REVIEW ARTICLE

A Literature Review of the Efficacy of Repetitive Transcranial Magnetic Stimulation on Epilepsy

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Abstract

Repetitive transcranial magnetic stimulation (rTMS), often recognized as a safe and tolerable method with promising therapeutic potential for the treatment of a variety of neurological disorders, has been extensively studied by medical engineering scientists in recent decades. Epilepsy has always been one of the vital foci in the therapeutic role of rTMS, especially its low-frequency type. However, various reports, clinical trials, and review articles published in recent years have yielded conflicting results regarding the efficacy and side effects of rTMS in patients.

In this review article, reviewing studies published from January 2000 to October 2021, we examined the efficacy and side effects of rTMS with a specific look at its therapeutic applications in epilepsy.

Our study indicates promising results in the clinical application of this technique for patients with epilepsy. Among other things, it has the ability to reduce interictal epileptic abnormalities, does not interfere with neuropsychological function in normal people, does not worsen cognitive function and even improves Stroop function, rarely has serious side effects such as seizures and psychotic symptoms, has low risk in children as adults, and has potential for improving suicidal ideation.

Despite some limitations in this study, including the small number of studies performed and the heterogeneity among studies, this review article suggests significant rtMS potentials in improving the complications of epilepsy. Our review also showed that the reported side effects of using this technique are not very common. Therefore, we can recommend further use of this technique as a promising tool in clinical research.

Keywords: Repetitive transcranial magnetic stimulation; rTMS; Epilepsy; Seizure

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Epilepsy and its traditional treatments

Epilepsy is a significant and universal neurological disease characterized by epileptic seizures (1, 2), in which affected individuals develop a wide range of chronic or long-term neurological symptoms. The crucial feature of epilepsy is recurrent and sometimes unexplained seizures, which can be short, mild, and imperceptible or sometimes cause the body to jerk and shake in a long-lasting manner (3). Depending on the type of epileptic seizures, epilepsy has been classified into three non-identical types: 1) Convulsive epilepsy with generalized seizures, which occurs in about 20% of cases, affects both hemispheres of the brain, and impairs consciousness. 2) Convulsive epilepsy with focal seizures is seen in roughly 40% of patients, in which not all of the brain is involved. Nevertheless, only certain areas or foci of the brain cause symptoms of epilepsy (it may lead to generalized seizures, though) (4), and 3) non-convulsive epilepsy, seen in another 40% of patients, manifests as a decrease in the level of consciousness and usually does not last more than a few seconds (5, 6). Several compelling reasons exist to argue that investing in research that leads to developing new treatments for epilepsy is crucial: First, epilepsy is the most common severe neurological disorder worldwide (7), severely affecting the life of one in twenty-six people during their lifetime (8). Accordingly, more than 65 million people worldwide (slightly less than 1% of the world's population) more or less struggle with it (9). Second, acceptingly, nearly80% of the patients live in low-and middle-income countries (3), which doubles the importance of exploring and developing new, practical, affordable, and inexpensive treatments.

Third, as epilepsy is more common in the elderly (10), unbelievably, the problems of the elderly multiply with epilepsy. Fourth, seizures occur in approximately one-third of patients with epilepsy that are medically incurable (11). Evidently, patients with drug-resistant epilepsy experience significant complications.

Although the exact mechanism of onset and spread of epilepsy is still unclear (12), in some circumstances, proposedly, epileptic seizures, which occur in some people due to brain damage, brain cancer, drug and alcohol abuse, and other causes, can originate in interactive thalamocortical systems or the brainstem (13).

Not all epilepsy syndromes are persistent, and most people recover to the point where they no longer need medication. Different disease management options may be on the table in drug-resistant cases, including following a specific diet, implanting a neurostimulator, or neurosurgery.

Transcranial magnetic stimulation

Over the last three decades, the study of transcranial magnetic stimulation (TMS) technique in treating patients with epilepsy has been increasingly considered by researchers and scientists. TMS is a non-invasive and tolerable method affecting the human motor cortex and stimulating and modulating the brain, in which small intracranial electrical currents are generated by inducing an extracranial solid magnetic field (14) (15).

The first modern device for magnetic stimulation of the brain was introduced in 1985 by Anthony T. Barker, Ian L. Freeston, and Reza Jalinous at the University of Sheffield (16). This technique sends a short-lasting alternating current through a stimulation coil to cause changes in a magnetic field. This variable magnetic field passes through the scalp and cerebrospinal fluid (CSF), causing a secondary electric current in conductive tissues, such as cortical neurons. Indeed, this secondary current produces neurobiological effects (17). TMS providers have successfully offered a non-invasive and safe way to activate the human motor cortex and assess the integrity of the central motor pathways, painless contrary to transcranial electrical stimulation (TES) (18).

TMS, which is theoretically based on Faraday's law of electromagnetic induction, is generally classified into three protocols: single-pulse TMS, paired-pulse TMS, and repetitive TMS (11).

rTMS and a promising future in controlling epileptic seizures

Repetitive transcranial magnetic stimulation, or its abbreviated form rTMS, is a state in which a train of TMS pulses of the same intensity is used in a specific area of the brain, and its frequency is a specific value that may vary from one stimulus per second to more than twenty (15). Although the first uses of the rTMS technique were limited to diagnosing neuromotor disorders, currently, one of the essential therapeutic potentials of this technique is its use to reduce cortical excitability as an alternative treatment for epileptic seizures.

In 2002, Health Canada approved the use of rTMS for treating treatment-resistant depression (this treatment is currently only available in Quebec and Saskatchewan, though). Subsequently, in 2008, the FDA approved several rTMS devices for treating mild, treatment-resistant depression (19).

At present, rTMS devices have become a structure in which various parameters, such as the ability to increase or decrease magnetic energy in cortical areas, can be precisely altered to treat various mental disorders in the best way.

