



## Quality assessment and comparison of evidence for electroconvulsive therapy and repetitive transcranial magnetic stimulation for schizophrenia: A systematic meta-review

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### ABSTRACT

**Background:** Randomized studies directly comparing the effects of electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS) for depression generally favour ECT. ECT and rTMS have also been investigated for chronic symptoms of schizophrenia although there are no direct comparisons available.

**Aims:** We sought to determine the relative benefits and adverse outcomes of ECT and rTMS by comparing effect sizes reported in systematic reviews and to quality assess this evidence using GRADE and QUOROM guidelines.

**Method:** Included are systematic reviews with meta-analysis published since 2000, reporting results for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Medline, Embase, CINAHL, Current Contents, PsycINFO and the Cochrane library were searched and hand searching was conducted. Data extraction and quality assessment were completed by two independent reviewers.

**Results:** Fifty-three of 58 reviews were excluded as they did not meet inclusion criteria. The remaining five have a low probability of reporting bias and show that high quality evidence suggests a short-term, medium to large treatment effect of rTMS for auditory hallucinations ( $d = 0.88$ ) but not other symptoms, for people treated with concurrent antipsychotics. For ECT, high quality evidence suggests a short-term small, significant effect for improvement in global symptoms, for people with or without concurrent antipsychotics ( $RR = 0.76$ ). There is no evidence for longer-term therapeutic or adverse effects of either treatment.

**Conclusions:** It is worthwhile considering rTMS in cases where auditory hallucinations have not responded to antipsychotic medications and ECT where overall symptoms have not responded to antipsychotic medications.

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### 1. Introduction

Many people with schizophrenia do not respond adequately to antipsychotic medication for which recourse to adjunctive treatments is a common clinical practice. Two somatic treatments used mainly for depression are electroconvulsive therapy (ECT) and, more recently, repetitive transcranial magnetic stimulation (rTMS). Randomized studies directly comparing the two treatments generally favour

ECT for depression (Malhi et al., 2006) and psychotic depression (Rodriguez-Martin et al., 2001). ECT and rTMS have also been investigated for treating chronic symptoms of schizophrenia although there are no direct comparisons between these treatments in this context. In the absence of direct comparisons, the aim of this meta-review is to quality assess the available evidence from systematic reviews with meta-analyses and to compare treatment effect sizes of both benefits and adverse outcomes of ECT and rTMS for schizophrenia.

### 1.1. ECT

The efficacy and safety of ECT are influenced by a number of parameters such as electrode placement, frequency of treatment, dose and duration of concurrent medications and the degree to which the stimulus dose exceeds the seizure threshold (The UK ECT Review Group, 2003). It is suggested from clinical observations that schizophrenia patients who are treatment resistant, in an acute phase of illness, or who have catatonic or depressive features may derive particular benefit from ECT. However empirical evidence is lacking (American Psychiatric Association, 2004; Greenhalgh et al., 2005).

Adverse effects of ECT on the cardiovascular system are common but are typically transient. Commonly noted side effects include headache, muscle aches, and nausea and/or vomiting. These are generally mild and can be treated with analgesics or anti-nausea medications. Adverse cognitive effects of ECT in people with schizophrenia are unclear since most studies of cognition following ECT have involved patients with depression (American Psychiatric Association, 2004).

### 1.2. rTMS

While ECT produces a generalized seizure and global central nervous system excitation, rTMS permits targeted stimulation of superficial layers of the brain which may be effective in relieving specific symptoms of schizophrenia (Burt et al., 2002). rTMS is usually given at an intensity around a person's motor threshold (i.e. the intensity required to activate the motor cortex to produce peripheral muscle responses) and involves placing a magnetic coil at the scalp surface so that trains of alternating magnetic pulses pass through the scalp and skull to induce an electric current in the brain tissue underneath (Reid et al., 1998). Unlike electrical fields, magnetic fields pass unimpeded through electric insulators like skin and bone. Thus, as the magnetic stimulus is not shunted over the scalp like an electrical stimulus, the resulting stimulation is more focal. rTMS is also less painful than electrical stimulation. As rTMS is subconvulsive, no anaesthetic or muscle relaxant is required.

Based on findings that the left temporoparietal cortex is involved in speech perception and is active during auditory hallucinations, some studies have assessed whether the application of low-frequency rTMS (1 Hz) reduces brain activity in that region and also reduces the severity of hallucinations. Studies have also assessed whether low-frequency rTMS applied to the temporal lobe relieves other positive symptoms such as delusions and whether the

application of high-frequency rTMS ( $\geq 5$  Hz) to the frontal lobe increases brain activity and relieves negative symptoms.

One review of adverse effects of rTMS in both healthy participants and patients found that of the few studies reporting adverse effects in schizophrenia, up to 40% of patients reported mild headache and neck pain (Machii et al., 2006). This varied depending on the frequency of application. They reported other very rare adverse effects such as migraine, seizure, tinnitus, mood alterations, and mild, transient cognitive complaints as well as onset of psychotic symptoms with high-frequency rTMS.

## 2. Method

### 2.1. Literature search

#### 2.1.1. Inclusion/exclusion criteria

Included are systematic reviews (systematic literature search with explicit inclusion/exclusion criteria and trial quality assessment) with meta-analysis published in full text, in English, from the year 2000. Reviews had to report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. We excluded reviews published prior to the year 2000, treatment guidelines and overviews of systematic reviews to reduce duplication. The decision to include or exclude reviews was conducted in duplicate by two of the authors (S.M. and M.G.) with any disagreements settled by discussion.

#### 2.1.2. Search strategy

Reviews of ECT and rTMS were identified by searching Medline, Embase, CINAHL, Current Contents, PsycINFO and the Cochrane library. The search terms were: exp Schizophrenia/, schizopreni\$.tw, exp Psychotic Disorders/, schizo\$.tw, ECT, electroconvulsive, electroconvulsive therap\$, electro shock therap\$, electroshock therap\$, rTMS, TMS, transcranial magnetic stimulation, review.pt and medline.tw, meta-analysis.pt, systematic\$.tw and (review\$ or overview\$.tw, meta?analy\$.tw, meta analy\$.tw, with a year limit from 2000 to current (July, 2009). Hand searching of reference lists of identified reviews was also conducted.

### 2.2. Quality assessment

Review reporting was guided by the QUOROM statement checklist which describes a preferred way to present a meta-analysis (Moher et al., 1999). Reviews were assigned a low, medium or high probability of reporting bias depending on how many items were checked. For instance, a low probability of bias would be assigned to reviews checking over 66% of items, a medium probability between 33 and 66% and a high probability would be given to reviews checking less than 33%. The QUOROM flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item.

Quality of evidence is assessed using the GRADE approach (GRADE Working Group, 2004; GRADEpro, 2008) where high

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