Clinical Pain Research

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Impact of antidepressant medication on the analgetic effect of repetitive transcranial magnetic stimulation treatment of neuropathic pain. Preliminary findings from a registry study

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Abstract

Objectives: Repetitive transcranial magnetic stimulation (rTMS) has been found to be effective in chronic neuropathic pain conditions. However, information about the combined effects of rTMS and antidepressant treatment is scarce. We studied the outcome of rTMS and concurrent antidepressant treatment in patients with neuropathic pain.

Methods: In this retrospective, real-world study, 34 patients with neuropathic pain, who were considered resistant or not benefitting from conventional treatment, received rTMS treatment between 2017 and 2020. Pain-related factors were measured using the Numerical Rating Scale (NRS), Global Impression of Change (GIC), and Beck Depression Inventory.

Results: A decrease in pain intensity and pain interference assessed with NRS was observed after 10 treatment sessions in 16 patients. The impression of change was positive in 20 patients. Half of the patients (n=17) used antidepressant medication, while half (n=17) did not. A concurrent use of antidepressants with therapeutic rTMS was significantly linked with less pain intensity relief when compared with the nonuse of antidepressants (p=0.019). The impression of change was significantly in favor of the antidepressant nonuser group (p=0.002). No group differences in pain interference were found between the groups.

Conclusions: Therapeutic rTMS for neuropathic pain is plausibly sensitive to interference with antidepressant medication. The exact mechanism of our findings remains to be elucidated; confirmatory studies are warranted.

Keywords: antidepressant; neuromodulation; neuropathic pain; pain intensity; pain interference; repetitive transcranial magnetic stimulation; treatment

Introduction

Neuropathic pain is considered difficult to treat. Major factor impacting outcomes is the presence of comorbidities such as poor sleep, depressed mood, and anxiety [1, 2]. In addition, the negative impact of neuropathic pain is higher in patients with greater pain severity [3].

Level-A evidence has been suggested for the analgesic effect of high-frequency (HF) rTMS of the primary motor cortex (M1) contralateral to the experienced neuropathic pain [4]. However, according to Gatzinsky et al. [5] the effect is transient and shows a great heterogeneity between studies. Further, a recent meta-analysis indicates that stimulation frequency, intervention site, and location of lesion were important factors affecting the therapeutic effect [6]. In rTMS treatment, focal cortical areas and connected large-scale neuronal networks are noninvasively stimulated [7]. Low-frequency (LF) (<1 Hz) repetitive TMS (rTMS) reduces neuronal excitability, whereas HF (>5 Hz) rTMS increases cortical excitability [8].

Pharmacological treatments that affect the central nervous system may aid in reducing pain intensity in neuropathic pain conditions psychotropic medications exert

There are no previous presentations of the study data at scientific meetings.

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significant effects on cortical excitability and plasticity, but the effects of drugs vary substantially across medication classes and may have differential consequences for clinical response to rTMS [9]. According to systematic reviews, the analgesic efficacy of tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitors, pregabalin, and gabapentin has been demonstrated [10, 11].

Antidepressants are effective in both neuropathic and non-neuropathic pain and have diverse mechanisms that are independent of their antidepressant effects [12]. The mechanism behind the analgesic effect of antidepressants is thought to involve their enhancement of the activity of norepinephrine and serotonin in the descending pain modulation pathways of the spinal cord [12]. Patients with chronic pain without depression have experienced significant pain reduction with tricyclic antidepressant drugs, suggesting an independent analgesic effect for antidepressants [13, 14]. The results of the efficacy of the analgesic effects of dual serotonin norepinephrine reuptake inhibitors (SNRI) and selective serotonin reuptake inhibitors (SSRI) are more limited and inconsistent [15].

The concomitant effects of rTMS treatment and use of central nervous system (CNS) active drug therapy comprise uncertainties. CNS active drugs may have an impact on cortical excitability when using rTMS. Motor threshold, motor evoked potential size, motor evoked potential intensity curves, cortical silent period, short-interval intracortical inhibition, intracortical facilitation, short-interval intracortical facilitation, long-interval intracortical inhibition, and short latency afferent inhibition represent possible drug effects on cortical excitability [16].

Aims of the study

Most neuropathic pain patients attending rTMS treatment use antidepressant medication, but the knowledge about the impact of drug therapy on the efficacy of rTMS when it comes to pain outcomes is insufficient. The aim of this retrospective, real-world study was to explore how the use of antidepressant medication affects the analgesic effect of rTMS treatment in patients with neuropathic pain. To the best of our knowledge, this topic has not been addressed in the literature.

