Psychiatr. Pol. 2021; 55(3): 565–583
PL ISSN 0033-2674 (PRINT), ISSN 2391-5854 (ONLINE)
www.psychiatriapolska.pl
DOI: https://doi.org/10.12740/PP/OnlineFirst/115556

Transcranial magnetic stimulation (TMS) in treatment of psychiatric disorders – review of current studies

Tomasz Wieczorek, Agnieszka Kobyłko, Filip Stramecki, Karolina Fila-Witecka, Jan Aleksander Beszłej, Marta Jakubczyk, Patryk Piotrowski, Adrianna Senczyszyn, Damian Siwicki, Dorota Szcześniak, Joanna Rymaszewska

Wroclaw Medical University, Department and Clinic of Psychiatry

Summary

Current progress of basic and clinical science creates background for new therapeutic appliances of brain stimulation methods in disorders of central nervous system. This review describes present state of knowledge regarding practical aspects of one of those methods – transcranial magnetic stimulation, TMS. The review was based on contemporary literature on use of transcranial magnetic stimulation in various diseases, particularly including present recommendations and guidelines as well as systematic reviews, published after year 2000. TMS is a quite novel, non-invasive, well tolerated treatment method with a low amount of transient adverse effects and complications. Development of new therapeutic protocols makes it possible to introduce this procedure in new groups of patients, including a wide range of mental disorders such as depression, bipolar disorder, schizophrenia, also cognitive function disorders and posttraumatic stress disorder. In Poland it is still hardly available, though more and more clinical centers start to perform this kind of therapy, providing proper equipment and trained personnel.

Key words: mental disorders, brain stimulation methods, transcranial magnetic stimulation

Introduction

Psychiatric disorders, including affective disorders, are the major causes of people's suffering and they are one of the biggest challenges for the current medicine [1]. There are over 322 million people diagnosed with depression [2] and this number is still raising. Among 25 most common causes of global DALYs (disability-adjusted life-years), for both sexes combined, depressive disorders changed their position from 15, through 14 into 11 respectively in 1990, 2005 and 2013. Moreover, psychiatric disorders influ-

ence the course and prognosis of many common somatic disorders, including ischemic heart disease, obesity and diabetes [3]. Unfortunately, effectiveness of treatment of mental disorders has still many limitations, e.g., approximately one-third of patients with major depressive disorder (MDD) do not respond to the available treatment with antidepressants and psychotherapy [4, 5].

Continuing progress in the field of neurophysiology, radiology, psychiatry, neurology, neurosurgery, and biomedical engineering, which has been progressing for several decades, results in the creation of new ways of neuron stimulation. These methods significantly enrich the range of therapeutic interventions used in psychiatry, finding, apart from pharmacotherapy and psychotherapy, an increasingly wider application in the treatment of mental disorders.

Technological progress in the production of focused high-intensity magnetic fields opened up the possibility of a non-invasive magnetic influence on the brain structure in the form of transcranial magnetic stimulation (TMS).

Currently, this method is becoming more and more available, also in Poland. This review is intended to present the current state of knowledge about its use, including indications, contraindications, effectiveness, safety and the possibility of the effect being potentiated by other methods of treatment.

In the process of preparing this review, following scientific search engines and databases were used: PubMed, EBSCO, OVID. An extensive search was conducted using the following terms: 'transcranial magnetic stimulation', 'psychiatric disorders', 'psychiatry', 'depression', 'schizophrenia', 'bipolar disorder', 'obsessive-compulsive disorder', 'psychiatric treatment', 'mental disorders'. The search results were limited to published guidelines and recommendations, systematic reviews (with or without meta-analyses) and literature reviews taking into account current guidelines and the latest randomized controlled trials (RCTs) not included in the guidelines due to a later date of publication. In the case of some disorders, limited data from systematic reviews and RCTs was available, so also observational studies and case reports were included. Texts published after 2000 were included. Secondly, the database of texts was extended through the use of bibliographic references.

