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Horizon Scanning Technology Prioritising Summary

Quantitative EEG for predicting patient response to antidepressants

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PRIORITISING SUMMARY

REGISTER ID: **000327**

NAME OF TECHNOLOGY: **QUANTITATIVE ELECTROENCEPHALOGRAPHY (QEEG) FOR PREDICTING PATIENT RESPONSE TO ANTIDEPRESSANTS**

PURPOSE AND TARGET GROUP: **QEEG IS USED TO PREDICT THE RESPONSE OR NON-RESPONSE OF PATIENTS TO ANTIDEPRESSANTS BASED ON CHANGES IN BRAIN ACTIVITY.**

STAGE OF DEVELOPMENT (IN AUSTRALIA):

- ☒ Yet to emerge
- ☐ Experimental
- ☐ Investigational
- ☐ Nearly established
- ☐ Established
- ☐ Established *but* changed indication or modification of technique
- ☐ Should be taken out of use

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL:

- ☒ Yes — ARTG number: several EEG units have TGA approval
- ☐ No
- ☐ Not applicable

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
Czech Republic	✓		
United States of America	✓		

IMPACT SUMMARY

QEEG cordance[1] prediction of antidepressant response would be provided by clinics and hospitals, using normal EEG equipment that has specific commercial software

[1] Cordance is a property derived from EEG signals using a specifically defined algorithm. It has been found to correlate with regional perfusion, which itself is a reflection of brain activity within that region.

algorithms to extract the cordance data from the EEG signals. This information would be used to assess whether a patient will respond to a specific antidepressant drug, at an early time point, before clinical signs of response/non-response are observable. If the QEEG cordance data indicates that the patient is responding to the specific drug, then therapy can be continued. If the patient is not responding, according to the QEEG cordance data, then the patient can be switched to another drug or class of drugs. This would facilitate the assignment of the patient to a therapy regimen which has the greatest likelihood of producing remission of depressive symptoms.

BACKGROUND

Electroencephalography (EEG) is the measurement of the electrical activity within the brain. It is non-invasive and does not require tracers or other contrast agents. In addition the equipment required is relatively small and inexpensive compared to techniques such as magnetic resonance imaging (MRI) or computed tomography (CT) scanning. An advantage over most other brain imaging/monitoring techniques is that EEG has a high temporal resolution, detecting changes within the brain's electrical signals in the millisecond range. It reflects the activity of a large group of neurons and as such its spatial resolution is lower than other techniques, such as functional magnetic resonance imaging (fMRI). EEG is performed by placing electrodes on the scalp and amplifying the voltage across pairs of electrodes. The amplified signals are passed through several filters to remove noise and artefacts to obtain the final signal. This final signal can be transmitted to a monitor or printed to paper. The signals obtained are thought to reflect activity within the brain. If performed digitally the signals can be processed in many ways to obtain different functional outcomes, e.g. a colour coded map of brain activity. The data obtained can be processed using a Fourier Fast Transform algorithm to calculate a power spectrum; this is known as Quantitative Electroencephalography (QEEG). In general usage, the power spectrum of 1 Hz to 20 Hz is considered of clinical utility. This range is usually designated with the familiar alpha (7.5–12.5 Hz), beta (12.5–20 Hz), delta (1.5–3.5 Hz), theta (3.5–7.5 Hz) naming system. Using an algorithm, a property known as "cordance" can be derived from EEG signals. This has been found to correlate with regional perfusion (blood flow), which in turn relates to the activity of the brain within that region (Hughes & John 1999).

CLINICAL NEED AND BURDEN OF DISEASE

Depression is a disorder where the state of a person's mood can be persistently lowered eg sadness, melancholia, or despair, and can accompany or induce other physical or psychological symptoms. It is distinguished from normal emotional variation in that it affects the sufferer's normal activities and/or social functioning(AIHW 1998). Clinical depression is a major health problem in Australia, causing eight per cent of years lost to disability in 1996, making it Australia's highest

non-fatal disease burden and fourth highest disease burden of any sort (Mathers et al 1999).