Methods

Patients

A total of 34 patients, with a mean age 49.5 years (range 17–82), with neuropathic pain were enrolled in this retrospective, real-world study. Neuropathic pain was classified, based on medical notes, by an experienced neurologist, into two categories: possible/probable (n=21) and definite (n=13), according to the criteria presented by Finnerup et al. [17], Table 1.

Table 1: Demographic characteristics and clinical data of the patients (n=34) at baseline.

Measures	Use of antidepressant		p-Value
	No n=17	Yes n=17	
Women, n (%)	13 (76)	14 (82)	0.67
Age, mean (SD)	51 (18)	48 (21)	0.61
BMI, mean (SD)	26.2 (6.9)	28.3 (3.9)	0.30
BDI at baseline, mean (SD)	18.1 (11.9)	11.5 (8.5)	0.090
Working or studying, n (%)	11 (65)	11 (65)	1.00
Smoking, n (%)	4 (24)	3 (18)	0.67
AUDIT-C, mean (SD)	1.4 (1.3)	1.4 (1.7)	0.99
Pain medication, n (%)			
NSAID	3 (18)	1 (6)	0.60
Paracetamol	5 (29)	6 (35)	0.71
Opiates	7 (41)	3 (18)	0.26
Mild	4 (24)	1 (6)	
Intermediate	1 (6)	2 (12)	
Strong	2 (12)	0 (0)	
Gabapentinoids	5 (29)	5 (29)	1.00
Comorbidity, n (%)			
Cardio circulatory disease	1 (6)	4 (24)	0.34
Psychiatric disorder	0 (0)	2 (12)	0.48
Diabetes mellitus	2 (12)	1 (6)	0.69
Neurologic disturbances	0 (0)	2 (12)	0.48
Neuropathic pain n (%), fulfilling the criteria			0.077
Possible or probable	8 (47)	13 (76)	
Definite	9 (53)	4 (24)	
Major diagnostic group, n (%)			
Diseases of the nervous system	5 (29)	5 (29)	
Musculoskeletal disorders	6 (35)	3 (18)	
Genitourinary system disorders	2 (12)	3 (18)	
Other symptoms and signs	4 (24)	6 (35)	
NRS (0–10), mean (SD)			
Intensity	5.41 (2.24)	4.94 (3.42)	0.64
Interference	5.06 (2.86)	5.75 (3.64)	0.55
RMT, median (IQR)	56 (52,62)	54 (50,67)	0.79

NRS, numerical rating scale; BDI, beck depression inventory; RMT, resting motor threshold; AUDIT-c, alcohol use disorders identification test, version C; IQR, interquartile range. ICD codes for major diagnostic groups: diseases of the nervous system G00-G99, Musculoskeletal disorders M00-M99, Genitourinary system disorders N00-N99, Other symptoms and signs (F00-F99, I00-I99, R00-R99, S00-S99).

The rTMS treatment was performed between 2017 and 2020. Exclusion criteria were recent cerebrovascular events (<6 months), cardiac pacemakers, inner ear transplants, medical pumps, and metallic clips or bodies in the head region. Epilepsy and bipolar disorder were considered relative exclusion criteria.

Drug consumption at the beginning of the treatment was evaluated and registered. Medication was classified using the Anatomical Therapeutic Chemical (ATC) Classification System (https://www.who.int/tools/atc-ddd-toolkit/atc-classification). The patients were divided into two groups based on their use of antidepressants.

Navigation of the rTMS treatment was performed using the Visor2 navigation system (ANT Neuro, Berlin, Germany) and stimulated with a Magstim Rapid2 stimulator (Magstim Co., Whitland, Wales, UK), here using an air-cooled figure-eight coil that gives biphasic pulses. Prior to treatment, head magnetic resonance imaging (MRI) was conducted for all patients with a 1.5-T Siemens Aera (Siemens, Erlangen, Germany) with a T1-weighted, three-dimensional sequence. The resting motor threshold (RMT) was determined, as recommended by the International Federation of Clinical Neurophysiology [18]. Motor evoked potentials (MEPs) were recorded either from the left-hand or right-hand thenar muscles, here by considering the location of the pain and injuries. MEP response was defined as a MEP with a peak-to-peak amplitude of >50 μV. The maximum-likelihood threshold-tracking algorithm [19] was used to determine TMS intensity, which yielded a 50 % probability of evoking an MEP [20].

