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Project Title: Novel Therapies in the Critical Care Management of Refractory and Super-Refractory Status Epilepticus

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Summary (250 words max single spaced):

Background: Refractory status epilepticus (RSE) is a common neurological emergency involving prolonged seizure activity whose management poses significant challenges for the clinician. Treatment plans are unclear after the failure of standard anti-epileptic drugs (AED). Thus, novel techniques for seizure control in RSE are required. Intravenous magnesium sulphate (IV $MgSO_4$), electroconvulsive therapy (ECT), and repetitive transcranial magnetic stimulation (rTMS) are such novel therapies with limited cases reported to date.

Methods: We performed three individual systematic literature reviews to determine the effectiveness of IV $MgSO_4$, ECT, and rTMS on seizure control in RSE. Articles from MEDLINE, BIOSIS, EMBASE, Global Health, Scopus, Cochrane Library, the International Clinical Trials Registry Platform, clinicaltrials.gov, and reference of articles were searched. Patient demographics and details of management were extracted from identified articles.

Results: IV $MgSO_4$, ECT, and rTMS were effective in reducing seizures in 50%, 57.9%, and 71.4% of patients, respectively. Complete resolution occurred in 42.8%, 36.8%, and 47.6% of patients, respectively. Therapeutic effects of these treatments were often short-term. Adverse effects were only documented in 10.7%, 15.8%, and 4.8% of patients and were not worrisome.

Conclusion: Our systematic literature reviews provide Oxford level 4, GRADE D evidence for the use of IV $MgSO_4$, ECT, and rTMS for seizure control in RSE. Although our reviews suggest a positive trend towards improving seizure control, routine use of these therapies cannot be recommended at this time. Further prospective study is required to fully elucidate their efficacies as anti-epileptic agents in RSE.

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Title

Novel therapies in the critical care management of refractory and super-refractory status epilepticus

Background

Status epilepticus (SE) is a common neurological emergency involving prolonged seizure activity. The definition of status epilepticus has changed over time, however a well-accepted clinically functional definition is given by the International League Against Epilepsy (ILAE) and the Neurocritical Care Society. They define SE as continuous seizure activity for more than 5 minutes or 2 seizures between which consciousness is not regained[1]. After initial assessment of the patient, first-line treatment includes the use of a benzodiazepine, followed by second-line therapy which includes the use of an anti-epileptic drug (AED) such as phenytoin or valproate[2]. However, seizure activity persists in approximately 31% of patients despite these anticonvulsant medications, this more severe form of SE is referred to as refractory status epilepticus (RSE)[3].

The management of RSE becomes more controversial, with limited randomized clinical trials and prospective studies outlining the efficacy and safety of different therapies. Few prognostic factors, other than age and etiology, are able to guide treatment. Etiology is often unknown. Duration of RSE, timing of therapies, and therapeutic agents themselves have limited evidence[1]. However, the goal of all treatments is to stop seizure activity quickly and prevent further morbidity. Patients are generally placed under continuous EEG monitoring and started on a general anesthetic such as propofol. In approximately 15% of patients, seizures persist for 24 hours after the onset of anesthesia or return when the anesthesia is weaned[4]. These patients are said to have progressed to super-refractory status epilepticus (SRSE)[1]. The long term prognosis of these patients in SRSE is very poor, with mortality rates shown to be as high as 48% in some centers[5]. Even when the seizures are controlled, many patients have severe neurological deficits from cerebral damage[4].

Current treatment guidelines for RSE are not clear due to the variable etiologies and progression of this condition. The use of different pharmacologic agents depends on the experience of the practitioner, the readings on the EEG, and previously unsuccessful AEDs that failed. Due to the nature of this condition, there are few prospective studies for the treatment of RSE[6]. The current evidence is based largely on retrospective case reports. In a systematic literature review of different therapies for RSE, one study identified 143 papers analyzing 1168 patients, of which only one study was a prospective study[6]. Thus, treatment recommendations are based on small retrospective studies and expert opinion.