Depression may respond to drug treatment, although finding a suitable drug regimen for the patient is often difficult, due to the mental state of the patient and also the long time period before a clinically detectable effect is seen in the patient in response to the drug. This period can be from weeks to months, and may result in non-compliance as the negative effects of the drugs often impact before the longer term beneficial effects are realised (Dodd & Berk 2004).

DIFFUSION

No Australian trials of QEEG for depression-related drug response prediction were found during the preparation of this summary.

COMPARATORS

Predicting the success of patient response to antidepressants is mainly based on a detailed clinical profile of the patient (known clinical course of illness, depression subtype, comorbidity, and stage of life), the known effects of a specific drug (tolerability, interactions, and cost) and patient preference (avoidance of certain side-effects and family history of drug response) (Zetin et al 2006). More recently, pharmacogenetic and other biological markers are being used to assess the suitability of drugs for specific patients, although these techniques are neither widely available nor utilised (Zetin et al 2006). Due to the successive failure of drugs to produce a positive response in patients being treated for depression, up to 15 per cent of patients will eventually be categorised as having treatment refractory depression (Berlim & Turecki 2007). It has also been estimated that 30 to 45 per cent of patients being treated for a major depressive disorder have either a partial response or no response to prescribed antidepressant drug treatments (Gayetot et al 2007). From this evidence it can be seen that a significant proportion of patients have an unsatisfactory outcome regarding the treatment of their illness with drug therapy, and that there is wide scope for improvement in the prediction of antidepressant response in patients.

SAFETY AND EFFECTIVENESS ISSUES

Several studies with small patient groups, but from a variety of locales and using a range of treatment types, show that there are significant neurological differences in responders and non-responders to drug treatment of depression. These differences are observable by QEEG, despite there being no clinically visible impact of treatment in the patient at this early time point. The main factor that was consistently linked to medication response in these studies was cordance. Cordance is measured along a continuum of values from negative to positive. Negative values are termed discordance and positive values are termed cordance. Cordance is derived from QEEG data using an algorithm comparing absolute and relative power signals within specific types of frequencies. A brain region is said to have discordance if the region

has a low absolute power as measured by QEEG yet high relative power in pathologic (ie slow wave) bands. Cordance is defined to be a normal level of absolute power and normal relative power of the slow wave bands (Leuchter et al 1994).

Fifty one patients diagnosed with depression underwent a QEEG at baseline, and at 48 hours and one week after being placed on treatment of fluoxetine or venlafaxine vs. placebo. The data were analysed for any changes that might predict the eventual response or lack of response to the medication or placebo. The patients were grouped, *post hoc*, into four categories, medication responders, medication nonresponders, placebo responders and placebo nonresponders. No significant differences in theta power or brain regional differences were seen between the groups. Nor were clinical differences observed at the early time points. One factor that was significantly linked to medication response was a decrease in prefrontal cordance. At four weeks post-medication initiation there were clinically observable differences in prefrontal cordance between the response and nonresponse groups. And at eight weeks the patients with the greatest changes in cordance showed the best response to therapy. The authors concluded that cordance may be a predictive marker for response to antidepressant therapy (Cook et al 2002) (level III-2 prognostic evidence).

Another study of 51 patients pooled data from two double-blinded placebo-controlled randomised controlled trials[2]. It was found that the patients with the most favourable neurophysiological response to the placebo, as measured by QEEG cordance changes, went on to have the best eight week response to medication (fluoxetine 20 mg or venlafaxine 150mg) after randomisation (Hunter et al 2006) (level III-2 prognostic evidence).

The above studies involved patients who were not on medication at the initiation of the trials. A study designed to test whether cordance changes could be linked to responders in a population that was undergoing a change from one therapy to another therapy, found that five of six responders, and only two of six nonresponders, showed the early cordance decrease associated with a positive therapy outcome (Cook et al 2005). The patients in this study had failed to respond to a prior treatment with selective serotonin reuptake inhibitor monotherapy. The six responders showed clinically observable signs of therapy response at eight to ten weeks (level III-3 prognostic evidence). The authors state that this technique may be used without a washout period between changes of drug therapy. This lack of wash out period would be beneficial to the patient as it is obviously the quickest method of transferring from one therapy regimen to another. Clinically, reducing the depressive status of the patient quickly is very important, as while the patient's current therapy is ineffective the depressive sequelae are still in full effect (Cook et al 2005).