Obviously, the neurobiological effects of rTMS on individuals have been different (14). These effects are also highly variable as a function of the frequency used, the stimulus number inside a train, the intensity of the stimulation, the type of coil, the coil's position, the stimulation's duration, and the like.

However, indicatively, high-frequency rTMS (abbreviated HF-rTMS;> 5 Hz) has facilitative effects on cortical excitability, and low-frequency rTMS (abbreviated LF-rTMS; ≤ 1 Hz) reduces cortical excitability (11).

In other words, low-frequency rTMS, applied for 15 to 30 minutes, inhibits neural activity and can reduce regional cortical excitability (20).

The effect of low-frequency rTMS is solid and long-lasting (21) (22) and can be applied to the motor cortex and other cortical areas to study the relationship between the brain and behavior.

Because the main pathophysiological features of epilepsy include disturbed networks resulting in cortical hyperexcitability, it is entirely defensible to support studies on reducing cortical excitability by rTMS as a potential alternative to existing treatments, primarily for treating refractory epilepsy and for epilepsy phenotypes that are not amenable to resection surgical treatments (23) (24).

Besides, the promising therapeutic potential exists for treating other neuropsychiatric disorders such as schizophrenia, Parkinson's disease, neuropathic pain, post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), borderline personality

disorder, major depression, bipolar disorder, and chronic pain (14) (15) (25).

rTMS and epileptic seizures: efficacy and adverse events

Numerous studies on the effect of rTMS on epileptic patients have reported a reduction in the seizures frequency and/or epileptic discharges (26) (27) (28) (29) (30) (31) (32) (33) (34).

Nevertheless, the efficiency of rTMS in reducing seizures is not well established. However, reports have shown that low-frequency rTMS can often drastically reduce seizures frequency and epileptic discharges, and some randomized clinical trials have shown no greater effect above control (35) (36)ndNote> (37).

This contradiction can be attributed to the heterogeneous nature of studies. In other words, one reason to justify the conflicting results of the studies may be that the patient populations studied differed in terms of the etiology of the disease.

Moreover, treatment parameters vary, such as stimulation intensity, frequency, duration, and the type of coil used. Seemingly, the abovementioned issues have led to heterogeneous results (19).

Notably, a study showed that multifocal epilepsy is more resistant to treatment with low-frequency rTMS (28).

Reportedly, several studies examined the therapeutic effects of rTMS on neocortical epilepsy that are better than mesial-temporal lobe epilepsy (37).

Probably because the mesial-temporal structure is farther from the brain's surface, making it harder for the magnetic field to reach (32).

Even though treating low-frequency rTMS is a reasonably low-risk clinical intervention, some side effects have been reported, the most common of which are transient headache, pain in the site of stimulation, muscle contraction, and transient tinnitus (38).

The rTMS activation of epileptic foci in patients with medically intractable complex partial seizures was reported (39), as well as seizure induction in healthy cases and patients with epilepsy (38) (40) (41).

However, Bae et al. reviewed thirty studies published from 1990 to 2007 involving 280 people and reported a crude per-subject seizure risk of 1.4%(40).

The present study aims to review the available data in the new millennium (2000–2021) to practically determine the effectiveness and adverse effects of the rTMS technique on epileptic people.

Materials & Methods

The primary purpose of this study was to conduct an up-to-date review of available data on the efficacy of rTMS in patients with epilepsy in the new millennium (2000–2021).

The present study carried out a comprehensive search of the articles indexed in the PubMed central database (PMC). These articles focused on the role of TMS in improving the condition of patients with various types of epilepsy. This search was done through the following query:

("Epilepsy"[mesh] OR epilep*[tiab] OR seizure*[tiab]) AND ("Transcranial Magnetic Stimulation"[mesh] OR Transcranial Magnetic Stimulation [tiab] OR rtms[tiab] OR repetitive tms[tiab] OR high frequency tms[tiab] OR low frequency tms[tiab])

Furthermore, according to the purpose of the present review article, the time of publication should be from 2000 to 2021. In the field of article type, randomized controlled trials, clinical trials, meta-analysis articles, and systematic reviews

were selected.

Apart from systematic reviews and meta-analysis articles, the researchers selected articles that met the following two criteria: 1) they reported original research, and 2) the title or content was more or less related to the effect of rTMS on the symptoms of people with epileptic seizures.

Results

The initial search consisted of 114 results. Twenty-seven articles (23.7%) remained eligible after exclusion based on title and abstract (Figure 1).

The selected articles included fourteen original research, eleven review articles, one brief communication, and one case study (Figure 2).

Content of included studies

In a double-blind sham-controlled study, Koren et al. (2001) examined the neuropsychological effects of the slow prefrontal rTMS at a frequency of one Hz in 46 healthy volunteers. They randomly categorized the volunteers into three groups: receive one session of right prefrontal, left prefrontal, and sham rTMS. All three groups showed significant improvements in processing speed and efficiency. Therefore, they concluded that a slow rTMS session at a frequency of one Hz does not interfere with neuropsychological function in healthy people (42).

Theodore et al. (2002) performed a controlled trial of transcranial magnetic stimulation on twenty-four patients with epilepsy and compared the frequency of weekly seizures for eight weeks before and after one week of one Hz TMS twice daily for 15 minutes. Twenty-four volunteers were randomly divided: 12 in the active group and 12 in the control group. No difference in the frequency of baseline weekly seizures was found between patients and controls. When comparing 8-week baseline and post-stimulation periods, although they observed a trend toward short-term seizure reduction in the active group, which was greater in patients with lateral than mesial temporal foci, none of these differences were significant. Finally, they concluded that the effect of TMS on the frequency of seizures was mild and short-lived, and in fact, this small controlled trial did not have a significant effect of TMS on partial or secondary generalized seizures. However, they eventually acknowledged that the controlled trial size was too small for the small effect observed, and they could not rule out the TMS possibility of a mild antiseizure effect (37).