Some poorly documented novel treatment options include the use of hypothermia, ketamine, vagal nerve stimulation (VNS), $MgSO_4$, electroconvulsive therapy (ECT), and repetitive transcranial magnetic stimulation (rTMS). The latter three ($MgSO_4$, ECT, and rTMS) already have clinically important roles in the treatment of eclampsia, depression, and psychiatric disorders, respectively[7,8]. Though the mechanisms behind their roles in the treatment of RSE have not been fully elucidated, $MgSO_4$ has been found to be an effective therapy in the treatment of eclamptic seizures[7]. It is believed to help control seizures in RSE through its anti-NMDA receptor properties, causing decreased neuronal excitation[9]. ECT has a wide range of applications in various psychiatric disorders. Electrodes are applied exteriorly and electrical currents are passed into the cerebral cortex, causing transient seizures. The exact mechanism is also not known, but is believed to involved inhibition of action potential propagation[10]. rTMS

involves the use of a magnetic coil to provide electrical current to the brain via electromagnetic induction[11]. Currently used for some psychiatric conditions and chronic pain, it's mechanism in seizure control is unknown.

There are only a few reported cases of the use of $MgSO_4$, ECT, and rTMS in the treatment of RSE. One major study in 2012 reviewed 1168 patients with RSE and identified only 8 and 3 patients that were treated with ECT and $MgSO_4$, respectively[6]. Our preliminary searches have shown that there have been more documented cases of these therapies in the literature. Thus, a systematic literature review of these novel therapies for the treatment of RSE/SRSE was performed in order to outline their effectiveness as well as to guide future research. Our goal was to systematically review the literature available for each of these novel treatments. All three reviews are currently published in peer reviewed journals[15-17], with this current paper describing the main features of each of the three extensive reviews.

Objectives

The objectives of this project are to perform 3 separate systematic reviews of the literature to answer the following questions: 1) what is the effectiveness of $MgSO_4$ on seizure control in RSE? 2) What is the effectiveness of ECT on seizure control in RSE? 3) What is the effectiveness of rTMS on seizure control in RSE? The safety profiles of these interventions were also documented. Our reviews will help guide future research into the optimal for treatment of RSE and allow clinicians to improve the management of this condition.

Methods

Inclusion and Exclusion criteria

The three separate systematic reviews were carried out in accordance with the Cochrane Handbook for Systematic Reviews[12]. The definition of SE followed the Neurocritical Care Society guidelines, where seizures longer than 5 minutes or experiencing 2 seizures without regaining consciousness between them is deemed SE. RSE was further defined as SE failing to respond to two front line medications designed to treat SE. Anticipating a limited number of case reports and retrospective studies, an all-inclusive approach was taken. The inclusion criteria for all three reviews were: human study, all study types including retrospective and prospective, any age group, and the documented use of IV $MgSO_4$, ECT, or TMS explicitly for the treatment of RSE, respectively. The exclusion criteria in all reviews were: animal studies and non-English literature. In the review of $MgSO_4$, 2 additional exclusion criteria were the use of oral $MgSO_4$ and the use of MgSO4 in eclamptic seizures.

Search Strategy

The following databases were searched: MEDLINE, BIOSIS, EMBASE, Global Health, HealthStar, SCOPUS, and Cochrane library from inception until June 2015. To include current clinical trials, the World Health Organizations International Clinical Trials Registry Platform and ClinicalTrials.gov were searched. Furthermore, the last 10 years of meeting proceedings from 15 professional societies were searched, including: American Academy of Neurology (AAN), American Association of Neurological Sciences (AANS), American Epilepsy Society (AES), Canadian Neurological Sciences Federeation (CNSF), European Federation of Neurological Sciences (EEFNS), European Neurosurgical Society (ENAS), Australian Society of Anesthesia & International Research (IARS), Japanese Society of Neuroanesthesia and Critical Care (JSNCC), Neurocritical Care Society (NCS), Society of Critical Care Medicine (SCCM), Society

of Neurosurgical Anesthesia and Critical Care (SNACC), World Congress of Neurology (WCN), World Federation of Neurological Surgeons (WFNS), World Federation of Societies of anesthesiology (WFSA). The references of the review articles were also searched. The primary outcome measure was electrographic seizure control (complete, partial reduction, or failure). The secondary outcome was the patient outcome (returned to baseline, severe, moderate, or mild deficits) and any adverse effects to treatment (absent or present, and if present, described). Electrographic seizure control was described qualitatively from seizure resolution to failure.