The rTMS schedule was based on evidence-based guidelines for treating neuropathic pain using HF (10 Hz) rTMS [4]. Patients received navigated rTMS over 10 consecutive (Mon-Fri) days in daily 35-min sessions, during which 1,500 pulses were given to the M1 motor cortex at location corresponding to the pain area of each patient. According to the clinical protocol, patients who did not show benefit in questionnaires (n=16) after five treatment sessions, received additional 750 pulses to the secondary somatosensory cortex (SII), which has been shown to be a promising novel target for treatment of drug-resistance pain [21]. Thus, in total, either 1,500 or 2,250 pulses were delivered at trains of 10 Hz for 5 s with 26-s intertrain intervals at a maximum intensity of 90–110 % of the RMT, here depending on the stimulation area. Thirty-one patients received 10 full sessions. The patients used ear plugs during the stimulation.

Behavioral measurements

Patients were evaluated at baseline, after fifth and immediately after tenth treatment sessions, using questionnaires concerning pain intensity, pain interference, and impression of change. Depressive symptoms were measured at baseline and immediately after 10th treatment sessions.

The Numerical Rating Scale (NRS) was used to evaluate the pain intensity and interference of the patients. The NRS ranges from 0 to 10, with 0 being “no pain” and 10 being “the worst pain imaginable.” For general purposes, the Numerical Rating Scale has good sensitivity and generates data that can be statistically analyzed for audit purposes [22]. A 2-point change on the NRS represents a clinically meaningful change that exceeds the bounds of measurement error [23].

The Global Impression of Change (GIC) scale was used to identify clinically significant subjective changes in the pain condition of the patients [24]. The patients were evaluated on GIC after 5 and 10 treatment sessions. The GIC comprises two companion one-item measures evaluating the following: (a) severity of psychopathology from 1 to 7 and (b) change from the initiation of treatment on a similar 7-point scale. The GIC consists of a 7-point scale ranging from “very much worse” via “no change” to “very much better.” It also measures the patient’s global functioning prior to and after initiating a treatment.

Depressive symptoms were measured using the 21-item Beck Depression Inventory, version II, (BDI–II) [25]. The 21 items are scored from 0 to 3, with a total score ranging from 0 to 63. The subject is instructed to provide answers regarding their feelings during the past two weeks, including on the day of answering the questions. According to the reference levels given in the BDI manual, 0–13 equals minor depression, 14–19 mild depression, 20–28 moderate depression, and 29–63 severe depression. The Finnish version has shown acceptable levels of reliability and validity [26]. A good agreement between the BDI score and diagnosis of depression has been found in patients with musculoskeletal pain [27].

Statistical analyses

The descriptive statistics are presented as means with standard deviation, as medians with interquartile range, or as counts with percentages. Statistical comparisons between groups were done using a t-test, Mann–Whitney tests, and Chi-square test. Repeated measures were analyzed using generalizing estimating equations (GEE) models with an exchangeable correlation structure; the bootstrap-type method (10,000 replications) was used to estimate the standard error (SE). In the case of a violation of the assumptions (e.g., non-normality) for continuous variables, a bootstrap-type method, or Monte Carlo P- values (small number of observations) for the categorical variables were used. The normality of variables was evaluated graphically and by using the Shapiro–Wilk test. All analyses were performed using STATA software, version 17.0 (StataCorp LP, College Station, TX).

Results

A total of 31 patients underwent the full rTMS protocol. For three patients who reported an increase in pain, the treatment was discontinued. No serious side effects were reported during the treatment or follow-up.

The baseline data of the patients are presented in Table 1. The mean age of the patients was 49.5 years (range 17–82 years). There were no statistically significant differences in the baseline data between the groups of antidepressant users and nonusers.

The difference in the baseline BDI scores between groups was not significant, but antidepressant users’ BDI scores corresponded to minor depression and nonusers’ BDI scores to mild depression, here according to the reference values (0–13 and 14–19 respectively) presented in the BDI manual [25].

The ATC categories for various antidepressants used among the patients are reported in Table 2. The most prevalent medication was the category of nonselective

Table 2: Antidepressant medication of the patients.

Antidepressant	ATC	n	%
Nonselective monoamine reuptake inhibitors	n06AA	8	47.1
Nonselective monoamine reuptake inhibitors + SSRI	n06AA+n06AB	1	5.9
SSRI	n06AB	1	5.9
Other antidepressant	n06AX	6	35.3
Other antidepressant + Nonselective monoamine reuptake inhibitors	n06AX + n06AA	1	5.9
Total		17	100.0

ATC, anatomical therapeutic chemical classification system; SSRI, selective serotonin reuptake inhibitor.

monoamine reuptake inhibitors, including amitriptyline (7 patients) and nortriptyline (1 patient).

