upper limb (FDI) and lower limb (abductor hallucis)) to detect MRI cord compression secondary to spondylotic degenerative phenomena. However, not all these MEP and MRI abnormalities point directly to clinical signs of cervical myelopathy, especially not in the more mildly affected groups. It can be concluded from this study that MEP might replace MRI as a relatively non-invasive test to screen for compression signs of the myelon in case of cervical spondylotic lesions. According to this study, the relationship between compression (detected by MRI or by MEP) on the one hand and clinical signs/symptoms of myelopathy on the other hand is not simple and needs further evaluation before it can be used to decide on therapeutic consequences. Ideally, these results are to be confirmed by another large and well-conducted study.

Other authors, who mainly studied the prognostic role of EP, also described the correlation between MEP and/or SEP abnormality, and (degree of) clinical cervical myelopathic signs/symptoms[187-190]. In all these studies the JOA or mJOA (modified JOA) scale is applied to quantify the clinical signs/symptoms. This scale uses qualitative descriptions for these signs. However, none of these studies is of high quality (see Appendix) and further evaluation is necessary.

In conclusion, in patients with clinical signs of cervical spondylosis (pain, paresthesia's), with or without objective symptoms of cervical myelopathy, cervical cord compression can possibly be reliably detected by performing TMS for MEP of FDI and abductor hallucis bilaterally. The relationship to cervical myelopathic symptoms is more complex, especially in milder cases, and needs further elucidation before results can be coupled to therapeutic consequences. Studies thus far seem to indicate that MEP is more helpful than SEP to evaluate this kind of patients, but this needs further confirmation. Also some questions remain concerning the problem of upper versus lower limb evoked potentials. Likewise, the relative role of the different stimulation or elicitation sites (ulnar, median or radial nerve; abductor hallucis or anterior tibial muscle etc.) needs further evaluation.

Key points

- **One study in patients with clinical signs of cervical spondylosis indicates that cervical cord compression can be reliably detected by performing TMS. (moderate quality of evidence) Further studies need to confirm this result.**

4.3.8.2 Prognostic studies on the use of EP in cervical spondylotic myelopathy

Eight studies were available on the prognostic value of EP. Four studies were of low quality and were subsequently excluded [187-190]. Consequently, the four remaining studies were included in the review, all of which were authored by Bednarik J et al.

A first prospective cohort study of these authors dealt with asymptomatic spondylotic or discogenic compression of the cervical cord found on MRI[191]. The question was whether in patients complaining of pain and/or of radicular signs (paresthesias, signs of hypesthesia and weakness confined to maximal one dermatome/myotome), SEP (median or posterior tibial nerve) or MEP (abductor digiti minimi or abductor hallucis)

can predict progression to cervical myelopathic signs and symptoms (hypesthesia and weakness in at least 2 dermatomes/myotomes, spasticity, weakness in upper limb, gait or sphincter disturbances). This study has been updated twice[178, 192], and the number of participants has been enlarged to N=199 (mean age 51 years, range 28-82). Other possible predictive factors have also been included like age, severity of compression on MRI, pre-existing clinical signs of radiculopathy and EMG signs of anterior horn compression. The average follow-up was 3.10 years (range 2-12 years), and 23% (N=45) of the patients developed new signs of symptomatic cervical myelopathy (SCM), accompanied by at least one point change on the mJOA scale. This scale uses qualitative descriptions for these signs. In the final model, the strongest predictor of SCM is the existence of clinical radiculopathy, followed by EMG signs of anterior horn compression, SEP abnormality (in upper or in lower limbs), MEP abnormality (in upper or in lower limbs) and intramedullar hyperintensity on MRI. When looked for early development of SCM, i.e. within 12 months of study entrance, clinical radiculopathy (Odds ratio 4.7 (1.6-13.7), p=0.004), EMG (Odds ratio 2.8 (1.0-8.3), p=0.044), MEP (Odds ratio 2.9 (1.0-8.8), p=0.046) and SEP (Odds ratio 4.0 (1.4-11.6), p=0.011) are significantly informative (Moderate quality of evidence). A model based on these results could correctly classify 81% of the patients.

Bednarik J et al also published a study on the value of SEP and MEP in predicting and monitoring the effect of therapy (surgery or conservative treatment) in spondylotic cervical myelopathy[193]. The conclusion of the authors is that longitudinal EP follow-up is of little use in the practical assessment of therapy results or natural course in an individual patient. In fact, the subgroups in this study including 61 patients were too small to allow for firm conclusions.

Conclusion: In patients with asymptomatic spondylotic (or discogenic) cervical cord compression on MRI, one study defines the existence of clinical radiculopathy signs as the most informative factor for the prediction of progression to clinical myelopathy signs and symptoms. However, SEP, MEP and EMG are also independent predictors of early (<12 months) appearance of myelopathy signs/symptoms (Moderate quality of evidence).

The role of SEP and MEP in predicting therapeutic outcome for symptomatic patients needs further clarification.

Key points

- **One study in patients with asymptomatic cervical cord compression indicates that progression to clinical myelopathy signs/symptoms can best be predicted by clinical radiculopathy signs/symptoms.**
- **SEP, MEP and EMG are also independent predictors of early (<12 months) appearance of myelopathy signs/symptoms. (moderate quality of evidence)**
- **Further studies need to confirm this result.**

4.3.9 Comatose patients

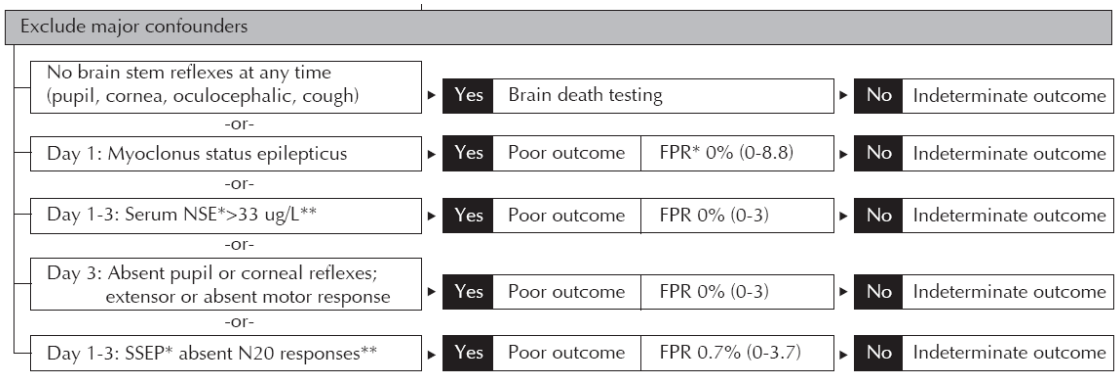
Evoked potentials may be used to predict unfavourable outcome in comatose patients, i.e. death or vegetative state.

Four guidelines and three systematic reviews were identified. One guideline[64] and two systematic reviews were excluded due to low quality[194, 195]. (Table 20)

The systematic review is of good quality, with an adequate search strategy and selection, and appropriate methods for meta-analysis. The results show that bilateral absence of the N20 component of a sensory evoked potential in the first week after an event causing anoxic-ischaemic coma, has a sensitivity between 28-73% and specificity of 100% for predicting death or vegetative state.

All guidelines agree on the value of somatosensory evoked potentials (SEP) 1-3 days after the arrest, to predict a poor outcome. A poor outcome can not be ruled out in case the SEP does not show bilateral absence, thus making the test suitable for ruling in poor outcome but not ruling out. (American Academy of Neurology: level of recommendation B)

Figure 23: Coma decision algorithm



Source: American Academy of Neurology, based on the practice parameter of Wijdicks et al.

4.3.9.1 Conclusions:

Bilateral absence of the N20 component of the SEP with median nerve stimulation predicts a poor outcome in patients with hypoxic –anoxic coma.

Key points

- **Somatosensory evoked potentials can be used reliably to predict poor outcome in comatose patients, but not to rule out poor outcome.**

Table 20: guidelines on comatose patients

Institute/Authors	Year of publication	Score AGREE	Diagnosis	Prognosis	Follow-up
American Academy of Neurology/Wijdicks[67]	2006	64	Ø	√	Ø
American Heart Association[196]	2005	60	Ø	√	Ø
Australian Government national Health and Medical Research Council[68]	2003	73	Ø	√	Ø
Royal College of Physicians[64]	2003	38: excluded			

√: recommended; —: not recommended; Ø: not mentioned

4.3.10 Patients suspected of or diagnosed with Dementia

Dementia can be described as a group of usually progressive neurodegenerative brain disorders characterised by intellectual deterioration and more or less gradual erosion of mental and later physical function, leading to disability and death.[83] Studies have found that patients with Alzheimer's dementia have longer P100 latencies of visual evoked potentials, by which visual evoked potentials might be used as a diagnostic tool for Alzheimer's disease.[197]

The literature search yielded 13 guidelines, one systematic review and one HTA report. One guideline was not available in full text[77], one was on radiology only[78] and one was of low quality[79]. An additional guideline was identified by an external reviewer and added to the list[82] The systematic review was excluded because it summarised case-control studies only[197]. This leaves 11 guidelines and one HTA report for inclusion in the report. (Table 21)

In the one, very recent HTA report (SBU HTA report 2008[75], which is of good quality with explicit search and selection criteria, clinical features that are thought to be associated with ischaemic vascular dementia but await further research include focal changes in EEG and evoked potentials.

In all ten guidelines that were included in this report, evoked or event related potentials are not mentioned for the diagnosis, prognosis or follow-up of dementia patients.

4.3.10.1 Conclusion

Evoked or event related potentials are not recommended for the clinical management of dementia patients, not for diagnosis, prognosis nor follow-up.

Key points

- **Evoked or event related potentials are not recommended for the diagnosis, prognosis or follow-up of patients suspected of or diagnosed with dementia**
- **Further research is awaited for the value of evoked potentials on distinguishing ischaemic vascular dementia.**

Table 21: guidelines on dementia

Institute/Authors	Year of publication	Score AGREE	Diagnosis	Prognosis	Follow-up
SIGN[74]	2006	79	Ø	Ø	Ø
Royal College of Psychiatrists[80]	2005	59	Ø	Ø	Ø
NICE[83]	2006	76	Ø	Ø	Ø
Singapore Ministry of Health[84]	2007	62	Ø	Ø	Ø
American College of Radiology/ Dormont[78]	2007	Only on radiology: excluded			
US Preventive Services Task Force[85]	2003	61	Ø	Ø	Ø
Alberta Clinical Practice Guideline Program[79]	2007	48: excluded			
British Columbia medical association[86]	2007	53	Ø	Ø	Ø
American Academy of Neurology/ Miyasaki [87]	2006	65	Ø	Ø	Ø
American Medical Directors Association[77]	2005	Full text not available			
American Academy of Neurology/ Petersen: [88]	2003	58	Ø	Ø	Ø
American Academy of Neurology/ Knopman[73]	2004	56	Ø	Ø	Ø
CBO[81]	2005	64	Ø	Ø	Ø
European Federation of Neurological Societies/Waldemar[82]	2007				

√: recommended; —: not recommended; Ø: not mentioned

4.3.11 Patients with Depression or bipolar disorder

In the RIZIV/INAMI survey, depression was, combined with hallucinations, the most common reason for performing evoked potentials by the physicians included in the sample.

Twelve guidelines, but no systematic reviews or HTA reports on the value of evoked or event related potentials were identified. (Table 22)

Evoked or event related potentials are not mentioned in any of the guidelines. ICSI mentions repetitive transcranial magnetic stimulation as a treatment modality, for which results are inconsistent and inconclusive, but nothing is mentioned for motor evoked potentials as a diagnostic tool.

It was stated by the external experts of this report, that loudness dependent auditory evoked potentials are used for the prediction of response to antidepressant therapy. A specific search was conducted for this question (search terms listed in appendix 9). In Medline, three articles were identified of which one was potentially relevant for the research question; in Embase, 45 articles were identified of which ten were potentially relevant. Three articles were narrative reviews[198-200], three included 20 patients or less[34, 201, 202], these six studies were excluded by which the remaining five studies were included in the review.

4.3.11.1 Conclusions

Evoked or event related potentials are not mentioned for the clinical management of patients with depression or bipolar disorder, not for diagnosis, prognosis nor follow-up.