Study Selection

The abstracts and citation information from the search results were stored in a database. A two-step review process was performed, where all the search results were screened to see if they met the inclusion criteria. The full articles from the chosen search results were then assessed to confirm the inclusion criteria were met and that the primary outcome (described above) was reported. From these final articles, patient data was extracted and tabulated in a database. The extracted data included patient demographics, the type of study, the number of patients, the characteristics of the treatment regimen of either $MgSO_4$, rTMS, or ECT, the number of medications prior to treatment, the duration of time before treatment, other AEDs on board, electrographic seizure response, whether seizures recurred, any adverse effects mentioned, and patient outcome.

Grading of Evidence

To assess the evidence of our literature reviews, two different criteria were chosen: the Grading of Recommendation Assessment Development and Education (GRADE) criteria and the Oxford criteria. Both are commonly used and have their own advantages and disadvantages. Both of these criteria were applied to each included study in the review. By utilizing both criteria, the evidence we present can be understood by a broader audience. The GRADE system is a simple rating system with 4 levels of evidence: high quality (A), moderate quality (B), low quality (C), and very low quality (D). Grade A evidence describes evidence that is backed by multiple high quality studies where further research would likely not change the confidence in the effect. On the contrary, Grade D evidence describes evidence that is based on limited studies with inconsistent results or expert opinion, and any estimate of the effect is considered uncertain[13]. Oxford criteria has 5 levels of evidence with multiple subcategories within them. Oxford level 1 evidence represents evidence gained from systematic reviews of randomized control trials (RCT) of homogeneity of data, while Oxford level 5 evidence represents expert opinion without critical appraisal[14].

Statistical Analysis

Descriptive statistics will be used to measure the effectiveness of MgSO4, rTMS, and ECT on electrographic seizure control in RSE. A meta-analysis could not be performed due to the due to the limited number of retrospective case studies

Results

1. $MgSO_4$

The results of our search strategies for $MgSO_4$ are summarized in Figure 1. The same search strategy was used for both the ECT and rTMS searches, although they are not shown. In

the $MgSO_4$ search, a total of 809 articles were identified. After removing duplicate results, there were 599 original articles. The two-step review of the abstracts and titles led to 47 articles being selected for further analysis, of which 19 met the inclusion criteria to be included in our systematic literature review. There were an additional 3 articles that described duplicate patients. Each article was retrospective, with 16 individual case reports and 3 retrospective case series.

A total of 28 patients were documented having received IV $MgSO_4$ for the treatment of RSE. 9 patients were pediatric with a (mean age 11.4 years), 11 were adult (mean age 27.5 years), and 8 had no documented age. The etiology of the seizures was documented and variable in 17 cases. The subtypes of the seizures included: 1 generalized status epilepticus (GSE), 13 generalized refractory status epilepticus (GRSE), 2 focal refractory status epilepticus (FRSE), 2 multi-focal refractory status epilepticus (MFRSE), 1 non-convulsive refractory status epilepticus (NCRSE), and 9 non-defined SE/RSE. The mean number of AEDs was 7.7 (documented in 17/19 studies). The mean duration prior to treatment with $MgSO_4$ was 19.2 days (documented in 10/19 articles). The mean duration of treatment was 4 days (documented in 9/19 articles).