Rossi et al. (2004) presented a case study on reducing cortical myoclonus-related epileptic activity due to low-frequency rTMS. In a drug-resistant epileptic patient, they recorded cortical jerk-related and electromyographic activity for 15 minutes before and after one Hz rTMS. In this case study, they claimed to have found in vivo evidence of the possibility of selectively modulating the activity of an epileptic focus by interfering with low-frequency local rTMS (43).

Kinoshita et al. (2005) investigated the effect of low-frequency rTMS (0.9 Hz) on seizure frequency in seven adults with medically intractable extratemporal lobe epilepsy (ETLE). The seven received two sets of 15-minute stimulation per day for five days a week. They compared the number of seizures two weeks before and one week after stimulation, indicating the frequency of seizures, complex partial seizures (CPSs), and simple partial seizures decreased by 19.1, 35.9, and 7.4%, respectively. They naturally concluded from this study that there is a favorable tendency to reduce seizures at two weeks after low-frequency rTMS in incurable ETLE patients. However, according

to the researchers in this study, this reduction in seizures was not statistically significant (34).

In a 2006 clinical trial conducted by Fregni et al., plasma valproate levels' hemostatic effects on corticospinal excitability changes due to transcranial magnetic stimulation at one Hz in patients with juvenile myoclonic epilepsy (JME) were investigated. In this study, in which 15 patients with JME and 12 healthy individuals of the same age participated, the effects of rTMS on corticospinal excitability in both high and low plasma valproate levels were evaluated. The results indicated that the effects of one Hz rTMS depended on plasma valproate levels. This finding is crucial because it is one of the few studies investigating the effects of rTMS in patients taking medications, affecting cortical excitability (44).

Fregni et al. (2006), in another study, examined the antiepileptic effects of rTMS in patients with refractory epilepsy and malformations of cortical development (MCD) in a randomized, double-blind, sham-controlled trial and achieved exciting results. They treated twenty-one patients with MCD and refractory epilepsy in five consecutive low-frequency rTMS sessions as a sham or active at one Hz. Then they compared the number of epileptiform discharges (EDs) on the electroencephalogram and the number of baseline clinical seizures over three periods: immediately after treatment, thirty days after treatment, and sixty days after treatment. They found that the number of seizures in the active group was significantly reduced compared to the sham group, and this effect lasted for at least two months. Correspondingly, a significant reduction in EDs was observed immediately after treatment and only in the active rTMS group at week four. Mild adverse effects were also observed, evenly distributed among the two groups. In this randomized controlled trial, they showed that 1) 5-day low-frequency active, but not sham, rTMS significantly reduced seizures in patients with MCD and pharmaco-resistant epilepsy, 2) Beneficial effects rTMS lasts approximately two months, 3) Active rTMS reduces the number of EDs observed on the EEG, 4) rTMS has mild adverse effects and is similar to active and sham treatments, 5) Contrary to some assumptions, the preliminary cognitive evaluation indicated that active rTMS does not worsen cognitive function, but rather, paradoxically, significantly improves Stroop performance, the subjective report of social interaction (31).

In a systematic review conducted by Machii et al. (2006), the literature and data were reviewed to assess the safety of rTMS in non-motor areas. They reviewed all published articles from January 1998 to December 2003 that used rTMS in non-motor areas for adverse effects and analyzed their studies' data. Specifically, they found that 1) Adverse effects were rare and mild, 2) Headache was the most common adverse effect, occurring in almost one in four subjects, and 3) More serious adverse effects such as seizures and psychotic symptoms were also infrequent(25).

In a clinical trial by Cantello et al. in 2007, forty-three patients with drug-resistant epilepsy underwent a randomized, double-blind, sham-controlled crossover study in which the clinical and EEG effects of slow rTMS (0.3 Hz) were evaluated. In the end, it was found that a 5-day cycle of 0.3 Hz rTMS, applied through a large circular coil at the vertex, was no different from placebo to reduce seizures. Nevertheless, slow rTMS significantly reduced interictal EEG epileptic abnormalities in one-third of patients. The researchers also rated rTMS technology as safe and well-tolerated (35).

In another clinical trial by Joo et al. In 2007, the antiepileptic effect of low-frequency rTMS was evaluated in patients with intractable epilepsy. Treatment with low-frequency rTMS (0.5 Hz) was performed for five days with thirty-one participants, and as a result, the frequency of complex partial seizures (CPS) with or without secondarily generalized seizures was reduced by nearly 14%, a statistically non-significant decrease. They also found that patients with epilepsy who received focal stimulation to the epileptic focus may have better treatment outcomes than those who received non-focal stimulation. Correspondingly, they suggested that administering more pulse per rTMS session might be effective. Although these findings failed to achieve significance, the study found that interictal spikes were significantly reduced by rTMS, which the researchers claim provides hope that rTMS could be a potential alternative treatment to intractable epilepsy (45).

In a 2008 clinical trial by Santiago-Rodríguez et al., the number of seizures and interictal epileptiform discharges (IEDs) in patients with focal neocortical epilepsy before, during, and after rTMS (0.5 Hz) were evaluated and compared. The average frequency of seizures, 2.25 times per week during the baseline period, decreased to 0.66 per week during the intervention period, indicating a more than 70% decrease. During the follow-up period, the average frequency of seizures was 1.14 per week, which meant a reduction of 50%. However, although there was a tendency to show a decrease in the frequency of IEDs, the differences were not significant, apparently due to the small sample size. In a nutshell, they concluded that two weeks of rTMS at 0.5 Hz with a figure-of-eight coil placed over the epileptic focus reduced the number of seizures in patients with focal epilepsy without significantly reducing the IEDs (46).

Rotenberg et al., in a 2009 clinical trial, examined the nature and severity of seizures that may be induced by low-frequency rTMS in patients with epilepsy. They subjected five patients with intractable epilepsy with a mean seizure frequency of more than one per day to low-frequency (1 Hz) rTMS. Unlike high-frequency (5 Hz) rTMS, in which seizures have resulted of a different origin from the patient's typical seizures (Reference 9), they reported that in the case of low-frequency rTMS, the in-session seizure was typical in semiology to the patient's habitual seizures, and the duration of each seizure was either similar or even shorter than the patients' baseline seizures (47).