A decrease either in pain intensity or pain interference was observed in 20 patients after 5 treatment sessions. Post-treatment, there was a significant decrease in pain intensity in the group of antidepressant nonusers only. There was a slight, nonsignificant trend of decrease in interference in both groups. The differences in pain intensity and pain interference, here adjusted for BDI scores, on NRS between the antidepressant users and nonusers groups are presented in Figure 1.

After 10 sessions of rTMS, there was a difference in pain intensity in favor of the group of antidepressant nonusers (p=0.019), with an average NRS decrease of −1.65 (95 % CI: −2.99 to −0.31, p=0.016). An insignificant increase of +0.33 (95 % CI: −0.80 to 1.46) in NRS was found in the group of antidepressant users. No statistically significant difference in pain interference was found between the groups. In both groups, there was a slight nonsignificant trend of a decrease of interference. In the group of antidepressant nonusers, the change was −0.94 (95 % CI: −2.57 to +0.68), and in the group of antidepressant users, the change was −0.79 (95 % CI: −2.53 to +0.94).

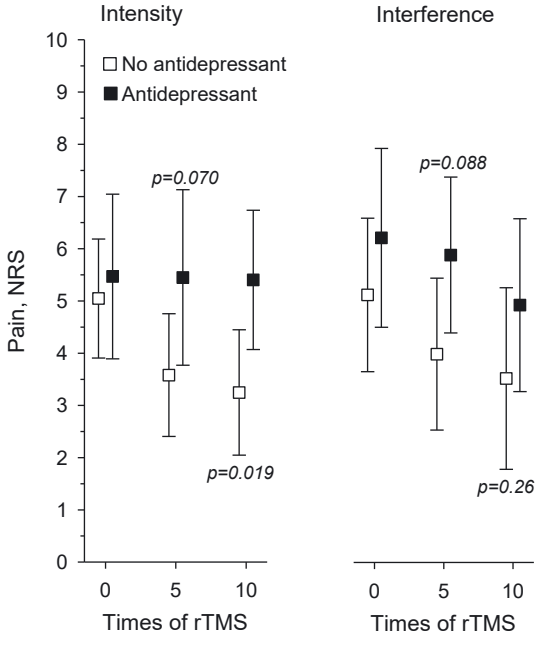

Figure 1: The pain intensity and interference (adjusted for BDI scores) with and without depression medication, at baseline, after 5 sessions of rTMS, and after 10 sessions of rTMS.

After 10 treatment sessions, the impression of change measured with GIC was positive in 20 patients. The GIC showed a positive change in the group of antidepressant nonusers, while in the group of antidepressant users, there was no change. The difference in GIC between these two groups was statistically significant (p=0.002) at the end of the treatment sessions.

There was a significant difference between the groups regarding continuing rTMS treatment after the initial 10 sessions. The percentage of patients continuing rTMS treatment was 29 % (5/17) in the antidepressant users group and 71 % (12/17) in the antidepressant nonusers group.

Discussion

Simultaneous use of antidepressants seems to attenuate the analgesic effects of therapeutic rTMS in patients with neuropathic pain. No change in pain interference was found between the groups. The difference in GIC regarding a positive change between these two groups was statistically significant, thus resembling the results on NRS regarding changes in the pain intensity and interference.

Although the difference in BDI scores between groups was not significant at baseline, antidepressant user scores corresponded to minor depression, while nonuser scores corresponded to mild depression. The difference in scores was controlled for in our analyses. Therefore, differences in depression baseline scores are unlikely to be one of the reasons for our findings of a more effective pain reduction in antidepressant nonusers.

These are novel findings, and there are little research data on the effects of antidepressants in rTMS treated patients. Typically, rTMS is administrated to pain patients using pain and other medication (i.e., antidepressants, anticonvulsants). Most real-world studies have been conducted on patients who have not benefited from pain medication; according to recommendations, additive rTMS has been administrated parallel to current medication in naturalistic settings. Little is known about how concurrent medication affects the efficacy of rTMS treatment in chronic pain conditions [9]. In Phillips et al.'s [28] study, patients with

comorbid pain and major depressive disorder (MDD) using SNRI during rTMS treatment showed a significant decrease in pain scores from baseline to post-treatment. However, the authors stated that it was unclear whether this was related to antidepressant treatment effects.