Seizure response occurred in 14 of the 28 patients (50%), with 12 patients (42.8%) showing complete resolution and 2 (7.1%) showing partial resolution. Outcome data was not well recorded across all studies, but seizure recurrence after IV $MgSO_4$ occurred in 7 of the 14 patients (50%). Adverse effects were documented in 3 of the 28 patients, 1 patient experiencing limb weakness and 2 patients developing heart block. No progression to cardiac arrest was reported. No identifiable pattern could be observed between responders and non-responders based on neither seizure subtype nor etiology. Each of the 19 articles was a retrospective case reports/series, and thus was of Oxford Level 4, GRADE D evidence. Overall, this review can provide Oxford level 4 and GRADE level D evidence criteria on the use IV $MgSO_4$ on seizure control in non-eclamptic RSE. However, its role is still not certain and its routine use cannot be recommended at this time.

2. ECT

The initial search strategy for ECT resulted in a total of 474 articles from the databases. Removing the duplicates yielded 351 unique articles. After initial screening of the titles and abstracts, 38 articles were identified. The two-step review process identified 14 articles that met the inclusion and exclusion criteria, with 1 additional article that contained duplicate patient information. These 14 articles were all retrospective, with 11 case reports and 3 case series.

A total of 19 patients (4 pediatric, mean age 10 and 15 adults, mean age 44) were described in the literature to have received ECT for seizure control in RSE. The etiologies were all variable. The subtypes of RSE included GRSE in 9, FRSE in 7, and NCRSE in 3. The mean duration prior to treatment with ECT was 40 days (documented in 7 articles). The mean number of AEDs prior to ECT was 7 (documented in all 14 studies).

Seizure response occurred in 11/19 patients (57.9%) with partial and complete resolution in 4/19 (21.1%) and 7/19 (36.8%) patients, respectively. Adverse effects were poorly documented in only 4/14 articles. In total, 3 patients were documented to have adverse effects, with all 3 experiencing transient lethargy and amnesia. Due to limited and heterogenous data from the articles, ECT cannot be recommended for routine use in RSE at this time. However, all 14 articles meet Oxford level 4 and GRADE level D evidence criteria, suggesting ECT may have

some potential impact on seizure control in RSE. Future prospective studies are required to delineate this effect.

3. rTMS

The database search yielded 434 articles matching our search terms. Removing the duplicate articles resulted in 176 unique articles. The two-step review process identified 24 articles to be assessed further. Finally, 8 articles were identified that met the inclusion and exclusion criteria. A review of the references identified 4 more articles, making a total of 12 articles. However, one article contained duplicate patient information so only 11 articles were used when presenting the data. All 11 articles were retrospective studies, with 6 being case reports and 5 being case series.

A total of 21 patients were described in the 11 articles, 8 being pediatric patients (mean age = 8.3 years) and 13 adult patients (mean age = 42.3 years). The etiologies of the SE/RSE were variable. The subtypes of SE/RSE included FSE in 10 patients, GRSE in 2, FRSE in 8, and 1 patient with non-defined status. The mean duration prior to use of rTMS was 22 days (reported only in 3 articles). The mean number of AEDs used prior to rTMS was 7.5 (reported in 8 articles).

Seizure response occurred in 15 of the 21 patients (71.4%), with complete and partial reduction in 10/21 (47.6%) and 5/21 (23.8%) patients, respectively. There was an identifiable pattern in seizure response based on SE subtype, with 8/10 patients in FSE and 4/8 patients with FRSE responding to treatment. Seizure recurrence was documented in 11 (73.3%) of the 15 patients who had initially responded within 4 months. The time until recurrence was variable, ranging from 2 weeks to 4 months. There was only one documented adverse effect, where one patient had transient leg sensory problems which resolved completely. All 11 articles fulfilled the criteria for. Oxford level 4 and GRADE level D evidence. This suggests that there is a potential role for the use of rTMS in the control of FSE/FRSE.

Table 1 summarizes the seizure responses of the patients in each of the three treatments, including the number of studies and patients identified. The fully extracted data from all the articles was tabulated and published within our reviews, however, but are not shown here for brevity[15-17].