In 2011, Hsu et al. conducted a meta-analysis to evaluate the antiepileptic effect of low-frequency transcranial magnetic stimulation on medically intractable epilepsy. They reviewed eleven articles involving a total of 164 participants and found that low-frequency rTMS had a beneficial effect on seizure reduction, and this positive effect is especially evident in patients with neocortical epilepsy or cortical dysplasia (33).

In another clinical trial conducted in 2011 by Sun et al., 17 refractory partial epilepsy patients were evaluated in an open-label study to evaluate the antiepileptic effect of rTMS. Patients were treated with low-frequency rTMS (0.5 Hz) for two weeks and three sessions daily. Indicators such as frequency of seizures, seizure days, and epileptic discharges in the EEG were measured and compared before, during, and after stimulation. The research team finally concluded that 1) The mean seizure days per week and the mean seizure frequencies per week in the rTMS treatment period significantly decreased compared to the pre-

treatment period, 2) The mean epileptic discharges in the EEG during the treatment period compared to the pre-treatment period decreased significantly in all 17 patients, and 3) The scales of the Global Severity Index, Depression, Anxiety, Paranoid Ideation, Obsession-compulsion, and the like, also decreased in patients based on the test of Symptom Checklist-90 (SCL-90). Therefore, they concluded that low-frequency rTMS could have a significant antiepileptic effect in patients with refractory partial epilepsy and even improve their mental status (48).

Sun et al. (2012) designed a randomized, single-blind, controlled clinical trial in sixty-four patients to evaluate the therapeutic effect of rTMS (0.5 Hz) on patients with refractory partial epilepsy. They randomly divided patients into two groups based on the intensity of stimulation: the first group, 90%, and the second group, 20% of resting motor threshold (rMT). In the high-intensity rTMS group (90% rMT), following two weeks of treatment, the seizure level and interictal epilepsy discharges were significantly reduced compared to the baseline level, and the scales of Symptom Checklist-90 were significantly improved. Seizures and spikes in the follow-up period in patients who received low-intensity rTMS (20% rMT) did not significantly differ from baseline data. This clinical trial had several distinct results: 1) High-intensity or low-intensity seizure stimulation yielded different results, so the mean seizure frequency decreased by 79.8% in high-intensity rTMS, while this number was about 2.3% in low-intensity rTMS. 2) In a significant proportion of subjects (22.6%), interictal discharges were abolished entirely at the end of follow-up. 3) rTMS was safe and tolerable, and no severe adverse effects of rTMS were found in these patients. 4) Focal rTMS can induce long-lasting off-line antiepileptic effects for approximately two months after treatment. 5) Finally, high-intensity stimuli significantly improve patients' mental states (32).

In a systematic literature review and meta-analysis published in 2012 by Muller et al., the safety of stimulation of potentially hyperexcitable cortex was assessed. In this study, 106 publications (1815 subjects) were identified with patients undergoing rTMS for pathologic positive sensory phenomena, and it was found that rTMS-related adverse events were generally mild and were seen in 16.7% of subjects. Seizures and aggravation of sensory phenomena were more serious adverse events with a risk of occurrence of about 0.16% and 1.54%, respectively. They also noted that the risk of seizures during rTMS is significantly higher for patients with epilepsy. However, they generally concluded that rTMS could be considered a safe and tolerable method (49).

In a 2013 clinical trial of 44 participants, Fuggetta et al. performed rTMS at different frequencies (1 Hz, 5 Hz, and 10 Hz) and used surface electroencephalography (EEG) to quantify the cortical oscillatory activity post-rTMS. They found that high-frequency rTMS (10 Hz) produced a transient synchronous activity for delta (δ) and theta (θ) rhythms, thus mimicking pathological oscillations similar to thalamocortical dysrhythmia (TCD). Furthermore, in contrast, rTMS one and five Hz have the opposite effect of synchronizing low-frequency brain rhythms (50).

Seynaeve et al. In a randomized crossover sham-controlled clinical trial in 2016, the efficacy and side effects of low-frequency transcranial magnetic stimulation for the treatment of refractory neocortical epilepsy were examined, and the effect differences between figure-8 and round coil were

evaluated. Eleven patients were randomized for the order in which the figure-8, round, and sham coil were used. The results were not promising: In addition to finding that no difference was between figure-8 and the round coil, they found that none of the patients achieved a 50% reduction in seizures, one patient within one month of treatment with both the active coil responded, followed by a significant increase in seizure frequency. In another patient, seizure frequency was even quadrupled during rTMS treatment. They concluded that rTMS could exacerbate seizures during treatment and increase seizure frequency after initial reduction (36).

Lage et al. (2016) found that although there is data that supports the positive effect of fast rTMS (≥10 Hz) on cognitive functioning, there is no such research in the field of slow rTMS (≤1 Hz). Thus, in 2016, they conducted a systematic review of randomized controlled trials to investigate the effects of low-frequency rTMS on cognition. After reviewing twenty records that met the inclusion criteria, they concluded that the data supported the overall safety of rTMS without adverse effects on cognitive functioning. Although some data have been found to indicate that rTMS may have the potential for cognitive enhancement, according to them, these data are insufficient for any firm conclusions (51).

Pereira et al. (2016) performed a systematic review of studies published from January 1990 to August 2015 that examined the safety and tolerance of rTMS in patients with epilepsy. As a result, it was found that among the studies that reported the presence or absence of adverse events, in 18.3% of cases, adverse events were observed, in 85% of which these adverse events were mild. Headache or dizziness was the most common adverse effect observed at 8.9%. The crude per-subject seizure risk was 2.9% as the most severe adverse event. As a result, they evaluated that the risk of seizures induced by rTMS in patients with epilepsy is small and also assessed the risk of other adverse effects similar to rTMS in other conditions or healthy individuals (11).