Transcranial magnetic stimulation – method description

Transcranial magnetic stimulation (TMS) is a relatively new treatment method used in psychiatry and neurology, still widely studied and finding more and more clinical application.

However, its history is quite long. A. d'Arsonval was the first one to describe the magnetic stimulation of the cerebral cortex in 1896. In 1958, J. Talairach and P. Tournoux proposed a standard reference system in human brain mapping, using coordinates in 3 dimensions. A. Barker used the magnetic stimulator to stimulate the human cerebral cortex for the first time in 1985. In 1995, M. George described mood

changes after using rTMS (repetitive TMS) and empirically defined ‘5 cm method’. In Poland, dr hab. T. Zyss, together with colleagues from Krakow center, was the first one who published a raft of valuable publications [6–8].

Currently, the availability of this method in Poland is still limited, nevertheless, there are more and more centers with appropriate equipment and trained staff, such as Department and Clinic of Psychiatry, Wroclaw Medical University, represented by the authors.

The assumption of this method is the interaction of neurons with a strong magnetic field (with a local intensity of up to 3 teslas), generated by the magnetic coil applied to the head. The depth of such an interaction is limited (up to 4 cm), therefore, from the technical point of view, it is possible to stimulate the cerebral cortex and the spinal cord only. The magnetic field induces changes in the electric field in the brain, which significantly affects the polarity and excitability of neurons. Therefore, this method can be used primarily in disorders in which dysfunction in brain cell excitability is described. The studies showed that low-frequency pulse effects (1–5 Hz) inhibit neurons, while high frequency (≥5 Hz) stimulates neurons [9].

The exact mechanism of magnetic stimulation effect on neurons is constantly being studied, however, it is believed that the changes occur at the level of individual neurons, as well as within the entire neural network. Moreover, short-term instant effects are observed as well as long-term benefits [9]. The strength of the pulse used in therapy depends on the individual excitability threshold. In turn, the application site on patient’s head is determined by simple anthropometric methods or using modern neuronavigation techniques based on the brain image obtained in magnetic resonance.

Therefore, many different TMS protocols are currently being tested, in which repetitive pulses of the same frequency (repetitive TMS, rTMS) or a series of high-frequency pulses and a relatively small amplitude are used (so-called theta burst stimulation, TBS) (Figure 1). The protocols also differ in the frequency of stimulation sessions – the accelerated TMS (aTMS) is currently investigated, in which up to 4 sessions per day are performed in order to obtain a rapid clinical response. Another approach is to carry out high-frequency stimulations first, before low-frequency sessions – the so-called priming TMS (pTMS). Thanks to the progress in the reduction of artefacts in the electroencephalographic record (EEG) during TMS, the possibility of pulse synchronization with the patient’s alpha rhythm synchronized TMS (sTMS) was also created.

Equipment manufacturers also design various new coil shapes. This should allow an influence on larger volume unit of neurons or the inclusion of deeper brain structures into the magnetic field. An interesting new feature is the H-coil in the shape of a helmet, which allows a stimulation of up to approximately 5 cm deep. It is called the deep TMS (dTMS) [10].