Some studies have shown that in patients with MDD, the use of benzodiazepines is associated with worse rTMS treatment outcomes when compared with the use of psychostimulants [29]. Specifically, the use of lorazepam has been shown to significantly reduce the effectiveness of and response rate to rTMS targeted to the dorsolateral prefrontal cortex (DLPFC) for the treatment of MDD in a large sample of real-world data [30]. Recently, a study reported that independently of confounding factors, neuroleptic medication attenuates the antidepressant effects of rTMS [31]. In patients experiencing pain, rTMS treatment is typically targeted at the primary motor cortex, but even stimulation of the left DLPFC, used in treating MDD, has also successfully reduced pain symptoms in experimental and clinical settings [32, 33].

It has been shown that HF-rTMS treatment affects the serotonergic system, more specifically the 5-HT2A receptor BI in the DLPFC and in the hippocampus [34]. Antidepressants have complex, not yet fully understood effects on cortical excitability and specific neurophysiological, TMS-derived parameters, such as intracortical inhibition and facilitation [35]. Further, antidepressants can have an impact on the cortical silent period (CSP) [36, 37], possibly modulating cortical "receptivity" for rTMS stimuli and actuate long-term cortical excitability and plasticity effects [9, 30].

Unilateral stimulation of the M1 or DLPFC induces bilateral analgesic effects. According to a review by Moisset et al. [7], rTMS stimulation of the M1 induces changes in several diencephalic areas involved in pain perception, such as the thalamus, anterior cingulate, insular, and prefrontal cortices. All are areas rich in opioid receptors. In addition, areas containing gamma-aminobutyric acid (GABA), serotonin, and dopamine receptors are activated [7]. When stimulating DLPFC in induced pain settings, changes in the activity of the structures involved in the integration and modulation of pain signals, including insular and cingulate cortices, as well as the thalamus, have been found [38, 39].

Differences were found between groups only in terms of a reduction of pain intensity, while pain interference showed a similar decrease in both groups. Differences in pain intensity can plausibly be explained by a negative interaction of pharmacological action and rTMS-derived effects. One underlying reason for the similar benefits regarding pain interference may be the activating effect of study participation on participants. Research shows that more engaged patients may have better health outcomes and better care experiences than those patients who are less engaged [40]. Participation in a study may alter the behavior of the participants because of an initial activation-related increase in motivational behavior. This behavior change has also been described as the Hawthorne effect [41], according to which the knowledge of participating in an experiment modifies the behavior of the participant from what it would have been without this knowledge.

Because both antidepressants and rTMS treatments have derivative effects on the common functions (i.e., serotonin and noradrenaline) of neural networks (i.e., prefrontal cortex, descending pathways) [11] the likely reasons for our findings are changes in the activation of these areas.

In summary, besides local neural factors, rTMS influences even long-distance functional connectivity [42], and the brain is affected by treatment as a global dynamical system [43]. The exact mechanism behind our findings remains to be elucidated, and further studies are warranted. However, therapeutic rTMS for neuropathic pain conditions is plausibly sensitive to interference with antidepressant drug therapies.

Limitations of the study

The register study design imposes some limitations on the research methods, which affect the reliability of the interpretations. The lack of sufficient data on sleep quality can be criticized because patients with neuropathic pain conditions have more sleep disorders than the general population. Even though these comorbidities of neuropathic pain and sleep disorders do not seem to predict the rTMS pain treatment outcome [44], the lack of sufficient sleep quality data is considered a limitation of the current study.

The small number of participants, as well as the limited clinical characterization of the study population, can be considered weaknesses of the study. Therefore, confirmatory studies are warranted, and studies with larger neuropathic pain populations need to be conducted.

The retrospective design of the study and thus the non-controlled use of antidepressants may hamper the main conclusion, i.e. that antidepressant use was mainly responsible for a lower analgetic response of rTMS in these patients. Several different categories of antidepressants, with different mechanisms of action were used and apparently were associated with lower pain relief only, which suggests the findings may not be related to antidepressant use per se.

Strengths of the study

The treatment procedures, including data collection, were carried out by the same personnel throughout the process. Validated methods were used. Furthermore, every rTMS intervention, including navigation, was performed with the same equipment. These can be considered strengths because they reduce variations and sources of error.

Conclusions

Independently of confounding factors, a simultaneous use of antidepressants attenuated the analgesic effects of therapeutic rTMS in patients with neuropathic pain. The use of antidepressants did not affect pain interference. The exact mechanism of our findings remains to be elucidated, and further studies are warranted. However, therapeutic rTMS is plausibly sensitive to negative interference with antidepressant therapies.

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