In a systematic review in 2017, Cooper et al. evaluated real-world evidence for the use of low-frequency (≤1 Hz) transcranial magnetic stimulation in treating drug-resistant epilepsy. Their study found: 1) Studies with a mean age ≤21 years and using targeted stimulation had a greater rate of seizure reduction than those with a mean age >21 years and no use of targeted stimulation. 2) Low-frequency rTMS using figure-8 coil may be an effective treatment for drug-resistant epilepsy in pediatric patients. Based on these results, they finally suggested that given the efficacy, cost-effectiveness, and relative safety of rTMS, this method be used as a treatment option, albeit exclusively in clinical trials (19).

In a literature search through PubMed published in 2017 by Allen et al., all TMS studies on children from 1985 to 2016 were reviewed, and any adverse events were documented. They concluded that the risk of TMS in children is similar to that in adults and recommended that TMS users in the pediatric age group follow the same adult safety guidelines until sufficient information is available for pediatric-specific guidelines (52).

In a systematic review in 2018, Boon et al. reviewed the clinical evidence of the effectiveness and safety of a variety of neurostimulation techniques in treating patients with drug-resistant epilepsy (DRE). Specifically, about TMS, they concluded in their study that there was not sufficient data to support its effectiveness in treating DRE yet (53).

In a 2020 clinical trial performed by Bender Pape

et al., they aimed to use transcranial magnetic stimulation as a treatment for coma recovery in people with severe traumatic brain injury; thirty participants underwent thirty rTMS sessions. In this study, apart from seventy-five non-serious adverse events, one case was observed with a severe adverse event, including seizures (54).

In a 2020 clinical trial of 14 right-handed children with benign epilepsy with centrotemporal spikes, Baumer et al. found that transcranial magnetic stimulation is safe and feasible for children with benign epilepsy with centrotemporal spikes (55).

In a 2021 systematic review on the effect of various neuromodulation techniques on suicidality, Kucuker et al. found that several studies reported a link between rTMS and improvements in suicidal ideation. Specifically, they found that in 12 studies, suicide was the primary outcome, ten of which significantly improved suicidal ideation (56).

In a systematic review of 2021 by Chen et al. aimed at the effects of seizure therapies and noninvasive brain stimulation on suicidality, nine specific records of rTMS were scrutinized, and as a result, they found inconsistencies in determining the anti-suicidal effect of rTMS. Accordingly, they ultimately failed to support the anti-suicidal effect of rTMS (57).

In a systematic review of 2021, Walton et al. assessed the evidence for the use of TMS in people with drug-resistant epilepsy compared to other available treatments. They searched the Cochrane Register of Studies (CRS Web) and MEDLINE (Ovid 1946 to June 2, 2020) and, after analyzing eight studies, found that two studies showed a statistically significant reduction in seizures relative to baseline, while the other six studies did not show a statistically significant difference in the frequency of seizures after rTMS compared with the control group. Adverse effects were assessed uncommonly in studies, which mainly included headache, dizziness, and tinnitus. However, an increase in seizures also occurred in a small number of people, which is a notable issue (58).

The results of the articles reviewed are summarized in Table 1, and the results of other articles are summarized in Table 2.