Discussion

Overall, seizure control in RSE was obtained in 50%, 57.9%, and 71.4% of patients with $MgSO_4$, ECT, and rTMS, respectively. These response rates suggest that there is definitely a potential role for these therapies in the treatment of RSE. Due to the small number of retrospective case reports and case series and the heterogeneity of the data, no identifiable trends could be seen between responders and non-responders to therapy. Patients who responded to therapy with $MgSO_4$ and rTMS had seizure recurrence rates of 50% and 73.3%, respectively. Many patients treated with ECT also had to undergo repeat treatment due to seizure recurrence. This suggests that although initial response rates were high, the effects were not permanent. These treatments may not be the curative therapy, but can be important achieving temporary seizure control while further AEDs can be titrated to therapeutic doses.

The safety profiles were promising given that there were very few adverse effects documented. This may be skewed by underreporting, however even the described adverse effects were not very worrisome. The transient lethargy and amnesia from ECT is a common

side effect of ECT in other therapies, and only 1 patient had transient leg sensory problems from rTMS but they resolved completely. 2 patients had reported heart block during IV $MgSO_4$ therapy, however it was not clear whether that was from hypermagnesemia itself, or a result of multiple drug interactions.

An interesting finding was that 71.4% of patients initially responded to rTMS therapy, with more of the responders presenting in FSE rather than FRSE. While 80% of patients in FSE responded to rTMS, only 50% of patients in FRSE had any amount of seizure control. This suggests that rTMS may have a role in the early and rapid control of FSE before switching to an appropriate anti-epileptic drug (AED). The lower rate of response in FRSE could represent the ongoing resistance of SE once it becomes refractory.

Our results show promising rates of seizure control with low rates of adverse effects. However, there are many limitations in our literature reviews. Firstly, the heterogeneity of the studies precluded meta-analyses from being performed, leaving us with only descriptive statistics on the effectiveness of the therapies. Since there were only a small number of retrospective case reports, the results cannot be generalized to all patients in SE/RSE. Secondly, many of the retrospective case reports were presented as meeting abstract with limited details of the therapy. Most patients had multiple AEDs on board and it was not always explicitly mentioned which ones were used concurrently with either $MgSO_4$, ECT, or rTMS. Thus, the electrographic seizure responses cannot be directly attributed to their effects. The timelines of the treatments were not always documented. The treatment regimen was not always outlined, so it is not possible to make significant conclusions or directly compare treatment regimens. Thirdly, there is a strong potential for publication bias. It is likely that many negative results were not published, and our reviews can be an overestimate of the true effectiveness.

Overall, our reviews provide GRADE D, Oxford level 4 evidence for the use of $MgSO_4$, ECT, or rTMS for seizure control in RSE. Our data does suggest a trend toward better seizure control with the use of these treatments, but the routine use of these therapies for the treatment of RSE cannot be recommended at this time. Further prospective studies are warranted to allow the treatment effect to be fully scrutinized.

Conclusion

Overall, seizure control was obtained in 50%, 57.9%, and 71.4% of patients with $MgSO_4$, ECT, and rTMS, respectively. Due to the heterogeneity of the studies, meta-analyses could not be performed, leaving us with only descriptive statistics for seizure control. Our data suggests that these therapies have a role in the management of seizures in RSE, as they have a relatively promising safety profile and were able to temporary control seizures in a majority of the patients. Due to the limitations of our study, their routine use cannot be recommended at this time. These limitations include a publication bias, the heterogeneity of the studies/patients precluding a meta-analysis, and fact that each patient was on a combination of different AEDs, precluding a definitive attribution towards $MgSO_4$, ECT, or rTMS. In conclusion, we present Oxford level 4/GRADE level D evidence for the potential impact of $MgSO_4$, ECT, and rTMS on seizure control in RSE/SRSE.

Figures

Figure 1: Flow diagram of search results for MgSO4. Note that the same search strategies were used for ECT and rTMS, but are not shown to avoid redundancy.