Key points

- **Evoked or event related potentials are not recommended for the clinical management of patients suspected of or diagnosed with depression or bipolar disorder.**

Table 22: guidelines on depression and bipolar disorder

Institute/Authors	Year of publication	AGREE Score	Diagnosis	Prognosis	Follow-up
NICE[104]	2005	73	Ø	Ø	Ø
SIGN[101]	2005	75	Ø	Ø	Ø
NICE[203]	2006	76	Ø	Ø	Ø
NICE[105]	2007	76	Ø	Ø	Ø
ICSI[106]	2007	62	Ø	Ø	Ø
American Psychiatric Association[108]	2005	57	Ø	Ø	Ø
American Psychiatric Association[107]	2005	60	Ø	Ø	Ø
University of Michigan Health System[100]	2005	56	Ø	Ø	Ø
American Academy of Child and Adolescent Psychiatry[99]	2007	59	Ø	Ø	Ø
Singapore Ministry of Health[109]	2004	57	Ø	Ø	Ø
Royal Australian and New Zealand College of Psychiatrists[110]	2004	54	Ø	Ø	Ø
Royal Australian and New Zealand College of Psychiatrists[111]	2004	59	Ø	Ø	Ø

√: recommended; —: not recommended; Ø: not mentioned

4.3.12 Traumatic brain injury/low responsive patients

Although the incidence of head injury is high, the incidence of death from head injury is low. As few as 0.2% of all patients attending emergency departments with a head injury will die as a result of this injury.[204, 205] In patients with traumatic brain injury, tests such as the Glasgow coma scale, papillary responses or evoked potentials are used to predict either favourable or unfavourable outcome. For unfavourable outcome, high specificity is needed to minimise false positive results that would induce the risk of stopping treatment wrongfully. For the prediction of a favourable outcome, high sensitivity is needed to minimise false negative results that would induce the risk of wrongfully not referring patients for rehabilitation.

Three guidelines and two systematic reviews were identified in the literature search. One systematic review was excluded due to low quality[206].

The other systematic review by Carter et al.[207] found that in patients with acute, severe brain injury, SEPs are superior to pupillary responses and Glasgow Coma Scale in predicting either unfavourable or favourable outcome. A favourable outcome is defined as Glasgow Outcome Scale normal or moderate; an unfavourable outcome as severe disability, vegetative state or death. Although specificity for predicting unfavourable outcome with SEPs approaches 100%, sensitivity and the specificity for favourable outcome prediction is not as good. Summary estimates are not provided.

Two guidelines state that SEPs may be useful for the prediction of outcome (no grades of recommendation provided), whereas the third guideline does not mention evoked or event related potentials (Table 23). The New Zealand guideline also states that event related potentials are able to predict a wider range of outcomes. Consulting the original article by Lew et al.[208], outcome is also defined by the Glasgow Outcome Scale-Extended scores, 6 months after the incident. The study is, however, a small study of 22 patients with unclear sampling procedure. The results for bilaterally absent SEP are based on only five patients and those for absent speech-evoked ERP on only ten patients. Confidence intervals, which are supposedly very large, are not provided in the article, and no formal testing on superiority of one test over the other was not done. Specificity of speech-evoked ERP is 100.0% and positive predictive value is 100.0% for both the worst and unfavourable outcome. For favourable outcome, abnormal or absent ERP have 100.0% sensitivity and 100.0% negative predictive value. Consequently, this study offers very low level of evidence on the value of any discernible waveform on ERP for the prediction of good or moderate recovery. Larger studies are necessary to estimate any prognostic value more precisely.

4.3.12.1 Conclusion

Somatosensory evoked potentials may be useful in patients with traumatic brain injury to predict an unfavourable outcome. Speech-evoked event related potentials may be able to predict favourable outcome, but higher level evidence is needed before making formal recommendations.

Key points

- **Somatosensory evoked potentials can be used to predict unfavourable outcome in traumatic brain injury patients**

Table 23: guidelines on head injury

Institute/Author	Year of publication	Score AGREE	Diagnosis	Prognosis	Follow-up
New Zealand Guidelines Group[133]	2006	74	Ø	√	Ø
NICE[135]	2007	80	Ø	√	Ø
Royal College of Physicians[209]	2003	66	Ø	Ø	Ø

√: recommended; —: not recommended; Ø: not mentioned

4.3.13 Patients with Migraine or headache

Visual evoked potentials have been proposed as a possible diagnostic tool for migraine.

Nine guidelines were available, systematic reviews or HTA reports were not identified. One guideline was on EEG specifically, and two guidelines were not available in full text, by which six guidelines were included in the report. (Table 24)

The only guideline mentioning evoked potentials is that of the European Federation of Neurological Societies. In this guideline, it is stated that the literature data, e.g. by Schoenen et al., are often conflicting and fail to demonstrate the usefulness of evoked potentials as a diagnostic tool in migraine.

Findings should therefore be replicated before visually evoked potentials (VEPs) can be recommended in the diagnosis of migraine (not enough data are available for other types of headache). In conclusion, the Task Force does not recommend the use of evoked potentials in the diagnosis of headache disorders. (Level of evidence II based on conflicting data of insufficiently understood clinical significance. Grade of recommendation B.)

All other guidelines do not mention evoked or event related potentials for the clinical management of headache or migraine patients.

4.3.13.1 Conclusion

Evoked or event related potentials are currently not recommended for the clinical management of patients presenting with headache or migraine, not for diagnosis, prognosis nor follow-up.

Key points

- **Evoked or event related potentials are not recommended for the clinical management of patients presenting with headache or migraine.**

Table 24: guidelines on headache and migraine

Institution/Authors	Year	AGREE Score	Diagnosis	Prognosis	Follow-up
National headache Foundation/ Pearlman	2004	Full text not available			
National Headache Foundation/ Martin	2004	Full text not available			
European Federation of Neurological Societies/ Sandrini [145]	2004	51	—	Ø	Ø
ICSI[148]	2007	63	Ø	Ø	Ø
American Academy of Neurology/ Lewis [146]	2005	62	Ø	Ø	Ø
American Academy of Neurology	2006	Summary statement			
British Association for the Study of the Headache[149]	2007	54	Ø	Ø	Ø
CKS[150]	2005	52	Ø	Ø	Ø
CKS[151]	2006	52	Ø	Ø	Ø

√: recommended; —: not recommended; Ø: not mentioned

4.3.14 Patients suspected or diagnosed with Multiple sclerosis

Multiple sclerosis (MS) is a progressive degenerative disease of the CNS with a pattern of symptoms that depends on the type of disease and the site of lesions. Epidemiological studies in England and Wales have given a range of prevalence estimates but the average is estimated at about 110 patients per 100,000 population. There is good international evidence of geographical variation in prevalence, best described by increasing prevalence with latitude (both north and south of the equator).[210]

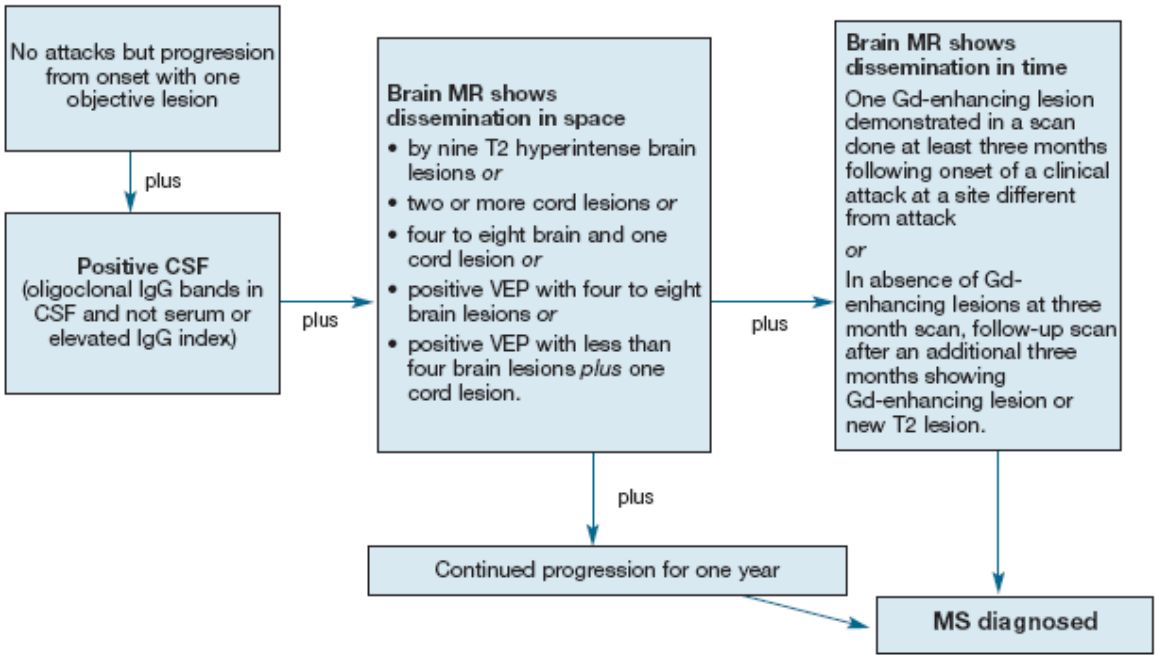
The literature search identified one guideline and two systematic reviews. One systematic review was excluded because of low quality[211].

The remaining systematic review, by the AHRQ[212] is of high quality, with an adequate search strategy and selection, quality assessment, and detailed description of included studies. Visual evoked potentials are part of the McDonald criteria.

These criteria include insidious neurological progression suggestive of MS; plus positive CSF, and dissemination in space, demonstrated by 9 or more T2 lesions in brain, or 2 or more lesions in spinal cord, or 4-8 brain lesions plus 1 spinal cord lesion, or abnormal VEP associated with 4-8 brain lesions, or abnormal VEP with fewer than 4 brain lesions plus 1 spinal cord lesion; and dissemination in time, demonstrated by MRI, or continued progression for 1 year. In patients presenting with clinically isolated syndrome, the McDonald criteria have a sensitivity of 73-94% and a specificity of 83-87% for the diagnosis of clinically definite MS over 1 to 4 years of follow up. Kappa of interrater reliability for MS (all categories) is 0.57[213, 214].

The guideline, developed by NICE, is based on a systematic review of the evidence[215] (Table 25), and finds of all evoked potentials, VEPs appeared to be the most accurate in diagnosing MS and may be used to demonstrate dissemination in space (grade of recommendation D). ERPs do not provide strong diagnostic evidence for the diagnosis of MS. Algorithms to guide decisions are provided.(Figure 24) In addition, VEP latency has been used in trials as a surrogate outcome for treatment efficacy. However, some trials have shown effect of treatment on VEP latency without effect on relapse rate.

Figure 24: diagnostic criteria for suspected MS (progressive from onset)



Copied from NICE guideline

4.3.14.1 *Conclusions:*

When doubt about the diagnosis remains, further investigation should exclude an alternative diagnosis, or find evidence that supports the potential diagnosis of MS. Dissemination in space should usually be confirmed, if necessary, using an MRI scan, using agreed criteria such as those described by McDonald and colleagues. Dissemination in space may also be confirmed using evoked potential studies. Visual evoked potential studies should be the first choice. Dissemination in time should be confirmed clinically, or by using the MRI criteria described.

Key points

- **Visual evoked potentials are recommended in case there is diagnostic uncertainty, by which they can be used to demonstrate dissemination in space.**

Table 25: guidelines and systematic reviews on multiple sclerosis

Institute/Authors	Year of publication	Score AGREE	Diagnosis	Prognosis	Follow-up	Other: prediction of treatment efficacy on relapse
NICE[215]	2004	79	√	Ø	Ø	—

√: recommended; —: not recommended; Ø: not mentioned

4.3.15 Patients suspected of suffering from Neuropathy

At the request of the member of the external experts, neuropathy was added as a potential indication for evoked potentials.

Searching for guidelines on mononeuropathies or polyneuropathies in which evoked potentials or event related potentials were cited, were not identified. In general, electromyography is the preferred diagnostic instrument and evoked potentials are not necessary for the diagnosis of neuropathy. Nevertheless, the American Association of Electrodiagnostic Medicine[216] states that somatosensory evoked potentials may be useful in cases where peripheral sensory responses are unobtainable. In such cases, they may be the only means of obtaining information about the conduction velocity of peripheral afferent fibres. The value of SEPs for diagnostic purposes in peripheral nerve disease, particularly acute inflammatory demyelinating polyradiculoneuropathy is not yet established. It should be noted, however, that this guideline does not describe its methodology and yielded an AGREE score of 28.

4.3.15.1 Conclusion

No evidence based guidelines were identified. Expert opinion states that somatosensory evoked potentials may be useful in cases where peripheral sensory responses are unobtainable.

Key points

- **Somatosensory evoked potentials may be useful in cases where peripheral sensory responses are unobtainable. This recommendation is not supported by evidence, but is based on expert opinion.**

4.3.16 Patients suspected of Radiculopathy

Estimates on low back pain incidence are as high as 42% over a 6 month period. Radiculopathy is a disease involving a spinal nerve root which may result from compression related to intervertebral disk displacement, spinal cord injuries, spinal diseases or other conditions. Clinical manifestations include radicular pain, weakness, and sensory loss referable to structures innervated by the involved nerve root.

Three guidelines were identified with the search term 'radiculopathy'. (Table 26) No systematic review or HTA report was available.

All three guidelines recommend imaging as the preferential test for diagnosis and selection for surgery, and do not recommend evoked or event related potentials. In the North-American Spine Society guideline, it is stated that, in isolated lumbar stenosis, electrodiagnostic studies do little to enhance the diagnosis or treatment of lumbar stenosis compared with history, physical examination and imaging studies. Electrodiagnostic studies are best utilized when there is concern about additional neurological compromise, such as peripheral polyneuropathy. This last statement refers to the paraspinal mapping technique, which is based on electromyographic testing and does not include evoked or event related potentials[217, 218]. Somatosensory evoked potentials are not considered helpful in the diagnosis of lumbar stenosis. This statement is based on a retrospective study of 92 patients.[219]

4.3.16.1 Conclusion

Somatosensory evoked potentials are not considered helpful in the diagnosis of lumbar stenosis.