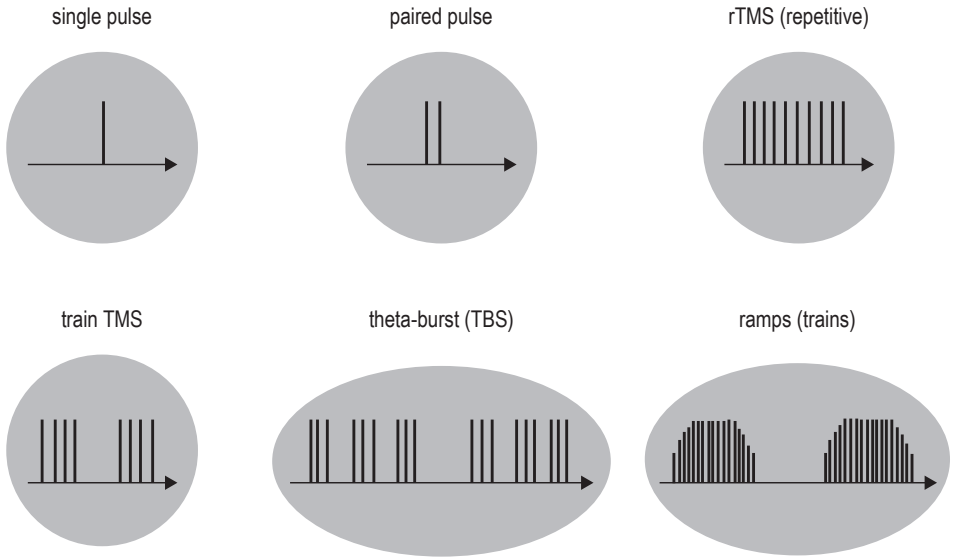

Figure 1. **TMS stimulation protocols**

A major advantage of TMS is its high tolerance, lack of serious adverse effects and the lack of the need for anesthesia and relaxation. The main disadvantage is the limited range of available brain structures for stimulation and the relatively high cost of the equipment.

The basic psychiatric indications for TMS use are recurrent depression and schizophrenia, but the spectrum of applications is becoming wider due to the development of subsequent TMS protocols and progress in the study of the pathophysiology of mental disorders. The use of TMS in obsessive-compulsive disorder, post-traumatic stress disorder, substance addictions or to stimulate cognitive functions is currently being investigated.

TMS in psychiatric disorders

Recurrent depressive disorder

The neurophysiological basis for the treatment of depressive episode using TMS is a characteristic way of activation of the cerebral cortex in these patients. Neurons of the dorsolateral prefrontal cortex (DLPFC) are characterized by an increased activity in the right brain hemisphere and decreased in the left hemisphere in some patients with depression [9]. Therefore, the therapeutic method is to inhibit neurons on the right side with low frequency pulses and to stimulate neurons on the left side with high frequency pulses or simultaneous use of both these methods (bilateral TMS). Currently,

the most recommended treatment protocols advice one session a day, 5 days a week. The best efficacy is observed when performing a total of 26–28 therapeutic sessions, however, the ineffectiveness of the therapeutic effect may be stated after 20 sessions [11]. Currently, aTMS protocols, assuming more than one session per day, are under the investigation, but there is a lack of sufficient evidence of higher effectiveness of this procedure [10, 11]. The predictors of the TMS response or its lack are also studied, but there is shortage of relevant publications at the moment.

Based on the studies conducted so far on the effectiveness and tolerance of TMS the guidelines were formulated. Milev et al. under the Canadian Network for Mood and Anxiety Treatments (CANMAT), developed recommendations which envisage the use of rTMS as a first-line treatment for patients with depressive episode who have not positively responded to at least one antidepressant therapy [11].

This approach has also proved to be cost-effective [12] and is consistent with the rTMS registration conditions for the treatment of depressive episodes by the Food and Drug Agency (FDA). What is important, the majority of research and therefore the recommendations are based on the use of rTMS together with pharmacological treatment. Berlim et al. in a meta-analysis of 6 RCTs (n = 4,392) indicate the superiority of the complementary use of both methods over rTMS as a self-referential method in response to treatment and remission [13].

These guidelines presuppose the high-frequency stimulation (HF-TMS) of the left brain hemisphere or the low-frequency (LF-TMS) stimulation of the right hemisphere. The results of meta-analyses suggest that in the absence of a positive response using one of these methods, there is a probability of obtaining a response using the other one. At the same time, the authors of the guidelines recommend bilateral stimulation as a second-line treatment because it does not show significantly higher efficacy [11]. However, the latest meta-analysis comparing different protocols, published in 2017, suggests the advantage of bilateral and pTMS stimulation (the latter one is based on a small number of tests) [10].

The efficacy of rTMS has been confirmed in a number of randomized and controlled trials on the treatment of depressive episodes, although a limitation of many of these studies is the simultaneous inclusion of patients with a diagnosed depressive episode in the course of both unipolar and bipolar disorder. A large meta-analysis demonstrated the efficacy of left-sided DLPFC HF stimulation: 58% of cases of positive response and 37% of remissions [14]. Right-sided DLPFC LF stimulation achieved 35% of remission cases [15].