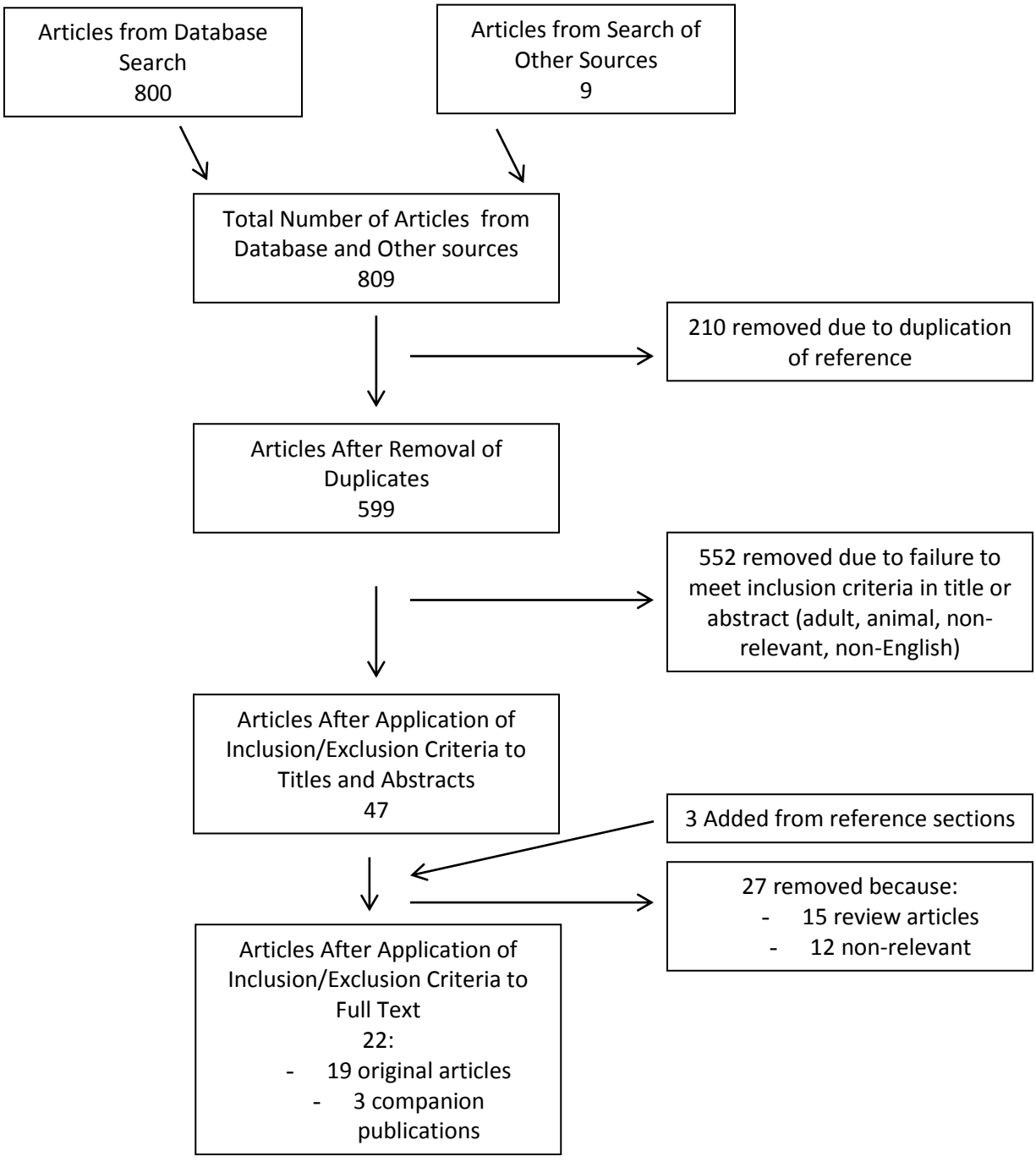

Table 1: Summary of the results of the literature reviews

	Number of studies	**Number of patients**	**Patients responding to treatment**	**Detailed Seizure response**			**Patients experiencing adverse effects**
				Complete	Partial	failed	
$MgSO_4$	19	28	50%	42.8%	7.2%	50%	10.7%
ECT	14	19	57.9%	36.8%	21.1%	42.1%	15.8%
rTMS	11	21	71.4%	47.6%	23.8%	28.6%	4.8%

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