Key points

- **Evoked potentials are not recommended in the clinical management of patients suspected of radiculopathy.**

Table 26: guidelines on radiculopathy

Institute/Authors	Year of publication	AGREE Score	Diagnosis	Prognosis	Follow-up	Other: suspicion of additional neurological compromise
American College of Physicians[220]	2007	69	—	Ø	Ø	Ø
ICSI[221]	2006	68	Ø	Ø	Ø	Ø
North American Spine Society[222]	2007	67	—	—	Ø	√

√: recommended; —: not recommended; Ø: not mentioned

4.3.17 Patients suspected of or diagnosed with Schizophrenia

Schizophrenia is a term used to describe a major psychiatric disorder (or cluster of disorders) that alters an individual's perception, thoughts, affect and behaviour. The symptoms of schizophrenia are usually divided into positive symptoms, including hallucinations and delusions, and negative symptoms, such as emotional apathy, lack of drive, poverty of speech, social withdrawal and self-neglect. Studies have reported changes in the amplitude and latency of event related potentials in patients diagnosed with schizophrenia.[223] Therefore, event related potentials have been proposed as a diagnostic tool for patients suspected of schizophrenia.

The literature search yielded five guidelines and five systematic reviews. All systematic reviews included case-control studies only, by which they were all excluded from the report[224-228].

In the five guidelines, evoked potentials or event related potentials are not mentioned for the clinical management of patients, not for diagnosis, prognosis nor follow-up.

4.3.17.1 Conclusions

At present, the clinical utility of evoked potentials for the management of patients suspected or diagnosed with schizophrenia is not established. Experts indicate that several studies are currently being undertaken in this field, by which the evidence base may evolve rapidly.

Key points

- **Evoked or event related potentials are currently not recommended for the clinical management of schizophrenia, not for diagnosis, prognosis nor follow-up.**

Table 27: guidelines and systematic reviews on schizophrenia

Institute/Authors	Year of publication	AGREE Score	Diagnosis	Prognosis	Follow-up
American Psychiatric Association[156]	2004	57	Ø	Ø	Ø
NICE[229]	2003	76	Ø	Ø	Ø
Singapore Ministry of Health[152]	2003	57	Ø	Ø	Ø
Canadian Psychiatric Association[153]	2005	66	Ø	Ø	Ø
Royal Australian New Zealand College of Psychiatrists[154]	2003	54	Ø	Ø	Ø

√: recommended; —: not recommended; Ø: not mentioned

4.3.18 Patients with Spinal cord injury/paraplegia

Three guidelines and no systematic reviews or HTA reports were identified. Two guidelines were excluded: one due to low quality and one because the acute management was not considered. (Table 28)

The only included guideline, by the Consortium for Spinal Cord Medicine, states that MRI findings or electrodiagnostic studies may be useful for determining prognosis if the clinical exam is unreliable. (Scientific evidence–I/III/IV; Grade of recommendation–A; Strength of panel opinion–5) Findings on early somatosensory evoked potentials predict ambulation recovery, but they are no more accurate than the clinical examination of a cooperative and communicative patient. Compared with clinical neurological assessment, motor evoked potentials provide no prognostic information on the likelihood of recovering strength in initially paralyzed muscles.

In patients in whom the diagnosis of hysterical paralysis is considered, more intensive tests, such as MRI or motor evoked potential testing may be performed if the patient fails to start improving in 2 to 3 days. (Scientific evidence–III/IV/V; Grade of recommendation–C; Strength of panel opinion–4)

4.3.18.1 Conclusion

Somatosensory evoked potentials may be useful in selected cases: SEP for the prediction of ambulation recovery and MEP if hysterical paralysis is suspected.

Key points

- **SEP may be indicated for the prediction of ambulation recovery**
- **MEP may be indicated in case of suspicion of hysterical paralysis**

Table 28: guidelines on spinal cord injury

Institute/Authors	Year of publication	AGREE Score	Diagnosis	Prognosis	Follow-up
Consortium for Spinal Cord Medicine[230]	2008	68	√	√ when clinical exam unreliable	Ø
Royal College of Physicians[231]	2008	Patients with chronic injury – excluded			
British Orthopaedic Association[232]	2006	32: excluded			

√: recommended; —: not recommended; Ø: not mentioned

4.3.19 Patients diagnosed with Stroke

Motor recovery in stroke patients seems to occur predominantly in the first few months after stroke, although some patients may show considerable recovery in later phases. The initial grade of paresis is generally regarded as the most important predictor for motor recovery; however, it is not yet possible to predict accurately the occurrence and extent of motor recovery in individual patients during the (sub)acute phase of their stroke.[233] Motor-evoked potentials (MEPs) obtained at various times after stroke have also been studied as valid predictors of motor recovery.

The literature search identified six guidelines and two systematic reviews. The two reviews overlapped substantially[233, 234], the review with the most information on evoked potentials was included. (Table 29)

The systematic review by Hendricks et al.[234] is of good quality with an adequate search strategy and selection, quality assessment and description of studies. This review summarises studies on patients with acute stroke, confirmed by CT or MRI. The prognostic value of motor evoked potentials (by transcranial magnetic stimulation) for motor recovery or functional recovery was evaluated.

Motor recovery was defined as the occurrence of some degree of motor recovery, functional recovery was defined using the Barthel index score (≥12). Heterogeneity prevented meta-analysis: sensitivity ranges from 62-94%; specificity ranges from 2-99%. Specificity was highest in patients with initial paralysis or very severe paresis.

On the other hand, not one of the guidelines mentions the use of evoked potentials for the clinical management of these patients, neither for diagnosis, prognosis or follow-up.

4.3.19.1 Conclusion

Motor evoked potentials have been evaluated for the prediction of motor recovery in stroke patients. Results are very heterogeneous, thus creating large uncertainty on the value in clinical practice. Clinical practice guidelines do not mention MEPs.

Key points

- **Evidence on MEPs in stroke patients is conflicting.**
- **Currently, clinical practice guidelines do not recommend their use.**

Table 29: guidelines and systematic reviews on stroke

Institute/Author	Year of publication	AGREE Score	Diagnosis	Prognosis	Follow-up
American Heart Association-American Stroke Association/Adams[158]	2007	63	Ø	Ø	Ø
Singapore Ministry of Health[159]	2003	63	Ø	Ø	Ø
NICE / Royal College of Physicians[157]	2008	81	Ø	Ø	Ø
Australian National Health and Medical Research Council/National Stroke Foundation (1)[160]	2007	84	Ø	Ø	Ø
Australian National Health and Medical Research Council/National Stroke Foundation (2)[161]	2005	83	Ø	Ø	Ø
New Zealand Guidelines Group[162]	2003	76	Ø	Ø	Ø

√: recommended; —: not recommended; Ø: not mentioned

4.3.20 Symptom-based guidance

Three symptoms were proposed by the external experts on this report as potentially relevant for the use of evoked or event related potentials in clinical practice.

4.3.20.1 Unilateral deafness

The scope of the report excludes purely audiological applications.

No guidelines were identified in the search (search terms are listed in appendix 10)

4.3.20.2 Vertigo

No guidelines were identified in the search (search terms are listed in appendix 13). A separate search in Medline revealed one potentially relevant systematic review on the management of vertigo including diagnosis[235]. The methodology of this review is fair, with a systematic and transparent search strategy, but unclear selection criteria and no quality assessment.

Evoked and event related potentials are not mentioned in the review, not for diagnosis, prognosis or follow-up.

4.3.20.3 Paraesthaesia

Two articles were potentially relevant, identified in the search described in appendix 13. However, one included less than 20 patients[236] and the other used a case-control design[237] by which both studies were excluded from the review.

Key points

- **No evidence on evoked or event related potentials for three symptom-oriented problems was identified.**

5 DISCUSSION

In this report, technical standards, current use and evidence-based recommendations were reviewed.

Technical standards are available for EEG and evoked potentials, the situation is less clear for event related potentials. Nonetheless, the accuracy and reproducibility of tests is highly dependent on their standardisation.

At present, the EEG is performed approximately 400,000 times per year. This number has remained stable over the last decade. The reimbursement of evoked potentials is divided in five categories, one test, two tests and three tests (two or three tests of a different modality respectively, e.g. VEP+SEP, or VEP + SEP + BAEP), MEP for physical therapy and MEP for neurology/psychiatry. In total, approximately 165,000 evoked potential tests were performed in 2006, of which 85,000 were single EP, 41,000 were two EP, 23,000 were three EP, 8,000 MEP tests in physical therapy and 8,000 MEP tests in neurology/psychiatry. The number of event related potentials is unknown, as these are coded as evoked potentials or EEG (in case of CNV).

Based on a systematic review of clinical guidelines, systematic reviews, meta-analyses, HTA reports and original studies where necessary, an evidence report has been constructed for the value of EEG, evoked potentials and event related potentials in routine clinical practice. Below, the conclusions of this review are summarised.

From this table, it shows that the EEG is mainly recommended in case of suspicion of seizure disorders. In addition, it can be used in the diagnosis of Creutzfeldt-Jacob disease, the diagnosis of encephalitis, the prognosis of anoxic-ischaemic encephalopathy in infants, and to predict outcome in comatose patients. In the latter case, however, SEP have better predictive value by which they are the preferred test. In addition, evoked potentials are recommended to predict outcome in traumatic head injury (SEP), the diagnosis of multiple sclerosis in case of diagnostic uncertainty to demonstrate dissemination in space (VEP), the diagnosis of neuropathy when peripheral sensory testing is not possible (SEP), in patients with paraplegia when hysterical paralysis is suspected (MEP) and to predict ambulation recovery (SEP). At present, event related potentials are not recommended for diagnosis, prognosis or follow-up of patients in routine clinical practice.

Table 30: summary of recommendations

	Diagnosis	Prognosis	Follow-up	Other
Acoustic neuroma	BAER when MRI is contraindicated or not tolerated	/	/	/
ADHD	/	/	/	EEG in case of suspicion of another problem
Alcoholism	/	/	/	/
Anxiety	/	/	/	/
Autism	/	/	/	EEG in case of suspicion of seizure disorder
Brain metastases	/	/	/	EEG in case of seizures that can not be identified as epileptic
Cerebral death	EEG can be used to confirm diagnosis	/	/	/
Cerebral palsy	/	/	/	EEG in case of suspicion of epilepsy
Cervical spondylosis	/	SEP or MEP to predict signs/symptoms of myelopathy	/	MEP to diagnose cervical cord compression
Coma or vegetative state	/	SEP (or EEG) to predict poor outcome		/
Dementia	EEG in case of doubt about Alzheimer disease	/	/	EEG in case of suspicion of Creutzfeldt-Jacob disease Or in case of suspicion of transient epileptic amnesia
Depression or bipolar disorder	/	/	/	/
Electroconvulsive therapy	NA	NA	NA	EEG before therapy if dicated by clinical assessment
Encephalitis	EEG to assess cerebral involvement	/	/	/
Epilepsy	EEG is gold standard in patients clinically suspected of epilepsy	/	/	/
Global developmental delay	/	/	/	EEG in case of suspicion of epilepsy
Head injury/ traumatic brain	/	SEP to predict poor outcome	/	/

	Diagnosis	Prognosis	Follow-up	Other
injury				
Headache or migraine	/	☐	/	EEG in case of suspicion of seizure disorder
Infants with hypoxic-ischaemic encephalopathy	/	Amplitude integrated EEG to predict poor outcome	/	/
Metabolic encephalopathy	/	/	/	/
Multiple sclerosis	VEP in cases of diagnostic uncertainty, to demonstrate dissemination in space	/	/	/
Neuropathy	SEP may be useful in cases where peripheral sensory responses are unobtainable	/	/	/
Paresthesia	/	/	/	/
Radiculopathy	/	/	/	/
Schizophrenia	/	/	/	EEG may be useful if clinically indicated
Spinal cord injury or paraplegia	MEP in case of suspicion of hysterical paralysis	SEP to predict ambulation recovery	/	
Stroke	/	/	/	EEG may be helpful in case of seizure
Unilateral deafness	/	/	/	/
Vertigo	/	/	/	/

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APPENDIXES

APPENDIX 1

	Search terms used
CRD	"electroencephalography" OR "evoked potentials" OR "event related potentials"
SumSearch	"electroencephalography" OR "evoked potentials" OR "event related potentials"
Medline via Pubmed	("electroencephalography" and "guidelines") OR ("electroencephalography" and "standards") OR ("evoked potentials" and "guidelines") OR ("evoked potentials" and "standards") OR ("event related potentials" and "guidelines") OR ("event related potentials" and "standards")
Google and Yahoo	("electroencephalography" and "guidelines") OR ("electroencephalography" and "standards") OR ("evoked potentials" and "guidelines") OR ("evoked potentials" and "standards") OR ("event related potentials" and "guidelines") OR ("event related potentials" and "standards") OR ("neurophysiology" and "society") OR ("neurophysiology" and "guidelines") OR ("neurophysiology" and "standards")
Professional organisations	"neurofysiologie" and "vereniging": www.nvknf.nl "neurophysiologie" and "société": http://www.snclf.net/0-0.php "neurophysiologie" and "Gesellschaft" : http://www.dgkn.de/ plus the links available on the websites of professional organisations identified

APPENDIX 2

Medline	**References**
pubmed "Electroencephalography"[Mesh]	96 609
clinical queries ("Electroencephalography"[Mesh]) AND systematic[sb]:	295
Embase	
'electroencephalogram'/exp	39,903
'electroencephalogram'/exp AND 'systematic review'/exp AND [embase]/lim	68
'electroencephalogram'/exp OR 'electroencephalography'/exp	110,376
'electroencephalogram'/exp OR 'electroencephalography'/exp AND 'systematic review'/exp AND [embase]/lim	98
CRD-DARE	
MeSH Electroencephalography EXPLODE 1 2	10
CRD-HTA	
MeSH Electroencephalography EXPLODE 1 2	6
NICE	
Electroencephalography Electroencephalogram	0 0
INAHTA	
Electroencephalography	10

APPENDIX 3

BY TEST: ELECTROENCEPHALOGRAPHY

Search terms: Electroencephalography.