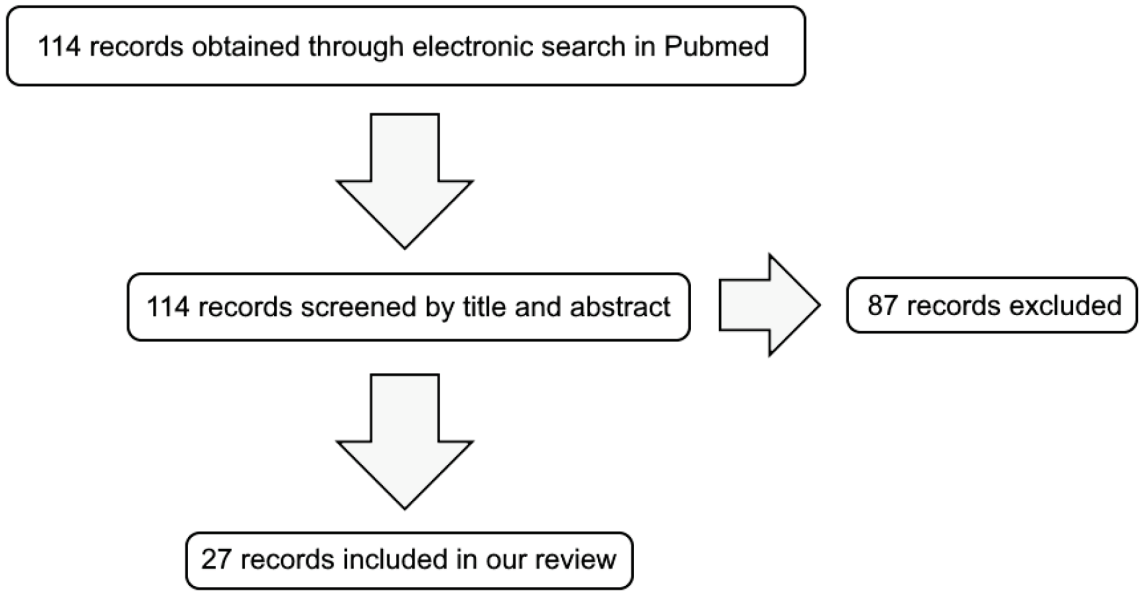

Figure 1. *Flow diagram that shows how the articles are selected*

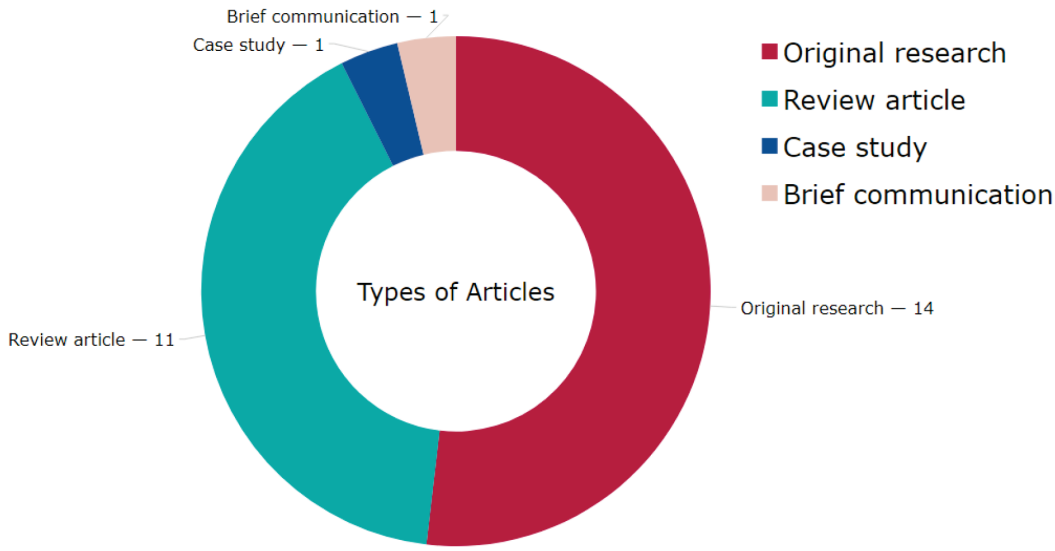

Figure 2. *Selected articles by type*

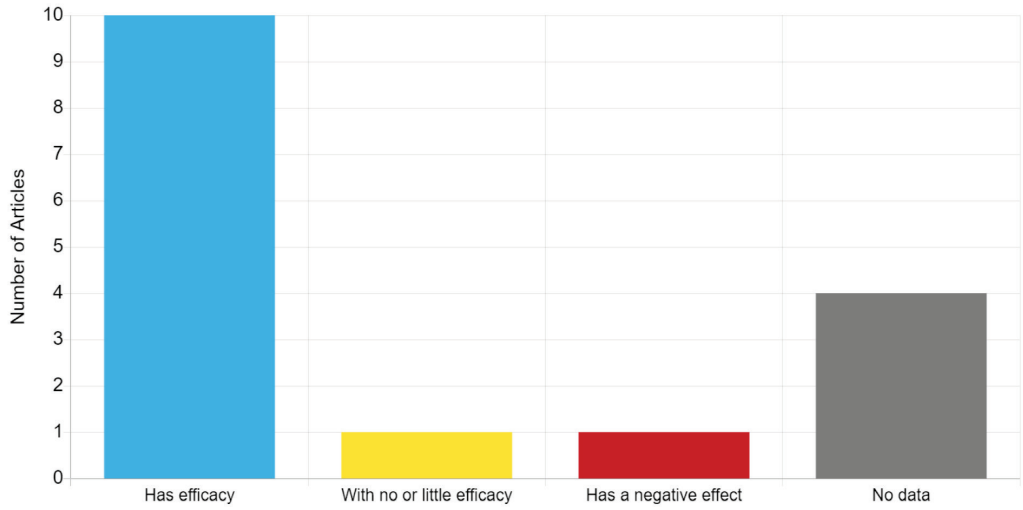

Figure 3. *Non-review articles by effectiveness*

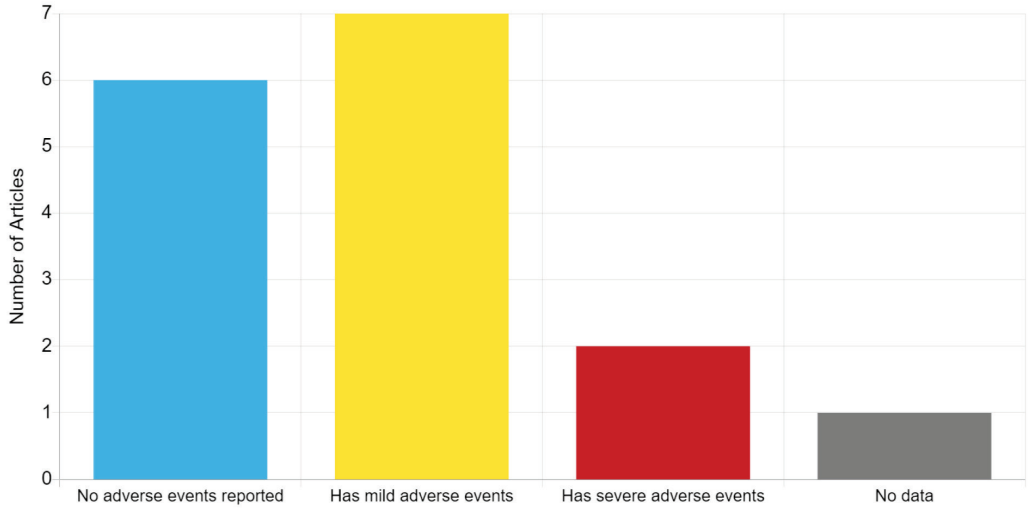

Figure 4. *Non-review articles by adverse events*

Table 1. A summary of the results of the review articles (In some cases, the result is quoted directly from the target article).