Theta burst stimulation (TBS) seems to be comparatively effective, and at the same time lasts shorter, involves using a pulse of lower strength and is less aggravating for the equipment. TBS still remains the protocol used mainly in experimental therapies [16], although CANMAT allows its use as second-line treatment with a third category of evidence quality [11]. In 2018, Blumberger et al. [17] published the results of

a large group study (n = 414) comparing the effectiveness of TBS with the standard FDA-registered rTMS protocol. Similar clinical response rates (47% for rTMS, 49% for iTBS) and remission rates (27% for rTMS, 29% for iTBS) were shown for both methods. At the same time similar tolerance and safety profile of both protocols were observed. In addition, the cost analysis carried out in parallel to this study showed a significant advantage of iTBS in terms of cost-effectiveness, resulting mainly from shorter duration of a single session, and of the whole therapy (fewer sessions) [18]. Based on this latest study, among others, the FDA has registered iTBS for the treatment of depression for two equipment manufacturers.

Another new kind of stimulation, which is still in the research phase, is the impact of rTMS on the dorsomedial prefrontal cortex (DMPFC) including the anterior cingulate gyrus. In one controlled study and several series of cases, a slightly higher effectiveness of stimulation of this area, compared to the DLPFC, was demonstrated in the treatment of depressive disorders. However, more research is needed on this solution to set stronger recommendations. Currently, CANMAT suggests this method of stimulation as the third-line treatment [11].

An important direction of research is also the assessment of the effectiveness of rTMS in the treatment of post-stroke depression. Currently, there is a lack of high quality randomized and controlled studies on this group of patients, but the analysis of previous reports has brought very promising conclusions, indicating a relatively high percentage of responses [19], being present in the group of patients refractory to pharmacotherapy and outweighing the SSRI effect [20]. At present, when the beneficial effect of rTMS in the treatment of depressive disorders is confirmed, there are studies comparing the efficacy and tolerance of transcranial magnetic stimulation and electroconvulsive therapy (ECT). Previous observations and analyses show greater effectiveness of ECT, especially in the group of patients with psychotic symptoms. In addition, patients refractory to electroconvulsive therapy are unlikely to respond to the rTMS treatment. Nevertheless, rTMS is a better tolerated method and it is recommended to start with it before the patient is subjected to ECT [3, 21]. The exception are patients who may benefit from ECT much more if performed as first-line treatment [9]. According to the World Federation of Societies of Biological Psychiatry (WFSBP) indications for ECT treatment in depression include: severe episode of major depression with psychotic symptoms or significant motor retardation, cessation of food and fluid intake, 'truly' treatment-resistant depression, and clinical situations when fast improvement is necessary (e.g., high suicidal risk) or other treatment options are contraindicated (e.g., pregnancy) [22].

An important issue regarding treatment with rTMS remains the durability of the obtained therapeutic effect. CANMAT recommends the use of maintenance therapy because many studies showed a high probability of recurrence within a few months after the end of treatment [11]. Cohen et al. [23] showed that after the acute phase of

treatment without maintenance therapy, the average duration of remission was 119 days, with the probability of being in remission of 75% after 2 months, 60% after 3 months, 42.7% after 4 months, and 22.6% after 6 months from the end of treatment. At the same time, the factors that increased the chance of maintaining remission were: a larger number of performed rTMS sessions and a younger patient age. Dunner et al. [24] demonstrated that the use of 12 months maintenance rTMS therapy allowed for remission in 71% of patients and maintenance of a good response in 63% of patients who obtained a response in the acute phase of treatment. In another study [25], patients after the acute phase of rTMS treatment received only supportive pharmacotherapy. Of these, 38% had a recurrence of symptoms within 24 weeks. They were again subjected to rTMS, finally obtaining 73% response and 60% remission at the end of the 24-week observation of the whole group of patients. At the same time, there was a lower probability of recurrence of symptoms in patients who achieved remission compared to patients who only had a partial response to treatment. According to these results, the authors of the study suggested only pharmacological treatment, with the rapid reintroduction of rTMS in the situation of deterioration of the mental state of the patient, as a possible solution. The CANMAT guidelines do not specify which protocol is the most recommended or what the maintenance rTMS frequency should be; further research is needed on this issue [11].