Search date: February 2008

Sumsearch (National guideline clearinghouse)	37
Tripdatabase	46
Websites of scientific societies*	24
Websites AHRQ, SIGN, NICE	8
guidelines found by the previous search of systematic reviews (Pubmed and Embase)	15

*Websites of the American Academy of Neurology, the American Epilepsy Society, the South-East European Society for Neurology and psychiatry, the European Heache Federation, the European Federation of Neurological Societies, and the websites of all the scientific societies which are members of the Belgian Brain Council.

36 guidelines were selected.

BY DISEASE

Search date: April 2008

ADHD Attention deficit hyperactivity disorder

Search term: "Attention Deficit Disorder with Hyperactivity"[Mesh].

Sumsearch (National guideline clearinghouse)	8
Tripdatabase	43

1. SIGN 2001 (reviewed 2005)

EEG is used only if an underlying medical problem is suspected, and not to diagnose ADHD. (Based on "unproven in the diagnosis of ADHD" Tannock R 1998) For the investigation of an underlying medical problem, blood analysis, electrophysiological studies (EEG) or MRI may be used.

EEG before methylphenidate chlorhydrate prescription or during follow-up is not mentioned.

2. Pliszka 2007 AACAP (American Academy of Child and Adolescent Psychiatry)

Unless there is strong evidence of such factors in the medical history, neurological studies (EEG, MRI,…) are not indicated for the evaluation of ADHD. …. (Based on "NE= not endorsed: practices that are known to be ineffective or contraindicated)

EEG before methylphenidate chlorhydrate prescription or during follow-up is not mentioned.

3. University of Michigan 2005

No specific diagnostic test (e.g., blood or neurologic) is necessary or sufficient to establish the diagnosis of ADHD. Blood lead levels, thyroid function tests, brain imaging or electroencephalogram have no discriminative ability in establishing the diagnosis of ADHD. (No references; no level of evidence)

EEG before methylphenidate chlorhydrate prescription or for the follow-up of patients with ADHD is not mentioned.

4. ICSI 2007

EEG is not mentioned as a diagnostic tool in this guideline.

EEG before methylphenidate chlorhydrate prescription or for the follow-up of patients with ADHD is not mentioned.

5. Cincinnati Children's Hospital 2004

For the evaluation of ADHD, imaging or EEG studies should not be routinely conducted, based on one prospective trial (Castellanos 2002) and one retrospective analysis (Lyoo 1996).

EEG before methylphenidate chlorhydrate prescription or for the follow-up of patients with ADHD is not mentioned.

6. NICE 2008

EEG is not mentioned as a diagnostic tool in this guideline

EEG before methylphenidate chlorhydrate prescription or for the follow-up of patients with ADHD is not mentioned.

Methylphenidate and seizures: "The possibility of methylphenidate lowering the seizure threshold for those with epilepsy has been investigated in recent studies in those patients whose seizures were under control. These studies did not find an increase in seizures (Feldman 1989, Gross-Tsur 1997). It is noted in the literature that patients with seizures are generally excluded from the majority of studies regarding treatment for ADHD (Hemmer 2001)."

Autism

Search term: "Autistic Disorder"[Mesh].

Sumsearch (National guideline clearinghouse)	5
Tripdatabase	42

1. Kagan-Kushnir. 2005

Currently insufficient evidence to recommend for or against the use of screening EEGs in autistic patients. Given the frequency of seizure disorders in this patient population, a high index of clinical suspicion should be maintained for subtle symptoms of seizures.

2. SIGN 2007

Whilst epilepsy is common in children with autism spectrum disorders, there is no indication for an electroencephalogram (EEG) in the absence of other clinical criteria. (Based on systematic review of Kagan-Kushnir 2005)

3. Filipek 2000 (reviewed 2006)

There is inadequate evidence at present to recommend an EEG study in all individuals with autism.

Indications for an adequate sleep-deprived EEG with appropriate sampling of slow wave sleep include clinical seizures or suspicion of subclinical seizures, and a history of regression (clinically significant loss of social and communicative function) at any age, but especially in toddlers and preschoolers.

Brain metastasis

Search term: Bain meatastasis is not a Meshterm. In Sumsearch: the terms 'BRAIN AND METASTASI* (Focus: DIAGNOSIS, ages: all, subjects: HUMAN)' were used. In Tripdatabase: brain metastases.

Sumsearch (National guideline clearinghouse)	33
Tripdatabase	114

Child with cerebral palsy

Search term: "Cerebral Palsy"[Mesh].

Sumsearch (National guideline clearinghouse)	18
Tripdatabase	240

Coma

Search term: "Coma"[Mesh].

Sumsearch (National guideline clearinghouse)	110
Tripdatabase	139

Note: Traumatic coma is classified with head inj.

1. Wijdicks 2006 (guideline based on systematic review)

In comatose survivors after cardiopulmonary resuscitation, generalized suppression to ≤20 μV, burst-suppression pattern with generalized epileptiform activity, or generalized periodic complexes on a flat background are strongly but not invariably associated with poor outcome. Burst suppression or generalized epileptiform discharges on EEG predict poor outcome but with insufficient prognostic accuracy (recommendation level C).

2. Australian Government 2003 (guideline based on systematic review)

In patients with vegetative state, there is a lack of correlation between EEG recordings and clinical status. In approximately 10% of patients in a vegetative state, the EEG is nearly normal late in the course of illness. Reactivity, if present, suggests a better prognosis, but its absence does not reliably predict post-coma unresponsiveness or death. The absence of reactivity does not rule out the possibility of emergence from post coma unresponsiveness. (Levels of evidence not provided)

Dementia

Search term: "Dementia"[Mesh].

Sumsearch (National guideline clearinghouse)	148
Tripdatabase	208

1. SIGN 2006 (based on systematic search)

EEG is not recommended as a routine investigation for dementia. There is evidence to support the limited use of EEG in the diagnosis of dementia, for example in the diagnosis of sporadic Creutzfeldt-Jacob disease, with reported sensitivity of 65% and specificity of 85%. (level 2+)

2. NICE 2006 (based on systematic review)

EEG should not be used as a routine investigation in people with dementia.

3. Royal College of psychiatrists 2006 (based on systematic review)

EEG may be useful in differential diagnosis, for Creutzfeld–Jacob disease and frontal lobe dementia.

4. Singapore Ministry of Health 2007 (evidence based review)

EEG is not mentioned for diagnosis in this guideline

5. US preventive services task force 2003 (evidence based review)

EEG is not mentioned for diagnosis in this guideline

6. British Columbia medical association 2007 (not based on systematic search)

EEG is not mentioned for diagnosis in this guideline

7. Miyasaki 2006 (based on systematic review)

Based on Class III study (case control study with 10 dementia cases and 10 controls), there is insufficient evidence to support the use of EEG as a screening tool of dementia in Parkinson disease.

8. Petersen 2001 (reviewed 2003) (based on systematic review)

EEG is not mentioned for diagnosis in this guideline

9. Knopman 2001 (reviewed 2004) (based on systematic review)

EEG is not mentioned for diagnosis in this guideline

10. CBO 2005 (based on systematic review)

It is probable that EEG has low sensitivity (± 45%) and reasonable specificity (± 90%) for the differential diagnosis between patients with Alzheimer disease and healthy patients. In case of doubt about Alzheimer disease, an abnormal EEG background pattern increases the likelihood of Alzheimer disease, while a normal EEG is not very significant (level 2). It is probable that EEG abnormalities, especially slowing down of dominant frequency and decreasing of alpha and beta activity, have an unfavourable prognostic significance for Alzheimer disease (level 2). There are no convincing indications that EEG can discriminate between Alzheimer disease and Lewy bodies' disease, or between healthy subjects and light cognitive disorder. EEG can not predict with reliability which patients with light cognitive disorder will receive a treatment for Alzheimer disease or not (level 2).

Depression

Search term: "Depression"[Mesh].

Sumsearch (National guideline clearinghouse)	427
Tripdatabase	900

Development delay

Search term: Development delay OR "Malformations of Cortical Development"[Mesh]

Sumsearch (National guideline clearinghouse)	0
Tripdatabase	0

Electroconvulsive therapy

Search term: "Electroconvulsive Therapy"[Mesh].

Sumsearch (National guideline clearinghouse)	26
Tripdatabase	63

Encephalitis

Search term: "Encephalitis"[Mesh].

Sumsearch (National guideline clearinghouse)	45
Tripdatabase	96

Encephalopathy (child)

Search term: Encephalopathy (non MESH).

Sumsearch (National guideline clearinghouse)	85
Tripdatabase	107

Epilepsy

Search term: "Epilepsy"[Mesh].

Sumsearch (National guideline clearinghouse)	90
Tripdatabase	192

Systematic reviews

There is wide interreader variation in sensitivity and specificity of EEG interpretations. In 25 studies including 4.912 patients, specificity ranges from 13 to 99% and specificity from 20 to 99% for epileptiform EEG interpretations. Diagnostic accuracy of the EEG and the thresholds for classifying EEG as positive varied widely. In the multivariate model, differences in readers' thresholds accounted for 37% of the variance in EEG diagnostic accuracy. This variations influence the ability of the EEG to discriminate between those who will and will not have seizure recurrence{Gilbert, 2003 #382}.

For the prediction of recurrence, seizure aetiology (known neurological injury, deficit or syndrome) and EEG combined were the strongest predictors: patients with normal EEG and absence of known neurological aetiology had a recurrence risks of 24% (95% CI 19-29) in, whereas patients with abnormal EEG and known neurological aetiology had a risk of 65% (95% CI 55-76) in.

In patients with a normal EEG and known neurological aetiology, the recurrence risk was 48% (95% CI 34-62), such as in patients with abnormal EEG and absence of known neurological aetiology also 48% (95% CI 40-55){Berg, 1991 #486}.

The predictive value of specific EEG abnormalities is not clear. Relative to children with normal EEGs, children with epileptiform abnormalities were more likely to have a seizure recurrence: pooled relative risk 2.0 (95% CI 1.6-2.6). Children with non epileptiform abnormalities only were somewhat more likely to have a recurrence than children with normal EEGs, pooled relative risk 1.3 (95% CI 0.9-1.8). The pooled risk of recurrence at 2 years was 27% (95% CI 21 to 33) with a normal EEG, 58% (95%CI 49 to 66) with epileptiform abnormalities, and 37% (95% CI 27 to 48) with non epileptiform abnormalities{Berg, 1991 #486}.

In patients with epilepsy who have been seizure free for some time while taking antiepileptic medication and who discontinue epileptic drugs, overall, the risk of relapse at 1 year was 0.25 (95% CI 0.21-0.30) and 0.29 (95% CI 0.24-0.34) at 2 years. An abnormal EEG (regardless of degree: mild, moderate or severe) was associated with a relative risk of seizure of 1.45 (95%CI 1.18 to 1.79). Most studies found some increased risk in patients with abnormal compared with normal EEGs, although there was evidence of substantial heterogeneity between the studies (p= 0.0002){Berg, 1994 #468}.

The gold standard to differentiate epileptic and non epileptic seizure is EEG linked to video recording of concurrent behaviour, to register the association of any epileptiform abnormalities with observed behaviour. No procedure (seizure induction, Minnesota multiphasic personality inventory, physiological methods –prolactin levels and SPECT, pre-ictal pseudo sleep and ictal and post ictal symptoms) attains reliability equivalent to EEG video-telemetry{Cuthill, 2005 #344}.

Neonatal seizures are generally an acute manifestation of disturbance of the developing brain and are very common in the first weeks of life. The incidence of epilepsy after neonatal seizures varied from 9.4 to 56%, most of the newborns that developed postneonatal epilepsy had epileptic syndromes with unfavourable prognosis. Clinical predictors of outcomes were seizure type, onset, aetiology and duration besides abnormal neonatal examination. EEG predictors of outcome were analyzed in eleven studies; the results showed that abnormal background rhythm, the presence of electrographic seizures and the presence of brief rhythmic discharges were consistently related to unfavourable outcomes{Nunes, 2005 #347}.