Authors	Records	Efficacy	Adverse Events (AEs)
Machii et al. (2006)	A review article on articles published from January 1998 to December 2003 that applied rTMS to non-motor areas [rTMS]	No data	— Infrequent and mild AEs — Headache as the most common AE — More serious AEs: seizures and psychotic symptoms induced by rTMS in patients with depression
Hsu et al. (2011)	A meta-analysis on articles published from 1990 to 2010 [LF-rTMS]	— Low frequency rTMS has a favorable effect on seizure reduction (particularly in patients with neocortical epilepsy or cortical dysplasia).	No data
Muller et al. (2012)	A review on literature search from January 1985 to April 2011 with patients undergoing rTMS for pathologic positive sensory phenomena [rTMS]	— The published data suggest rTMS for the treatment or diagnosis of pathologic positive sensory phenomena appears to be a relatively safe and well-tolerated procedure.	— Adverse events associated with rTMS were generally mild. — Seizure was the most serious adverse event. — The second most severe adverse event involved aggravation of sensory phenomena.
Cooper et al. (2017)	A meta-analysis that searched PubMed, Medline, etc. [≤ 1 Hz rTMS]	— Real-world evidence suggests that low-frequency rTMS using a figure-8 coil may be an effective therapy for the treatment of drug-resistant epilepsy in pediatric patients.	— Between 17% and 23% of participants reported AEs. — AEs: headache (most common), fatigue, dizziness, hearing loss/tinnitus, difficulty sleeping, and tremor. — Serious AEs: seizure during stimulation and an increase in seizure frequency following stimulation protocol.
Allen et al. (2017)	A systematic review included 23 rTMS studies involving children with CNS disorders, and epileptic children (EP) [rTMS]	No data	— We report 23 rTMS studies involving 230 CNS and 24 EP with AE rates of 3.78% and 0.0% respectively.
Boon et al. (2018)	A systematic search in the MEDLINE database [TMS]	No data	— TMS appears well tolerated, with no severe adverse events reported.
Kucuker et al. (2021)	A systematic review of the literature from 1940 to 2020 [10 Hz rTMS]	— Most rTMS studies showed a significant decrease of suicidal ideation.	No data
Chen et al. (2021)	A systematic review of the literature in the PubMed, EMBASE, etc. [HF-rTMS]	— Statistically significant effects of active rTMS on suicidal ideation were reported in four different studies. — Five studies revealed a beneficial, but nonsignificant effect, of active rTMS on suicidality over sham. — some others failed to report any superiority of active rTMS over sham.	No data
Walton et al. (2021)	An intervention review in the Cochrane Register of Studies and MEDLINE [LF-rTMS]	— Two studies analysed showed a statistically significant reduction in seizure rate from baseline, one study showed improvement in quality of life scores with active treatments compared to the sham treatment, six studies showed no statistically significant diference in seizure frequency following rTMS treatment compared with controls, three studies showed a statistically significant reduction in discharges afer active rTMS treatment.	— AEs were uncommon in the studies. — AEs typically involved headache, dizziness, and tinnitus. — Increased seizure frequency did occur in a small number of individuals.

Table 2. A summary of the results of the case study, brief communication, and original researches (In some cases, the result is quoted directly from the target article).

Authors	Patient(s)	Efficacy	Adverse Events (AEs)
Koren et al. (2001)	A double-blind sham-controlled study on forty-six normal volunteers [1 Hz rTMS]	— A signifcant improvement over time in processing speed (reaction time) and effciency (correct responses per unit of time).	— A single session of slow rTMS does not interfere with neurospychological functioning in normal volunteers, supporting clinical reports of no adverse cognitive effects.
Theodore et al. (2002)	A controlled study on twenty-four patients with localization-related epilepsy [1 Hz rTMS]	— The effect of TMS on seizure frequency was mild and short lived.	— One patient reported mild discomfort during stimulation.
Rossi et al. (2004)	A case study on a drug-resistant epilepsy patient with continuous forearm/hand positive myoclonia due to a focal cortical dysplasia of the right motor cortex [1 Hz rTMS]	— The result represents in vivo evidence of the possibility to selectively modulate the activity of an epileptic focus by intervening with local low-frequency rTMS.	— The patient reported neither side effects due to stimulation nor changes in myoclonia perception.
Kinoshita et al. (2005)	A pilot study on seven patients with medically intractable extratemporal lobe epilepsy (ETLE) [0.9 Hz rTMS]	— The frequency of all seizure types, complex partial seizures (CPSs) and simple partial seizures was reduced.	— During rTMS, two patients complained of headache in the region attached to the TMS coil. — No convulsive seizure was induced by TMS in this study.
Fregni et al. (2006)	A clinical trial on fifteen patients with juvenile myoclonic epilepsy (JME), and 12 age-matched healthy subjects [1 Hz rTMS]	— In patients with chronic use of valproate and low-plasma concentrations, 1 Hz rTMS had a similar significant inhibitory effect on corticospinal excitability as in healthy subjects. — In the same patients when the serum valproate concentration was high, 1 Hz rTMS increased the corticospinal excitability significantly.	No data
Fregni et al. (2006)	A randomized clinical trial on twenty-one patients with malformations of cortical development and refractory epilepsy [1 Hz rTMS]	— rTMS significantly decreased the number of seizures in the active compared with sham rTMS group, and this effect lasted for at least 2 months. — There was a significant decrease in the number of epileptiform discharges in the active rTMS group only.	— There were few mild adverse effects.
Cantello et al. (2007)	A randomized, double- blind, sham-controlled, crossover study on forty-three patients with drug-resistant epilepsy (DRE) [0.3 Hz rTMS]	— Active rTMS was no better than placebo for seizure reduction. — It decreased interictal EEG epileptiform abnormalities significantly in one-third of the patients.	— No increase in the weekly seizures occurred after treatment. — A minority complained of dizziness or headache associated with the "active" or "sham" rTMS cycle, with no significant difference. — No major or consistent side effects were reported.
Joo et al. (2007)	A clinical trial on 35 patients with localization-related epilepsy [0.5 Hz rTMS]	— Mean weekly seizure frequency was non-significantly decreased after rTMS. — Interictal spikes significantly decreased after rTMS and they totally disappeared in 6 patients.	— Without serious side effects. — Five patients complained of a mild and transient headache during and immediately after rTMS.
Santiago-Rodríguez et al. (2008)	A clinical trial on twelve patients (seven men and five women) [0.5 Hz rTMS]	— Decreases the number of seizures in patients with focal epilepsy, without reduction in interictal epileptiform discharges (IEDs).	— One patient complained of headache after rTMS, other showed a light rest tremor in the hands at the end of the first week of rTMS treatment, which disappeared to the end of the rTMS period.
Rotenberg et al. (2009)	A brief communication about five patients with intractable epilepsy and average seizure frequency greater than one per day [1 Hz rTMS]	No data	— Seizure exacerbation or secondary generalization was not identified after rTMS. — In each instance the in-session seizure was typical in semiology to the patient's habitual seizures —— The duration of each documented in-session seizure was either the same as or shorter than the patients' baseline seizures.