Treatment-resistant depression

The issue of treatment-resistant depression (TRD) raises the growing interest of researchers as a significant and still unsolved clinical problem. Research is ongoing on the use of TMS in the treatment of TRD. A meta-analysis published in 2019 [26] compiled previous studies in which TMS therapy was performed in the area of the DLPFC (left or right) of patients with this diagnosis. For unilateral protocols, the weighted mean difference (WMD) between the test and control groups in the results obtained on the Hamilton Depression Scale (HAM-D) was 3.36; at the same time, it was higher in patients treated concurrently with pharmacological treatment compared to those without pharmacotherapy (3.64 vs. 2.47). The analysis of subgroups and metaregression showed higher efficiency of protocols using the 20 Hz frequency than those using the lower values. For bilateral protocols, the corresponding WMD was 2.67; however, it was calculated based on a much smaller number of publications. Regarding the potential for achieving remission in TRD, the pooled remission rate using unilateral protocols was 16% for the test group and 5.7% for the control group. In patients stimulated with concomitant pharmacotherapy, the remission rate was 17.5% (and 15.1% in patients without pharmacotherapy). For bilateral protocols, 16.6% remissions were obtained for the study group and 2.0% for the control group. Further analysis found that the use of unilateral protocol treatment in about 11 patients allows one remission (number needed to treat, NNT), and in the

case of bilateral protocols pooled NNT equaled 8. However, these results should be interpreted carefully because studies using protocols with different stimulation parameters, as well as using different methods of neuroanatomical target determination, were included in the meta-analysis. The authors interpreted the results, stating that rTMS has moderate efficacy in the treatment of TRD, though it was not possible to describe the durability of the obtained therapeutic effect.

In the aforementioned study by Blumberger et al. [27], which compared iTBS protocols to rTMS, it was shown that patients with TRD achieved a significantly lower remission rate in the group of patients who had 3 failed treatment attempts before the stimulation than in the group with two or less failed attempts (17.3% vs. 29.4%), regardless of the method used (iTBS or rTMS). Such a result would therefore indicate a comparable efficacy of both these methods in the treatment of not only 'classic' depressive episodes, but also TRD.

Bipolar disorder

The CANMAT and ISBD [28] recommendations published in 2018 include the use of rTMS as a pharmacotherapy potentiation in the acute phase of both depressive and manic episodes in bipolar disorder type I. In the case of depressive episode, rTMS of the right or left DLPFC is proposed as second-line treatment, with the second category of evidence quality. rTMS of the right DLPFC is the third-line treatment in manic episodes, with the third category of evidence quality. At the same time, the recommendations do not specify which medications should be combined with stimulation. There is still no recommendation for rTMS in bipolar disorder type II.

Schizophrenia

The use of rTMS in schizophrenia is currently the subject of many promising studies, primarily in two areas: persistent hallucinations and reduction in the severity of negative symptoms.

The effect on reducing the severity of hallucinations through inhibition (low frequency stimulation, LF-rTMS) of the temporoparietal cortex or superior temporal gyrus (STG) is increasingly being investigated. In the recommendations of Lefaucheur et al. [9], based on the European experts team, the combination of this method of treatment with pharmacotherapy is currently recommended (category C), primarily in the group of patients whose hallucinations persist despite significant improvement in other symptoms due to antipsychotic drugs.