Based on a review of 47 articles, EEG/MRI concordance was a prognostic indicator of seizure remission (positive predictor) after epilepsy surgery (OR 0.52; 95%CI 0.32 – 0.83){Tonini, 2004 #356}.

Guidelines

1. Hirtz: American Academy of Neurology 2000 (reaffirmed 2006)

In children experiencing a first, non febrile seizure, the EEG is recommended as part of the neuro-diagnostic evaluation (standard). The majority of evidence of Class I and II studies confirms that an EEG helps in determination of a seizure type, epilepsy syndrome, and risk of recurrence, and therefore may affect further management decisions. Experts commonly recommend that an EEG be performed after all first non febrile seizures.

2. NICE 2004: The diagnosis and management of the epilepsies in adults and children in primary and secondary care

The standard EEG has variable sensitivity and specificity in determining whether an individual has had an epileptic seizure. In the primary papers reviewed by the authors of NICE guideline, the sensitivity ranged from 26% to 56% and the specificity from 78% to 98%. The likelihood ratio for a positive test ranged from 2.5 to 13 and for a negative test from 0.5 to 0.76 (level of evidence III for adults, IIb for children). The finding of interictal epileptiform activity on EEG can be used to help confirm the clinical diagnosis of an epileptic seizure. A negative EEG cannot be used to rule out the clinical diagnosis of an epileptic seizure (III).

Individuals with a clinical diagnosis of non epileptic seizure disorder are unlikely to have, but may occasionally have, epileptiform abnormalities on EEG (III). There is insufficient high quality evidence to determine whether performing an EEG within the first 24 hours after a seizure increases the likelihood of obtaining epileptiform activity (III).

Great caution is required in performing investigations such as EEG when the clinical history offers limited support for a diagnosis of epilepsy, as the risk of false positive result may lead to misdiagnosis. The misdiagnosed patient may experience social and financial deprivation as a result of having the wrong diagnostic label and from side effects of antiepileptic medication.

In adults, an EEG should be performed only to support a diagnosis of epilepsy in whom the clinical history suggests that the seizure is likely to be epileptic in origin (C). An EEG may be used to help determine seizure type and epilepsy syndrome in individuals in whom epilepsy is suspected. This enables individuals to be given the correct prognosis (C). The standard EEG can help classify individuals with a clinical diagnosis of an epileptic seizure into different epilepsy seizure types and epilepsy syndromes (III).

Repeating a standard EEG in a selected adult population has been shown to increase the likelihood of obtaining epileptiform activity (III). Repeated standard EEGs may be helpful when the diagnosis of the epilepsy or the syndrome in unclear. However, if the diagnosis has been established, repeat EEGs are not likely to be helpful (C).

Repeated standard EEGs should not be used in preference to sleep or sleep-deprived EEGs (C). When a standard EEG has not contributed to diagnosis or classification, a sleep EEG should be performed (C). Recording of the EEG whilst asleep or after sleep deprivation increases the likelihood of obtaining epileptiform activity (III).

Long-term video or ambulatory EEG may be used in the assessment of individuals who present diagnostic difficulties after clinical assessment and standard EEG (C). Long-term video or ambulatory EEG can help differentiate between epileptic and non epileptic seizures in individuals who present diagnostic difficulties after clinical assessment and standard EEG (III). Long-term video or ambulatory EEG can help classify seizure type and seizure syndrome in individuals who present diagnostic difficulties after clinical assessment and standard EEG (III).

There is conflicting evidence in adults as to the role of induction protocols; there is no evidence for children (III). Provocation by suggestion may be used in the evaluation of non-epileptic attack disorder. However, it has a limited role and may lead to false positive results in some individuals (C). Photic stimulation is necessary to determine if the individual is photo-sensitive but carries a small risk of inducing a seizure (III). Hyperventilation is routinely employed to increase the sensitivity of an interictal EEG (IV). Photic stimulation and hyperventilation should remain part of the standard EEG assessment. The individual and family and/or carer should be made aware that such activation procedures may induce a seizure and they have the right to refuse (GCP).

In individuals presenting with a first unprovoked seizure, unequivoqual epileptiform activity shown on EEG can be used to assess the risk of seizure recurrence (B). Individuals presenting with a first unprovoked seizure who have epileptiform activity on their initial EEG have an increased risk of seizure recurrence (IIb children, III adults). The specificity of an epileptiform EEG in predicting further seizures ranges from 0.13 to 0.99, and sensitivity from 0.20 to 0.91 (II).

In children, an EEG should be performed only to support a diagnosis of epilepsy. If an EEG is considered necessary, it should be performed after the second epileptic seizure but it may, in certain circumstances as evaluated by the specialist, be considered after a first epileptic seizure (C).

In unselected individuals with syncope, EEG monitoring is of little use. In the absence of a history of seizure activity, an EEG should not be performed in case of probable syncope because of the possibility of a false-positive result (C).

The EEG should not be used to exclude a diagnosis of epilepsy in an individual in whom the clinical presentation supports a diagnosis of a non-epileptic event (C).

3. SIGN 2005: Diagnosis and management of epilepsies in children and young people

Children: An EEG should only be requested after careful clinical evaluation by someone with expertise in childhood EEG and epilepsy (D). Particular care is required in interpretation of the paediatric EEG. Age specific patterns may be misinterpreted as epileptiform discharges. The sensitivity of interictal EEG recordings is too low to be a reliable diagnostic test for epilepsy. Around 40% of children with seizures will have a normal record on a first standard EEG recording. Even with expert clinical evaluation and repeated recordings, the sensitivity of EEG is only 56% after a single event and 70% after multiple events, with a specificity of 78%.

The EEG may show paroxysmal activity or background changes in up to 32% of normal children that could be misinterpreted as abnormal. Epileptiform abnormalities are seen in 5% of normal children. These rates are higher where there are pre-existing neurological abnormalities. The rates of EEG abnormality may be further increased during the course of a sleep EEG recording and this may be a pitfall in children who do not have epilepsy.

All children with recurrent epileptic seizures should have an EEG. An early recording may avoid the need for repeated EEG investigations (C).

In case of first unprovoked convulsive epileptic seizure, the use of EEG is discussed. To support it: the information regarding recurrence risk (an abnormal EEG doubles recurrence risk), provoking factors (such as photosensitivity) or syndromic epilepsy. Against performing an EEG: the accuracy of the test and the small impact of treatment about recurrence risk after the first seizure. When a first seizure has been diagnosed as epileptic, an EEG may be considered for the purposes of assessing recurrence risk, making a syndromic diagnosis and identifying precipitating factors. It should not be used to guide a decision on whether or not to commence antiepileptic drug medication (GCP).

Febrile seizures: An EEG is not indicated for children with recurrent or complex febrile seizures (GCP). The yield of abnormality of an early post-ictal EEG is low and similar to reported rate of abnormality in children with simple febrile seizures.

Standard EEG with synchronic video: It is particularly useful in case of juvenile myoclonic epilepsy, infantile spas and absence seizures.

Repeat EEG recording: If a first standard inter-ictal EEG is normal, there is evidence that a second recording increases the yield of diagnostically helpful abnormalities.

Sleep EEG: When used appropriately, sleep recordings may contribute significantly to epilepsy classification and particularly in syndromes such as benign rolandic epilepsy with centro-temporal spikes, juvenile myoclonic epilepsy and infantile spasms. Sleep recordings may be particularly difficult to achieve in children; there is no clear evidence that one method of obtaining sleep is significantly more productive than another. For children with recurrent epileptic seizures and a normal standard EEG, a second EEG recording including sleep should be used to aid identification of a specific epilepsy syndrome (D).

Ictal EEG recording: Where the clinical diagnosis of epilepsy is uncertain and if events are sufficiently frequent, an ictal EEG should be used to make a diagnosis of an epileptic or non epileptic seizure.

Adults: Over-interpretation of normal variants as epileptiform abnormalities is a recognized pitfall in adult recordings.

4. American college emergency physicians 2004: Adult patients presenting to emergency department with seizure

No clear recommendation for ordering emergency EEG may be made on the basis of available data. Consider an emergent EEG in patients suspected of being in non convulsive status epilepticus or in subtle convulsive status epilepticus, patients who have received a long-acting paralytic, or in patients who are in a drug-induced coma (level C: inconclusive or conflicting evidence, consensus).

The most compelling argument for emergent EEG is for the detection of generalized convulsive status epilepticus that may have evolved into subtle status epilepticus with continuing abnormal EEG discharges.

5. Riviello American Academy of Neurology 2006: Diagnostic assessment of the child with status epilepticus

An EEG may be considered in a child presenting with new onset status epilepticus as it may determine whether there are focal or generalized abnormalities that may influence diagnostic and treatment decisions (level C, class evidence III). Data from six class III studies revealed generalized or focal epileptiform activity in 43.1% of the EEGs done for SE. Abnormalities on EEG occur in 62% of children with SE compared with 41% of children with a first unprovoked seizure less than 30 minutes duration.

Although non convulsive status epilepticus occurs in children who present with status epilepticus, there are insufficient data to support or refute recommendations regarding whether an EEG should be obtained to establish the diagnosis (level U: unproven)

An EEG may be considered in a child presenting with SE if the diagnosis of pseudo status epilepticus (non epileptic event that mimics SE) is suspected (level C, class III evidence). One small class III study reported that 21% of children initially though to be in convulsive SE had pseudo status.

6. SIGN 2003: Diagnosis and management of epilepsy in adults

EEG can be used to support the diagnosis in patients in whom the clinical history indicates a significant probability of an epileptic seizure or epilepsy (C). EEG is not routinely indicated and should not be performed to exclude a diagnosis of epilepsy (C).

Non specific EEG abnormalities are relatively common, especially in the elderly, patients with migraine, psychotic illness and psychotropic medication. Non specific abnormalities should not be interpreted as supporting a diagnosis of epilepsy. A normal EEG does not exclude a diagnosis of epilepsy. A single routine EEG will show definite epileptiform abnormalities in 29-38% adults who have epilepsy. With recordings, this rises to 69-77%. The sensitivity is improved by performing an EEG soon after a seizure, and by recording with sleep or following sleep deprivation. Incidental epileptiform abnormalities are found in 0.5% of healthy young adults.

In a patient in whom the clinical history suggests an epileptic seizure but is not conclusive, the prevalence of epilepsy will be high. The finding of epileptiform abnormalities is specific, and the diagnostic value of the test is good. In a patient in whom the history is typical of some other disorder, such as syncope, the prevalence of the epilepsy will be low, and any epileptiform abnormalities are more likely to be incidental. The test should not be performed in this circumstance.

EEG should be used to support the classification of epileptic seizures and epilepsy syndromes when there is clinical doubt (C). EEG should be performed in young people with generalized seizures to aid classification and to detect a photo-paroxysmal response (C), which allows appropriate advice to be given.

Video EEG and other specialist investigations should be available for patients who present diagnostic difficulties (C). For recording, the attack should usually be occurring at least once a week.

If status epilepticus persist more than 30 minutes, monitor using EEG within 60 minutes to assess seizure control (level D). EEG recording may be necessary to confirm the diagnosis and assess control when seizures are clinically subtle (eg in partial status, or following treatment of tonic-clonic status epilepticus).

7. Garcia-Monco EFNS 2005: Diagnosis and management of alcohol-related seizures

The incidence of EEG abnormalities is lower amongst patients with alcohol withdrawal seizures than in those with seizures of other aetiology. EEG pathology suggests that the seizure may not have been caused exclusively by alcohol withdrawal.

EEG should be recorded after a first seizure. Subsequent to repeat alcohol withdrawals seizures, EEG is considered necessary only if an alternative aetiology is suspected (level C: possibly effective).

8. Krumholz American Academy of Neurology 2007: Evaluating an apparent unprovoked first seizure in adult

For adults presenting with a first seizure, a routine EEG revealed epileptiform abnormalities in approximately 23% of patients, and these were predictive of seizure recurrence. EEG should be considered as part of routine neuro-diagnostic evaluation of adults presenting with an apparent unprovoked first seizure (level B).

9. Singapore 2007: Epilepsy in adults

EEG should be performed to support a diagnosis of epilepsy in adults in whom the clinical history suggests that the seizure is likely to be epileptic origin (grade D level 3). Individuals requiring an EEG should have the test performed soon after the attack. The earlier the test is performed, the more likely a helpful result will emerge from the EEG (grade D level 3).

An EEG should not be performed in the case of probable syncope because of the possibility of a false positive result (grade D level 3).

EEG should not be used in isolation to make a diagnosis of epilepsy because it can be falsely positive (grade D level 3).

Repeated EEG may be helpful when the diagnosis of epilepsy is unclear. When a standard EEG has not contributed to diagnsosis or classification, a sleep EEG should be performed (grade D level 3).

Long-term video or ambulatory EEG may be used in the assessment of individuals who present diagnostic difficulties after clinical assessment and standard EEG (Grade C, level 2+).

Photic stimulation and hyperventilation should be a part of standard EEG assessment (grade D level 3).

10. Meierkord EFNS 2006: management of status epilepticus

EEG is considered for the diagnosis of non convulsive status epilepticus (GPP).

EEG is performed in case of refractory general convulsive status epilepticus and subtle status epilepticus to monitoring anaesthetic treatment. They recommend the titration of the anesthetic against an EEG burst suppression pattern. This goal should be maintained for at least 24 hours (GPP).