Table 2 Continued. A summary of the results of the case study, brief communication, and original researches (In some cases, the result is quoted directly from the target article).

Authors	Patient(s)	Efficacy	Adverse Events (AEs)
Sun et al. (2011)	An open-label study on seventeen refractory partial epilepsy patients [0.5 Hz rTMS]	— Mean seizure frequencies per week significantly decreased in the following 4-week rTMS treatment period compared with the pretreatment period — Mean seizure days per week during the treatment period and the post-treatment period were lower than that of the pre-treatment period — Mean epileptic discharges in the EEG decreased significantly during the treatment period compared to that of the pre-treatment period. — The scales of Global Severity Index, Depression, Anxiety, Phobic anxiety, Paranoid ideation, Psychoticism, Somatization, Obsession-compulsion, Interpersonal sensitivity, Hostility in patients decreased at the post-treatment periods compared with those of the pre-treatment periods.	— No adverse event of rTMS was found.
Sun et al. (2012)	A controlled clinical study on sixty-four patients with refractory focal epilepsy [LF-rTMS]	— Low-frequency high intensity rTMS delivered into the epileptogenic zone had a significant antiepileptic effect on patients with refractory partial seizures. — rTMS treatment can also reduce the interictal epileptic discharge frequency and improve the psychological condition of these patients.	— The most common adverse events were mild or moderate headache and tinnitus. — The majority of patients tolerated rTMS treatment well.
Fuggetta et al. (2013)	A sham-controlled study on forty-four healthy volunteers (19 males, 25 females) with no reported neurological history [1 Hz, 5 Hz, and 10 Hz rTMS]	— high-frequency rTMS (10 Hz) induces a transient synchronised activity for delta (δ) and theta (θ) rhythms thus mimicking the pathological TCD-like oscillations. In contrast, rTMS 1 and 5 Hz have the opposite outcome of desynchronising low-frequency brain rhythms.	— No adverse side effects were reported by any of the participants during all experimental conditions.
Seynaeve et al. (2016)	A single-center randomized sham-controlled crossover trial on 11 patients with well-defined focal epilepsy [0.5 Hz rTMS]	— This study provides evidence that rTMS is on average not effective for reducing seizure frequency.	— Has negative effect on seizure frequency. — AEs were minor according to the patients (except in one patient in whom the headache started within minutes of active treatment). — Other AEs: hearing problems after stimulation, headache, fatigue, difficulties concentrating.
Bender Pape et al. (2020)	A clinical trial on seven persons in states of disordered consciousness (DoC) after severe traumatic brain injury (sTBI) [rTMS]	No data	— 75 nonserious AEs and one serious AE (seizure).
Baumer et al. (2020)	A clinical trial on 14 right-handed children with benign epilepsy with centrotemporal spikes [1 Hz rTMS]	No data	— TMS is safe and feasible for children with benign epilepsy with centrotemporal spikes.

Discussion

Studies in the present century continue to support rTMS as a tolerable and low-risk technique that has the potential to reduce cortical excitability and reduce epileptic seizures. However, notably, due to the controversy over the effectiveness of rTMS in some studies, it is too early to consider rTMS as a proven treatment for improving the health status of epileptic patients. The included non-review studies (a total of 16 articles) on the effectiveness of rTMS can be divided into four categories:

1. Studies that are in the majority and show promising therapeutic effects (10 articles, 62.5%).
2. One study (6.25%) has not found a significant therapeutic effect of rTMS.
3. One study (6.25%) has not only seen the potential for treatment but also found rTMS to be a factor in exacerbating the patient's symptoms.
4. Studies that essentially have not investigated any efficacy for rTMS (these articles focused on adverse events) (4 articles, 25%). (Figure 3)

Regarding adverse events, the present review showed that in the non-review studies that investigated the presence or absence of adverse events (15 articles, 93.75%), either no reported adverse events (6 articles, 40%) or the reported adverse events were mild and tolerable (7 articles, 46.67%). However, severe adverse events were reported in some cases (2 articles, 13.33%) (Figure 4).

Accordingly, apart from the controversial effects of rTMS on reducing epileptic seizures, the review of recent 21-year studies shows that many promising results have also been observed with rTMS. For instance, as we have seen, it does not interfere with neuropsychological function in healthy people, does not worsen cognitive function, and even improves Stroop performance. In addition, it rarely has severe side effects such as seizures and psychotic symptoms; it can reduce interictal epileptic abnormalities; it has a low risk in children as adults; it has the potential for improving suicidal ideation.

Finally, we recommend further studies in the following areas: the effects of exact frequency, type of coil, the intensity of the stimulation on rTMS performance, the effect of magnetic field focus and penetration depth quantity, the effect of focusing on the underlying layers of the cerebral cortex, the effect of medications that affect cortical excitability on rTMS effects (for example, low or high plasma valproate levels), comparison of the effectiveness of focal stimulation to the epileptic focus and non-focal stimulation, the effect of epilepsy type on rTMS function, the effect of patient age, the long-lasting off-line antiepileptic effects of rTMS in controlling epileptic seizures, and finally the anti-suicidal effects of rTMS.

Limitations of study

Notably, the substantial limitation of the current research is its restriction to the articles indexed in the PMC; therefore, possibly, compelling articles conducted in the field of rTMS effect on epilepsy patients have been ignored in the current review.

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Author's contribution

H.T. conceived of the presented idea and supervised the findings of this work. A.H. searched for relevant articles and edited the manuscript. All authors discussed the results and contributed to the final manuscript.

Conflict of interest

None declared.

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