Research on successive protocols also indicates a promising rTMS effect in reducing the severity of negative symptoms. In 2014, a recommendation of category B for left-sided HF-rTMS in the DLPFC area was proposed [9]. The extensive meta-analysis, published in 2017 [29], showed a small but statistically significant reduction

in their severity (measured with the PANSS – *Positive and Negative Syndrome Scale*) during rTMS combined with pharmacotherapy. However, due to the relatively high heterogeneity of the examined groups and the differences between the used protocols, authors treated the obtained results cautiously and proposed a recommendation based on middle-class evidence for rTMS in this indication. Interesting observations, which could explain the discrepancy of the results of the conducted research, were carried out by Dlabac-de Lange et al. [30], noting a significant improvement (average of 7.6 points) in the severity of negative symptoms measured by the SANS (*Scale for Assessment of Negative Symptoms*), however, not observing a similar effect using the PANSS. What is also important – bilateral rTMS was tested in this study.

For both indications, further research is required as previous reports differ significantly in the range of used protocols, including stimulation parameters, while displaying divergent efficacy results. Another issue that requires further research is the durability of the obtained therapeutic effect and the justification for the implementation of maintenance therapy [9].

In a meta-analysis from 2017, He et al. [31] found a lack of efficacy of 10 Hz TMS of the DLPFC in reducing the severity of negative symptoms, while the effect of TPC inhibition on hallucinations was small. Therefore the results of studies should be treated with a great caution. The very good tolerance of this method remains an encouraging fact to use rTMS and conduct further research. In addition, the use of rTMS in the presented indications is also supported by the fact that there are no alternative methods for both persistent hallucinations and negative symptoms, therefore Slotema et al. [32] recommend using TMS despite limited evidence of efficacy.

Cognitive impairment

The use of magnetic stimulation to improve cognitive functioning in various mental disorders and neurodegenerative diseases rises growing interest of scientists. The extensive meta-analysis of Hsu et al. [33] published in 2015, dedicated to the use of HF-rTMS in Alzheimer's disease (AD), confirmed a significant beneficial therapeutic effect in comparison with healthy people. In patients with AD, an improvement in cognitive functioning has been observed, particularly when using the so-called 'online protocols' – magnetic stimulation (usually within the DLPFC, bilaterally or alternately left – and right-sided) while performing cognitive exercises. In the analysis different studies were compared: with only one rTMS session or with sessions performed for 5 days, 2 weeks or even 6 weeks. Interestingly, there was no significantly higher efficacy after performing a higher number of treatment sessions. On the other hand, relatively short observation period does not allow to evaluate long-term therapeutic effects in these studies.

In healthy elderly people the effect of improving cognitive functioning was much smaller. In addition, the effect was stronger in the case of using the 'offline protocol'

(without simultaneous cognitive exercises) and increased during the subsequent therapeutic sessions [33]. In patients with AD, first of all, improvement in memory and language functions is observed, and the most visible effect is observed in patients with mild cognitive decline [34, 35]. In the case of advanced, severe AD, very little or no therapeutic effect is observed. One promising solution seems to be stimulation in several different locations in one patient – in addition to the DLPFC, stimulations of Broca's and Wernicke's areas as well as somatosensory association cortex of the parietal lobes of both brain hemispheres are also proposed [36]. Certainly, further research requires the issue of durability of the obtained beneficial therapeutic effect.

The majority of studies included in current systematic reviews were placebo-controlled randomized trials in which participants did not take pro-cognitive drugs during the study. There were few studies on the efficacy of combining rTMS and pharmacotherapy in AD, they included small groups of participants, and they also provided contradictory conclusions [37]. Therefore, it is difficult to clearly state whether the combination of both therapeutic methods is clinically justified.

The studies on improving the functioning of people with mild cognitive impairment (MCI) were also conducted. In a comprehensive systematic review from 2017, Birba et al. [38] compared the results of research on stimulation of the prefrontal cortex, parietal cortex, inferior frontal gyrus, and superior temporal gyrus. They noticed large discrepancies in results. Some of the examined protocols did not show any therapeutic efficacy, while some of the studies confirmed improvement in face and name association, recognition of non-verbal messages, attention, psychomotor speed, and the memory of everyday events. Discrepancies in the results were explained by differences in methodologies (stimulation parameters, selection of the stimulated area), as well as the fact of technical unavailability of some of the brain regions crucial for MCI (e.g., hippocampus). In addition, only one publication included in this review concerned a randomized controlled trial, and the rest were based on relatively few groups of participants. Due to the mentioned discrepancies, the authors emphasize the need to continue research, primarily to establish the most effective protocols.