11. CKS 2005: Febrile convulsion

EEG is not considered for diagnosis and management of febrile convulsions

12. CKS 2006: Epilepsy

In adults, an EEG should be performed only to support a diagnosis of epilepsy in people whose clinical history suggests that the seizure is likely to be epileptic in origin.

In children, an EEG should be performed only to support a diagnosis of epilepsy. If an EEG is considered necessary, it should be performed after the second seizure but may, in certain circumstances as evaluated by the specialist, be considered after a first epileptic seizure.

An EEG should not be used:

in the case of probable syncope because the possibility of a false positive result

to exclude a diagnosis of epilepsy in an individual in whose clinical presentation supports a diagnosis of a non epileptic event

in isolation to make a diagnosis of epilepsy.

Head injury / traumatic coma

Search term: "Craniocerebral Trauma"[Mesh] OR "Coma, Post-Head Injury"[Mesh].

Sumsearch (National guideline clearinghouse)	44
Tripdatabase	3

1. Attia 1998

In adults with traumatic coma, SSEP and BAEP are more sensitive than EEG (45-60% sensitive versus 35%)

2. NICE 2007

EEG is not mentioned for diagnosis or follow-up.

3. Chang 2003

No data were found to base a recommendation on the use of EEG before deciding whether to use antiepileptic drug prophylaxis in patients with severe traumatic brain injury. Only one of the studies (Servit 1981) reported that EEGs were obtained routinely in the early posttraumatic period, but the findings were not reported in detail.

4. NZGG 2006

EEG is not mentioned for diagnosis or follow-up.

Migraine/headache

Search term: "Migraine Disorders"[Mesh] OR "Headache"[Mesh].

Sumsearch (National guideline clearinghouse)	16 + 250
Tripdatabase	66

1. Sandrini 2004 (EFNS): Non acute headache

Interictal EEG is not indicated in the diagnostic evaluation of headache patients (except if the clinical history suggests a possible diagnosis of epilepsy).

Ictal EEG is indicated during episodes suggesting complicated aura and during auras associated with decreased consciousness or confusion.

Quantitative EEG methods are not routinely indicated in the diagnostic evaluation of headache patients.

2. ICSI 2007: Migraine and headache

EEG is not mentioned for diagnosis or follow-up in this guideline

3. Lewis American Academy of Neurology 2002 (reviewed 2005): Children and adolescents with recurrent headaches

The guideline is based on a systematic search of the literature.

Data from four studies of children with all headaches and four studies of children with migraine demonstrate that the EEG is either normal or demonstrates non-specific abnormalities in most patients. Furthermore, in those patients in whom the EEG was abnormal, there was no indication the findings provided any diagnostic information concerning the aetiology of the headache, or specifically that the headache was due to a seizure for the majority of recurrent headache types in children.

Furthermore, the data do not suggest that there are differences in the EEG between children with migraine compared with other recurrent headache types that would be diagnostically useful in the individual patient to determine aetiology or to make a diagnosis of migraine.

Data from one class III study suggest that children may have seizure-related headaches and that in these children the EEG is likely to be paroxysmal. The limited available literature suggests that this condition is infrequently diagnosed and its existence as a clinical entity is questioned.

Data from 8 studies did not report any patients who subsequently went on to develop new-onset seizures after clinical evaluation for headaches even when the EEG showed paroxysmal abnormalities.

Consequently, the American Academy of Neurology does not recommend the EEG in the routine evaluation of a child with recurrent headaches, as it is unlikely to provide an aetiology, improve diagnostic yield, or distinguish migraine from other types of headaches (Level C; class II and class III evidence). Although the risk for future seizures is negligible in children with recurrent headache and paroxysmal EEG, future investigations for epilepsy should be determined by clinical follow up (Level C; class II and class III evidence). (Lewis AAN 2002).

4. American Academy of Neurology 1995 (reaffirmed October 2006).(based on summary statement)

The American Academy of Neurology states that no study has consistently demonstrated that the EEG improves diagnostic accuracy for the headache sufferer. The EEG has not been convincingly shown to identify headache subtypes, nor has it been shown to be an effective screening tool for structural causes of headache. Therefore, the EEG is not useful in routine evaluation of patients with headache. This does not exclude the use of EEG to evaluate headache patients with associated symptoms suggesting a seizure disorder, such as atypical migraine aura or episodic loss of consciousness. EEG is not recommended to exclude a structural cause for headache.

5. BASH British association for the study of the headache 2007

Migraine and headache

EEG is not mentioned for diagnosis or follow-up.

6. CKS 2005 Headache

EEG is not mentioned for diagnosis or follow-up.

7. CKS 2006 Migraine

EEG is not mentioned for diagnosis or follow-up.

Schizophrenia

Search term: "Schizophrenia"[Mesh].

Sumsearch (National guideline clearinghouse)	38
Tripdatabase	110

1. Singapore 2003

EEG is not mentioned for diagnosis or follow-up.

2. American Psychiatric Association 2004

EEG can be performed if clinically indicated for initial assessment.

3. CKS 2007

EEG is not mentioned for diagnosis or follow-up in this guideline

4. Canadian Psychiatric Association 2005

EEG is not mentioned for diagnosis or follow-up in this guideline

5. Royal Australian and New Zealand College of Psychatrists 2003

EEG is not mentioned for diagnosis or follow-up.

APPENDIX 4

BRAIN DEATH

Search terms used in Sumsearch and Tridatabase: “brain death”.

Search terms used in Medline: ("Brain Death"[Mesh] AND "Electroencephalography"[Mesh]) AND systematic[sb].

Search terms used in Embase: 'brain death'/exp/mj AND 'electroencephalogram'/exp AND ([meta analysis]/lim OR [systematic review]/lim).

CREUTZFELDT-JACOB DISEASE

Search terms used in Medline: ("Creutzfeldt-Jakob Syndrome"[Mesh] AND "Electroencephalography"[Mesh]) AND (specificity [Title/Abstract]

Search terms used in Embase: 'creutzfeldt jakob disease'/mj AND 'electroencephalography'/mj and also 'creutzfeldt jakob disease'/exp/mj AND 'electroencephalogram'/mj

DEMENTIA WITH LEWY BODIES

Search terms used in Medline: ("Lewy Body Disease"[Mesh] AND "Electroencephalography"[Mesh]) AND (specificity [Title/Abstract])

Search terms used in Embase: ‘diffuse lewy body disease'/mj AND 'electroencephalogram'/mj and also 'diffuse lewy body disease'/mj AND 'electroencephalography'/mj

APPENDIX 5

Medline	Number of hits
"Evoked Potentials"[Mesh]	77 127
("Evoked Potentials"[Mesh]) AND systematic[sb]	175

Embase	
'evoked response'/exp	46 983
'evoked response'/exp AND [systematic review]/lim	34
'event related potential'/exp	7 709
'evoked response'/exp OR 'event related potential'/exp	53 274
'evoked response'/exp OR 'event related potential'/exp AND [systematic review]/lim	46

DARE	
MeSH Evoked Potentials EXPLODE 1 2	3

CRD-HTA	
MeSH Evoked Potentials EXPLODE 1 2	6

NICE	
Evoked potentials	20

INAHTA	
Evoked potentials	0

APPENDIX 6

BY DIAGNOSTIC TECHNOLOGY

Search terms: 'evoked potentials OR event related potentials OR P300 OR MMN OR P50 OR LDAEP'

Search date: February 2008

National guideline clearinghouse	20
Tripdatabase	10
Websites of scientific societies*	11
Websites AHRQ, SIGN, NICE, National Library of Health	65
Guidelines found by the previous search of systematic reviews (Pubmed and Embase)	34

*Websites of the American Academy of Neurology, the American Epilepsy Society, the European Headache Federation, the European Federation of Neurological Societies, American Clinical Neurophysiology Society, International Federation of Clinical Neurophysiology, American Association of Neuromuscular and Electrodiagnostic Medicine, and the websites of all the scientific societies which are members of the Belgian Brain Council were searched for guidelines.

BY DISEASE

An additional search was done for guidelines for each disease or clinical problem for which studies or guidelines were selected by the previous search.

The following sites were searched using the corresponding MeSH term: National Guideline Clearinghouse and Tripdatabase. Other sites were hand searched for each topic: NICE, SIGN, AHRQ, American Academy of Neurology, American Psychiatry Association, American Heart Association, Singapore Ministry of Health, Veteran's Affairs/Department of Defence, Australian National Stroke Foundation, New Zealand Guidelines Group, Royal College of Physicians, Canadian Psychiatric Assocation, Royal Australian and New Zealand College of Psychiatrists

BRAIN INJURY – LOW RESPONSIVE PATIENTS

1. New Zealand Guidelines Group 200652

In severe traumatic brain injury, somatosensory evoked potentials (SEPs) may be useful in predicting severe negative outcomes, and event related potentials (ERPs) are able to predict a wider range of negative outcomes. Both SEPs and ERPs may predict positive outcomes. (based on 2 studies)

2. NICE 200753

This guideline on mild traumatic brain injury lists somatosensory evoked potentials (SEPs) as one of many variables for which studies were found without specifying its value (reference to guideline on rehabilitation by the RCP)

3. Royal College of Physicians 200354

Evoked potentials or event related potentials not mentioned in guideline.

COMATOSE PATIENTS

1. American Academy of Neurology 2006[48]

In comatose survivors of cardiopulmonary resuscitation, bilateral absence of the N20 component of median nerve stimulation 1-3 days after the event has a pooled sensitivity of 46% and false positive rate of 0.7% (95% CI 0.1-3.7) for predicting a poor outcome (based on 8 studies). Poor outcome is defined as death or persisting unconsciousness after 1 months, or death, persisting unconsciousness or severe disability requiring full nursing case after 6 months. (level B evidence)

2. American Heart Assocation 2005[49]

Based on the systematic review of Zandbergen et al. the AAN recommends median nerve sensory evoked potentials to predict fatal outcome in comatose patients after cardiac arrest. Bilateral absence of the N20 at least 72 hours after the arrest has 100% specificity based on 18 prospective studies.

3. Australian Medical Research Council 2003

SEPs have been used as a prognostic aid in determining the likelihood that patients in an acute stage of coma after trauma or hypoxia will ultimately enter an unresponsive state.

MULTIPLE SCLEROSIS

1. NICE 2004 (based on systematic review)[65]

EPs and ERPs were assessed in 8 studies, including 40 test evaluations: visual evoked potentials (VEP) (n = 18), auditory event-related potentials (AERP) (n = 1), brainstem auditory evoked potentials (BAEP) (n = 4), long latency auditory evoked potentials (LLAEP) (n = 2), middle latency auditory evoked potentials (MLAEP) (n = 2), motor-evoked potentials (MEP) (n = 2), somatosensory evoked potentials (SEP) (n = 6), sympathetic skin response (SSR) (n = 1), and various combinations of these (n = 4). DORs range from 0.6 to 90. The majority of the evaluations (28) reported DORs less than 25, suggesting poor diagnostic performance. Of the 28 evaluations which reported DORs less than 25, 15 (53%) included an appropriate range of patients. This compares to one (8%) of the 12 evaluations which reported DORs greater than 25.

There is disagreement regarding which EP is the most accurate for the diagnosis of MS. Overall, VEPs appeared to be the most accurate in diagnosing MS. ERPs do not provide strong diagnostic evidence for the diagnosis of MS.

In addition, VEP latency has been used in trials as a surrogate outcome for treatment efficacy. However, some trials have shown effect of treatment on VEP latency without effect on relapse rate.

2. AHRQ (systematic review)[66]

Visual evoked potentials are part of the McDonald criteria. These criteria include insidious neurological progression suggestive of MS; plus positive CSF, and dissemination in space, demonstrated by:

- 9 or more T2 lesions in brain, or
- 2 or more lesions in spinal cord, or
- 4-8 brain lesions plus 1 spinal cord lesion, or
- abnormal VEP associated with 4-8 brain lesions, or
- abnormal VEP with fewer than 4 brain lesions plus 1 spinal cord lesion; and

dissemination in time, demonstrated by:

- MRI, or
- Continued progression for 1 year.

In patients presenting with clinically isolated syndrome, McDonald criteria have a sensitivity of 73-94% and a specificity of 83-87% for the diagnosis of clinically definite MS over 1 to 4 years of follow up. Kappa of interrater reliability for MS (all categories) is 0.57. (Dalton Ann Neurol 2002; Tintoré Neurology 2003).

RADICULOPATHY

1. American College of Physicians 2007

Evaluations recommended in patients suspected of radiculopathy include MRI (preferred) or CT, only if they are potential candidates for surgery or epidural steroid injection (for suspected radiculopathy). (strong recommendation, moderate-quality

evidence) Recommendations for additional work-up (EMG and nerve conduction studies) are beyond the scope of the guideline, but may be considered after imaging. These decisions should be based on the clinical correlation between symptoms and radiographic findings, severity of symptoms, patient preferences, surgical risks (including the patient's comorbid conditions), and costs, and will generally require specialist input.