[2] This report and Cook et al (2002) share the same second author, patient number and drug types. It is possible that there is some duplication of patients across these trials.

Another important question is whether the QEEG response prediction technique is applicable to different drugs and also to different classes of drugs available for the treatment of depression. This question was addressed in a study of 17 patients, in which a wide variety of drugs from distinct classes were given, to treat depression, as appropriately prescribed by clinicians. Clinical response was measured at four weeks. All five of the responders showed early, QEEG-measured, prefrontal cordance decreases, and only two of 12 nonresponders had an early, QEEG-measured, prefrontal cordance decrease. These decreases were statistically significant ($p < 0.05$). These results are evidence that QEEG cordance can predict the response to a wide range of drug classes (Bares et al 2007) (level III-3 prognostic evidence).

A systematic review of existing literature in December 2004, on the subject of neuroimaging for treatment of depression or anxiety, found that the majority of studies were conducted on either sufferers of obsessive-compulsive disorder or major depression. The review identified 15 papers and found that there was evidence that early brain activity imaging was predictive of the outcome of drug based therapy. It was noted that the long term clinical benefits of this prediction were not yet established (Evans et al 2006) (Level IV prognostic evidence)[3].

Although not confined to QEEG early response prediction, a recent meta-analysis of randomised, double- blind, placebo controlled antidepressant trials addressed the question of whether "early responders" were "true responders" or just responding to a placebo effect of the initiation of therapy. 7,121 major depression patients were included in the meta-analysis (4,076 on antidepressants and 3,045 on placebo). It was concluded that those subjects treated with antidepressants were more likely to have a sustained clinical response by two weeks than those subjects treated with placebo (the odds of antidepressant treated subjects having a sustained clinical response were twice as high as placebo controlled subjects) (Level I intervention evidence). This finding indicates that, in principle, it is possible to detect early clinical responses in patients which reflect the "true" longer term response (Papakostas et al 2006).

COST IMPACT

No cost information was found for the Australian market.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified/raised in the sources examined.

OTHER ISSUES

A trial designed to investigate early (1 week) QEEG biomarkers which may predict response or non-response to antidepressants for subjects with major depression disorder is currently being undertaken in the USA., sponsored by Aspect Medical

[3] Although this review was conducted systematically, the papers reviewed are of poor quality. The review was therefore given the same level of evidence of the papers reviewed.

Systems. The trial is designated “Biomarkers for Rapid Identification of Treatment Effectiveness in Major Depression” (BRITE-MD). The trial is prospective, randomised, and multi-centred; treatments consist of Escitalopram, Bupropion XL, and a combination treatment regimen. The study recently finished recruiting and enrolled 375 individuals. Results should be published in the near future (Aspect Medical Systems 2006).

SUMMARY OF FINDINGS

The quality of the evidence for QEEG response prediction found in this summary is of average quality, overall, and all the evidence suggests that early QEEG cordance can successfully predict the eventual “true” outcome of antidepressant therapy. A larger clinical trial, currently underway, will publish its results in the near future.

HEALTHPACT ACTION:

Based on the potential usefulness of this technology for a large patient group, and the likelihood of further, higher quality evidence being made available in the near future, HealthPACT have recommended that this technology be monitored for 12-months.

NUMBER OF INCLUDED STUDIES

Total number of studies	
Level I intervention evidence	1
Level III-2 prognostic evidence	2
Level III-3 prognostic evidence	2
Level IV prognostic evidence	1

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SOURCES OF FURTHER INFORMATION

No other sources were identified.

SEARCH CRITERIA TO BE USED:

Electroencephalography/ drug effects
Humans
Prefrontal Cortex/ drug effects/ physiology
Algorithms
Antidepressive Agents/ therapeutic use
Depressive Disorder/ drug therapy/ pathology
Drug Resistance
Depression/drug therapy/ therapy
Depressive Disorder/drug therapy/therapy
Drug Combinations
Brain/ drug effects/ physiology
Brain Mapping