2. ICSI 2006

Similarly as in the ACP guideline, MRI or CT are recommended. Other special diagnostic tests such as myelogram, EMG (electrorayography), RNS (radio nucleoid studies), and bone scan should be ordered as each medical group dictates and consider the preference of the specialist when referral is planned. Level of evidence C, R (C=non-randomised trial, diagnostic accuracy study; R=consensus).

3. North American Spine Society 2007

The most appropriate, non-invasive test for imaging is MRI. CT myelography is a useful study in patients who have a contraindication to MRI, for whom MRI findings are inconclusive or in patients for whom there is a poor correlation between symptoms and MRI findings. CT is a useful noninvasive study in patients in whom CT myelogram is deemed inappropriate. (Grades of recommendation B)

Little evidence is dedicated to evaluating the utility of standard electrodiagnostic studies in lumbar spinal stenosis. In 2006, Haig et al performed a prospective, masked, double-controlled trial of 150 patients to determine if electrodiagnostic studies relate to the clinical or radiographic diagnosis of lumbar spinal stenosis. This study utilized a paraspinal mapping technique described by Haig in 1997 and showed that electrodiagnostic findings were not significantly predictive of the clinical diagnosis. In addition, Molitor et al determined that somatosensory evoked potentials were not helpful in the diagnosis of lumbar stenosis. It is the consensus of this work group that, in isolated lumbar stenosis, electrodiagnostic studies do little to enhance the diagnosis or treatment of lumbar stenosis compared with history, physical examination and imaging studies. Electrodiagnostic studies are best utilized when there is concern about additional neurologic compromise, such as peripheral polyneuropathy

STROKE

1. American Heart Association 200758

Evoked potentials or event related potentials are not mentioned in the guideline.

2. Singapore Ministry of Health 200359

Evoked potentials or event related potentials are not mentioned in the guideline.

3. NICE / Royal College of Physicians 200860

Evoked potentials or event related potentials are not mentioned in the guideline.

4. Australian National Health and Medical Research Council (1) 200761

Evoked potentials or event related potentials are not mentioned in the guideline.

5. Australian National Health and Medical Research Council (2) 200562

Evoked potentials or event related potentials are not mentioned in the guideline.

6. New Zealand Guidelines Group 200363

Evoked potentials or event related potentials are not mentioned in the guideline.

APPENDIX 7

Acoustic neuroma

Sumsearch: Clinical Effectiveness Guidelines: Acoustic Neuroma (Vestibular Schwannoma). Published in 2002: excluded.

National Guideline Clearinghouse: acoustic neuroma OR vestibular schwannoma: 8 hits, of which none was relevant to the research question

Tripdatabase: acoustic neuroma: 3 hits of which one was potentially relevant to the research question: International RadioSurgery Association (IRSA).

APPENDIX 8

Search terms used in Medline and DARE: (cervical spondylosis OR Spinal Osteophytosis [MeSH]) AND (evoked potentials [MeSH] OR evoked response tests OR event related potentials OR P300 OR MMN OR P50 OR LDAEP).

Search terms used in Embase: 'cervical spondylosis'/exp AND ('evoked response'/exp OR evoked AND potentials OR event AND related AND potentials OR p300 OR mmn OR p50 OR ldaep).

Medline, search date 19/08/2008: 135 hits

Embase, search date 19/08/2008: 73 hits

Medion, search date 21/08/2008: 11 hits

DARE, search date 21/08/2008: 0 hits

APPENDIX 9

Medline, search date 16/01/2009, search terms: "("Depression"[Mesh] AND ("Antidepressive Agents/therapeutic use"[Mesh] OR "Antidepressive Agents/therapy"[Mesh])) AND "Evoked Potentials, Auditory"[Mesh]", hits: 3

Embase, search date 16/01/2009, search terms: "'depression'/exp AND 'antidepressant agent'/exp AND 'evoked auditory response'/exp AND [embase]/lim", hits: 45

DARE, search date 16/01/2009, search terms: "("Depression"[Mesh] AND ("Antidepressive Agents/therapeutic use"[Mesh] OR "Antidepressive Agents/therapy"[Mesh])) AND "Evoked Potentials, Auditory"[Mesh]", hits: 0

Medion, search date 16/01/2009, search terms: 'Neurological OR psychological' AND 'Electrodiagnostic tests', hits: 14

APPENDIX 10

Unilateral hearing loss

National Guideline Clearinghouse: Unilateral hearing loss (search date 07/11/2008): 13 hits of which none was relevant for the research question

Medline: "Hearing Loss, Unilateral"[Mesh] (search date 07/11/2008): 109 hits, of which none treated the value of evoked or event related potentials.

Tripdatabase: unilateral hearing loss (07/11/2008): 28 guidelines of which none was relevant for the research question

Sumsearch: unilateral hearing loss (07/11/2008): 72 possible guidelines, of which none was relevant to the research question

Vertigo

National Guideline Clearinghouse: vertigo, search date 07/11/2008, hits:

One potentially relevant guideline, but treated radiology recommendations only.

Medline: "Vertigo"[Mesh], search date 07/11/2008, hits:

Trip database: vertigo AND evoked potentials, search date 07/11/2008, hits: 1 which was not relevant to the research question

Sumsearch: vertigo AND evoked potentials, search date 07/11/2008, hits: 6 of which none was potentially relevant

Paraesthesia

National Guideline Clearinghouse: 'paresthesia', search date 16/01/2009, hits: 24, of which none was relevant to the research question

SumSearch: Paresthesia AND evoked potentials, search date 20/01/2009, hits: 4, of which none was relevant to the research question

Trip database: paresthesia AND evoked potentials, search date 20/01/2009, hits: 0

Medline: ("Paresthesia"[Mesh] AND "Evoked Potentials"[Mesh]) AND (specificity[Title/Abstract]), search date 16/01/2009, hits: 3

Embase: 'paresthesia'/exp AND 'evoked response'/exp AND 'sensitivity and specificity'/exp AND [embase]/lim, search date 16/01/2009, hits: 4

APPENDIX 11

AMERICAN ACADEMY OF NEUROLOGY

Levels of evidence	
Class I	Evidence provided by a prospective study of a broad spectrum of persons who may be at risk for developing the outcome (e.g. target disease, work status). The study measures the predictive ability using an independent gold standard for case definition. The predictor is measured in an evaluation that is masked to clinical presentation, and the outcome is measured in an evaluation that is masked to the presence of the predictor. All patients have the predictor and outcome variables measured.
Class II	Evidence provided by a prospective study of a narrow spectrum of persons at risk for having the condition, or by a retrospective study of a broad spectrum of persons with the condition compared to a broad spectrum of controls. The study measures the prognostic accuracy of the risk factor using an acceptable independent gold standard for case definition. The risk factor is measured in an evaluation that is masked to the outcome.
Class III	Evidence provided by a retrospective study where either the persons with the condition or the controls are of a narrow spectrum. The study measures the predictive ability using an acceptable independent gold standard for case definition. The outcome, if not objective, is determined by someone other than the person who measured the predictor.
Class IV	Any design where the predictor is not applied in an independent evaluation OR evidence provided by expert opinion or case series without controls.
Grades of recommendations	
A	Established as effective, ineffective, or harmful for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)
B	Probably effective, ineffective, or harmful for the given condition in the specified population. (Level B rating requires at least one Class I study or at least two consistent Class II studies.)
C	Possibly effective, ineffective, or harmful for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)
U	Data inadequate or conflicting; given current knowledge, predictor is unproven.

AMERICAN PSYCHIATRIC ASSOCIATION

[I] Recommended with substantial clinical confidence

[II] Recommended with moderate clinical confidence

[III] May be recommended on the basis of individual circumstances

CBO

Grades of recommendation	
Intervention studies	
A1	systematic reviews with at least a few studies of level A2, of which the results are consistent
A2	Randomised controlled trials of good quality (randomised, double blind) of sufficient size and consistancy.
B	Randomised trials of moderate quality or insufficient size or other controlled studies (non-randomised cohort studies)
C	Non-controlled studies
D	Expert opinion
Diagnostic studies	
A1	Studies of diagnostic testing on patient outcome in a prospective, well defined patient group with a priori defined decisions after test results, or decision making research of the effects of diagnostic tests on clinical outcome,, of which the results of studies of level A2 are used as basis en with sufficient adjustment for the non-independence of diagnostic tests.
A2	Studies comparing with a reference standard, in which criteria were predefined for both index test and reference standard, with a good description of the test and the population, sufficient sample size, predefined cut-offs and independent reading of index test and reference standard. Analyses of multiple tests should adjust for non-independence
B	Studies comparing with a reference standard, description of test and population, but without the criteria of level A
C	Non-controlled studies
D	Expert opinion
Levels of evidence	
1	1 systematic review (A1) or at least 2 independent studies of level A1 or A2
2	At least 2 independent studies of level B
3	1 study of level A2 or B or C
4	Expert opinion

CONSORTIUM FOR SPINAL CORD MEDICINE

Levels of evidence	
I.	Evidence based on randomized controlled clinical trials (or meta-analysis of such trials) of adequate size to ensure a low risk of incorporating false-positive or false-negative results.
II.	Evidence based on randomized controlled trials that are too small to provide level I evidence. These may show either positive trends that are not statistically significant or no trends and are associated with a high risk of false-negative results.
III.	Evidence based on nonrandomized, controlled, or cohort studies; case series; case-controlled studies; or cross-sectional studies.
IV.	Evidence based on the opinion of respected authorities or of expert committees as indicated in published consensus conferences or guidelines.
V.	Evidence that expresses the opinion of those individuals who have written and reviewed this guideline, based on experience, knowledge of the relevant literature, and discussions with peers.
Grades of recommendation	
A	The guideline recommendation is supported by one or more level I studies.
B	The guideline recommendation is supported by one or more level II studies.
C	The guideline recommendation is supported only by one or more level III, IV, or V studies.
Panel agreement on recommendations	
Low	1.0 to less than 2.33
Moderate	2.33 to less than 3.67
Strong	3.67 to 5.0

EUROPEAN FEDERATION OF NEUROLOGICAL SOCIETIES

Therapeutic interventions	
Class I:	An adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required: randomization concealment; primary outcome(s) is/are clearly defined; exclusion/inclusion criteria are clearly defined; adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias; relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences
Class II:	Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a–e above or a randomized, controlled trial in a representative population that lacks one criteria a–e
Class III:	All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment
Class IV:	Evidence from uncontrolled studies, case series, case reports, or expert opinion
Rating of recommendations	
Level A	Effective, ineffective, or harmful: at least one convincing class I study or at least two consistent, convincing class II studies
Level B	Probably effective, ineffective, or harmful: at least one convincing class II study or overwhelming class III evidence
Level C	Possibly effective, ineffective, or harmful: at least two convincing class III studies
Diagnostic measures	
Class I	A prospective study in a broad spectrum of persons with the suspected condition, using a _gold standard_ for case definition, where the test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy
Class II	A prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by _gold standard_) compared to a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy
Class III	Evidence provided by a retrospective study where either persons with the established condition or controls are of a narrow spectrum, and where test is applied in a blinded evaluation
Class IV	Any design where test is not applied in blinded evaluation OR evidence provided by expert opinion alone or in descriptive case series (without controls)
Rating of recommendations	
Level A	Useful/predictive or not useful/predictive: at least one convincing class I study or at least two consistent, convincing class II studies
Level B	Probably useful/predictive or not useful/predictive) requires at least one convincing class II study or overwhelming class III evidence
Level C	Possibly useful/predictive or not useful/predictive: at least two convincing class III studies

NEW ZEALAND GUIDELINES GROUP

Levels of evidence	
+	strong study where all or most of the validity criteria are met
~	fair study where not all the validity criteria are met, but the results of the study are not likely to be influenced by bias
x	weak study where very few of the validity criteria are met and there is a high risk of bias.
Grades of recommendation	
A	The recommendation is supported by good evidence (where there are a number of studies that are valid, consistent, applicable and clinically relevant).
B	The recommendation is supported by fair evidence (based on studies that are valid, but there are some concerns about the volume, consistency, applicability and clinical relevance of the evidence that may cause some uncertainty but are not likely to be overturned by other evidence).
C	International expert opinion
Best practice recommendation	Experience of guideline development team or feedback from consultation within New Zealand

NICE

Levels of evidence	
I:	Evidence from: • meta-analysis of randomised controlled trials, or • at least one randomised controlled trial
II:	Evidence from: • at least one controlled study without randomisation, or • at least one other type of quasi-experimental study
III:	Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case–control studies
IV:	Evidence from expert committee reports or opinions and/or clinical experience of respected authorities
C	Directly based on: • category III evidence, or • extrapolated recommendation from category I or II evidence
D	Directly based on: • category IV evidence, or • extrapolated recommendation from category I, II, or III evidence
A (NICE)	Recommendation taken from NICE Guideline or Technology Appraisal
GPP	Good practice point based on the clinical experience of the GDG

SIGN

Attention deficit/hyperactivity disorder guideline

Levels of evidence	
Ia	Evidence obtained from meta-analysis of randomised controlled trials.
Ib	Evidence obtained from at least one randomised controlled trial.
IIa	Evidence obtained from at least one well-designed controlled study without randomisation.
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study.
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
IV	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.
Grades of Recommendations	
A	Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation. (Evidence levels Ia, Ib)
B	Requires the availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation. (Evidence levels IIa, IIb, III)
C	Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. (Evidence level IV)
Good practice point	Recommended best practice based on the clinical experience of the guideline development group

Other guidelines

Levels of evidence

Levels of evidence	
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort or studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion
Grades of recommendations	
A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+
Good practice point	Recommended best practice based on the clinical experience of the guideline development group

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Dépôt légal : D/2009/10.273/22

KCE reports

1. Efficacité et rentabilité des thérapies de sevrage tabagique. D/2004/10.273/2.
2. Etude relative aux coûts potentiels liés à une éventuelle modification des règles du droit de la responsabilité médicale (Phase 1). D/2004/10.273/4.
3. Utilisation des antibiotiques en milieu hospitalier dans le cas de la pyélonéphrite aiguë. D/2004/10.273/6.
4. Leucoréduction. Une mesure envisageable dans le cadre de la politique nationale de sécurité des transfusions sanguines. D/2004/10.273/8.
5. Evaluation des risques préopératoires. D/2004/10.273/10.
6. Validation du rapport de la Commission d'examen du sous financement des hôpitaux. D/2004/10.273/12.
7. Recommandation nationale relative aux soins prénatals: Une base pour un itinéraire clinique de suivi de grossesses. D/2004/10.273/14.
8. Systèmes de financement des médicaments hospitaliers: étude descriptive de certains pays européens et du Canada. D/2004/10.273/16.
9. Feedback: évaluation de l'impact et des barrières à l'implémentation – Rapport de recherche: partie 1. D/2005/10.273/02.
10. Le coût des prothèses dentaires. D/2005/10.273/04.
11. Dépistage du cancer du sein. D/2005/10.273/06.
12. Etude d'une méthode de financement alternative pour le sang et les dérivés sanguins labiles dans les hôpitaux. D/2005/10.273/08.
13. Traitement endovasculaire de la sténose carotidienne. D/2005/10.273/10.
14. Variations des pratiques médicales hospitalières en cas d'infarctus aigu du myocarde en Belgique. D/2005/10.273/12
15. Evolution des dépenses de santé. D/2005/10.273/14.
16. Etude relative aux coûts potentiels liés à une éventuelle modification des règles du droit de la responsabilité médicale. Phase II : développement d'un modèle actuariel et premières estimations. D/2005/10.273/16.
17. Evaluation des montants de référence. D/2005/10.273/18.
18. Utilisation des itinéraires cliniques et guides de bonne pratique afin de déterminer de manière prospective les honoraires des médecins hospitaliers: plus facile à dire qu'à faire.. D/2005/10.273/20
19. Evaluation de l'impact d'une contribution personnelle forfaitaire sur le recours au service d'urgences. D/2005/10.273/22.
20. HTA Diagnostic Moléculaire en Belgique. D/2005/10.273/24, D/2005/10.273/26.
21. HTA Matériel de Stomie en Belgique. D/2005/10.273.28.
22. HTA Tomographie par Emission de Positrons en Belgique. D/2005/10.273/30.
23. HTA Le traitement électif endovasculaire de l'anévrysme de l'aorte abdominale (AAA). D/2005/10.273.33.
24. L'emploi des peptides natriurétiques dans l'approche diagnostique des patients présentant une suspicion de décompensation cardiaque. D/2005/10.273.35
25. Endoscopie par capsule. D2006/10.273.02.
26. Aspects médico-légaux des recommandations de bonne pratique médicale. D2006/10.273/06.
27. Qualité et organisation des soins du diabète de type 2. D2006/10.273/08.
28. Recommandations provisoires pour les évaluations pharmacoéconomiques en Belgique. D2006/10.273/11.
29. Recommandations nationales Collège d'oncologie : A. cadre général pour un manuel d'oncologie B. base scientifique pour itinéraires cliniques de diagnostic et traitement, cancer colorectal et cancer du testicule. D2006/10.273/13.
30. Inventaire des bases de données de soins de santé. D2006/10.273/15.
31. Health Technology Assessment : l'antigène prostatique spécifique (PSA) dans le dépistage du cancer de la prostate. D2006/10.273/18.
32. Feedback: évaluation de l'impact et des barrières à l'implémentation - Rapport de recherche: partie II. D2006/10.273/20.
33. Effets et coûts de la vaccination des enfants Belges au moyen du vaccin conjugué antipneumococcique. D2006/10.273/22.
34. Trastuzumab pour les stades précoces du cancer du sein. D2006/10.273/24.

35. Etude relative aux coûts potentiels liés à une éventuelle modification des règles du droit de la responsabilité médicale – Phase III : affinement des estimations. D2006/10.273/27.
36. Traitement pharmacologique et chirurgical de l'obésité. Prise en charge résidentielle des enfants sévèrement obèses en Belgique. D/2006/10.273/29.
37. Health Technology Assessment Imagerie par Résonance Magnétique. D/2006/10.273/33.
38. Dépistage du cancer du col de l'utérus et recherche du Papillomavirus humain (HPV). D/2006/10.273/36
39. Evaluation rapide de technologies émergentes s'appliquant à la colonne vertébrale : remplacement de disque intervertébral et vertébro/cyphoplastie par ballonnet. D/2006/10.273/39.
40. Etat fonctionnel du patient: un instrument potentiel pour le remboursement de la kinésithérapie en Belgique? D/2006/10.273/41.
41. Indicateurs de qualité cliniques. D/2006/10.273/44.
42. Etude des disparités de la chirurgie élective en Belgique. D/2006/10.273/46.
43. Mise à jour de recommandations de bonne pratique existantes. D/2006/10.273/49.
44. Procédure d'évaluation des dispositifs médicaux émergeants. D/2006/10.273/51.
45. HTA Dépistage du Cancer Colorectal : état des lieux scientifique et impact budgétaire pour la Belgique. D/2006/10.273/54.
46. Health Technology Assessment. Polysomnographie et monitoring à domicile des nourrissons en prévention de la mort subite. D/2006/10.273/60.
47. L'utilisation des médicaments dans les maisons de repos et les maisons de repos et de soins Belges. D/2006/10.273/62
48. Lombalgie chronique. D/2006/10.273/64.
49. Médicaments antiviraux en cas de grippe saisonnière et pandémique. Revue de littérature et recommandations de bonne pratique. D/2006/10.273/66.
50. Contributions personnelles en matière de soins de santé en Belgique. L'impact des suppléments. D/2006/10.273/69.
51. Besoin de soins chroniques des personnes âgées de 18 à 65 ans et atteintes de lésions cérébrales acquises. D/2007/10.273/02.
52. Rapid Assessment: Prévention cardiovasculaire primaire dans la pratique du médecin généraliste en Belgique. D/2007/10.273/04.
53. Financement des soins Infirmiers Hospitaliers. D/2007/10 273/06
54. Vaccination des nourrissons contre le rotavirus en Belgique. Analyse coût-efficacité
55. Valeur en termes de données probantes des informations écrites de l'industrie pharmaceutique destinées aux médecins généralistes. D/2007/10.273/13
56. Matériel orthopédique en Belgique: Health Technology Assessment. D/2007/10.273/15.
57. Organisation et Financement de la Réadaptation Locomotrice et Neurologique en Belgique D/2007/10.273/19
58. Le Défibrillateur Cardiaque Implantable.: un rapport d'évaluation de technologie de santé D/2007/10.273/22
59. Analyse de biologie clinique en médecine général. D/2007/10.273/25
60. Tests de la fonction pulmonaire chez l'adulte. D/2007/10.273/28
61. Traitement de plaies par pression négative: une évaluation rapide. D/2007/10.273/31
62. Radiothérapie Conformationelle avec Modulation d'intensité (IMRT). D/2007/10.273/33.
63. Support scientifique du Collège d'Oncologie: un guideline pour la prise en charge du cancer du sein. D/2007/10.273/36.
64. Vaccination HPV pour la prévention du cancer du col de l'utérus en Belgique: Health Technology Assessment. D/2007/10.273/42.
65. Organisation et financement du diagnostic génétique en Belgique. D/2007/10.273/45.
66. Drug Eluting Stents en Belgique: Health Technology Assessment. D/2007/10.273/48.
67. Hadronthérapie. D/2007/10.273/51.
68. Indemnisation des dommages résultant de soins de santé - Phase IV : Clé de répartition entre le Fonds et les assureurs. D/2007/10.273/53.
69. Assurance de Qualité pour le cancer du rectum – Phase I: Recommandation de bonne pratique pour la prise en charge du cancer rectal D/2007/10.273/55
70. Etude comparative des programmes d'accréditation hospitalière en Europe. D/2008/10.273/02
71. Recommandation de bonne pratique clinique pour cinq tests ophtalmiques. D/2008/10.273/05
72. L'offre de médecins en Belgique. Situation actuelle et défis. D/2008/10.273/08

73. Financement du programme de soins pour le patient gériatrique dans l'hôpital classique : Définition et évaluation du patient gériatrique, fonction de liaison et évaluation d'un instrument pour un financement approprié. D/2008/10.273/12
74. Oxygénothérapie Hyperbare: Rapid Assessment. D/2008/10.273/14.
75. Guideline pour la prise en charge du cancer oesophagien et gastrique: éléments scientifiques à destination du Collège d'Oncologie. D/2008/10.273/17.
76. Promotion de la qualité de la médecine générale en Belgique: status quo ou quo vadis ? D/2008/10.273/19.
77. Orthodontie chez les enfants et adolescents D/2008/10.273/21
78. Recommandations pour les évaluations pharmacoéconomiques en Belgique. D/2008/10.273/24.
79. Remboursement des radioisotopes en Belgique. D/2008/10.273/27.
80. Évaluation des effets du maximum à facturer sur la consommation et l'accessibilité financière des soins de santé. D/2008/10.273/36.
81. Assurance de qualité pour le cancer rectal – phase 2: développement et test d'un ensemble d'indicateurs de qualité. D/2008/10.273/39
82. Angiographie coronaire par tomodensitométrie 64-détecteurs chez les patients suspects de maladie coronarienne. D/2008/10.273/41
83. Comparaison internationale des règles de remboursement et aspects légaux de la chirurgie plastique D/2008/10.273/44
84. Les séjours psychiatriques de longue durée en lits T. D/2008/10.273/47
85. Comparaison de deux systèmes de financement des soins de première ligne en Belgique. D/2008/10.273/50.
86. Différenciation de fonctions dans les soins infirmiers :possibilités et limites D/2008/10.273/53
87. Consommation de kinésithérapie et de médecine physique et de réadaptation en Belgique. D/2008/10.273/55
88. Syndrome de Fatigue Chronique : diagnostic, traitement et organisation des soins. D/2008/10.273/59.
89. Evaluation des certains nouveaux traitements du cancer de la prostate et de l'hypertrophie bénigne de la prostate. D/2008/10.273/62
90. Médecine générale: comment promouvoir l'attraction et la rétention dans la profession ? D/2008/10.273/64.
91. Appareils auditifs en Belgique: health technology assessment. D/2008/10.273/68
92. Les infections nosocomiales en Belgique : Volet I, Etude Nationale de Prévalence. D/2008/10.273/71.
93. Détection des événements indésirables dans les bases de données administratives. D/2008/10.273/74.
94. Soins maternels intensifs (Maternal Intensive Care) en Belgique. D/2008/10.273/78.
95. Implantation percutanée des valvules cardiaques dans le cas de maladies valvulaires congénitales et dégénératives: A rapid Health Technology Assessment. D/2007/10.273/80.
96. Construction d'un index médical pour les contrats privés d'assurance maladie. D/2008/10.273/83.
97. Centres de réadaptation ORL/PSY : groupes cibles, preuves scientifiques et organisation des soins. D/2009/10.273/85.
98. Évaluation de programmes de vaccination généraux et ciblés contre l'hépatite A en Belgique. D/2008/10.273/89.
99. Financement de l'hôpital de jour gériatrique. D/2008/10.273/91.
100. Valeurs seuils pour le rapport coût-efficacité en soins de santé. D/2008/10.273/95.
101. Enregistrement vidéo des interventions chirurgicales par endoscopie : une évaluation rapide. D/2008/10.273/98.
102. Les infections nosocomiales en Belgique: Volet II: Impact sur la mortalité et sur les coûts. D/2009/10.273/100.
103. Réformes dans l'organisation des soins de santé mentale : étude d'évaluation des 'projets thérapeutiques' - 1er rapport intermédiaire. D/2009/10.273/05.
104. Chirurgie assistée par robot: health technology assessment. D/2009/10.273/08
105. Soutien scientifique au Collège d'Oncologie: recommandations pour la pratique clinique dans la prise en charge du cancer du pancréas. D/2009/10.273/11
106. Imagerie par résonance magnétique : analyse de coûts. D/2009/10.273/15
107. Indemnisation des dommages résultant de soins de santé. Phase V: impact budgétaire de la transposition du système français en Belgique. D/2009/10.273/17

108. Le Tiotropium dans le traitement des BronchoPneumopathies Chroniques Obstructives: Health Technology Assessment. D/2009/10.273/19
109. A propos de la valeur de l'EEG et des potentiels évoqués dans la pratique clinique. D/2009/10.273/22