Interesting results were published by Trebbastoni et al. [39] who, using rTMS and electromyography (EMG), determined the value of motor-evoked potential (MEP) in muscles in the group of patients diagnosed with amnesic subtype of MCI (aMCI) and in a healthy control group. In the experimental group, statistically lower amplitudes of the MEP values were recorded during subsequent series of pulses and a lower resting motor threshold (rMT). During the four-year follow-up, 60% of participants developed Alzheimer's disease, while lower values of the previously mentioned parameters correlated with the conversion time to AD. The authors concluded that the reduced thresholds of excitability in patients with aMCI may be an adverse prognostic factor in the faster development of AD.

In the case of cognitive impairment in the course of Parkinson's disease (PD), attention is drawn to the fact that there are very few reliable data on the effectiveness of rTMS in improving cognitive functioning. The existing data are not sufficient to unambiguously determine the effect of magnetic stimulation and the indication of its use [40, 41]. At the same time, attention is drawn to the lack of unequivocal results in terms of the impact of rTMS on specific domains of cognitive functioning, which may be related to the insufficient sensitivity of the used neuropsychological tests, as well as the fact that depressive symptoms are present in patients with PD, therefore it is difficult to distinguish the improvement dependent on emotional and affective improvement and the actual improvement of cognitive functions [36]. In patients with the diagnosis of Lewy bodies dementia, one uncontrolled study [42] showed a relatively high efficacy of rTMS in reducing the severity of depressive symptoms, but there is still no research on the use of this method in improving cognitive functioning.

Another group of cognitive disorders, in which the use of TMS is examined, is the vascular cognitive impairment (VCI) and vascular dementia (VaD). In the extensive review, Lanza et al. [43] emphasize the high potential of TMS in determining groups with particularly high risk of developing VaD, as recent studies showed the existence of characteristic cortical excitability profiles in various VCI subtypes. However, after the diagnosis of VaD, TMS may be useful in determining the optimal pharmacotherapy (by registering electrophysiological changes in neurons), restoring plasticity of neural networks and improving cognitive functioning.

Deep TMS (dTMS) may also be a promising therapy in cognitive impairments. A number of previously published research results suggest good efficacy of this method in improving cognitive function in patients with depression and, to a lesser extent, schizophrenia. It is associated with the possibility of stimulation of deeper localized brain structures as compared to the classic rTMS stimulation. Nevertheless, these observations require confirmation in larger, randomized and controlled trials [44].

Obsessive-compulsive disorder

To date, many published papers on the effectiveness of rTMS in the treatment of obsessive-compulsive disorder (OCD) have had diverging results. However, the latest meta-analysis, including 20 studies, published in 2017 by Zhou et al. [21], confirmed that the use of rTMS in this diagnosis is justified, although high heterogeneity in research results necessitates careful interpretation of the data. The therapeutic effectiveness reported in subsequent studies over the years has been increasing, which may have involved the development of more and more effective protocols and the increasing technological advancement of the used equipment. At the moment, stimulation of the right area of DLPFC, both in high-and low-frequency protocols, seems the most efficient, which indicates the need to continue research aiming to determine the neurophysiological basis of this phenomenon. Left or bilateral stimulation showed a weaker therapeutic effect.

Nevertheless, there is a need for high-quality randomized and controlled trials, including longer follow-up of patients after treatment (previous studies usually included a maximum of several months of observation) and alternative brain areas of stimulation (relatively few studies included stimulation of the orbitofrontal cortex or supplementary motor cortex) [21]. It is possible that specific guidelines regarding the use of rTMS in OCD will be formulated based on these data in the coming years.

Deep TMS (dTMS) is also a promising therapeutic method, which allows the interaction of neurons within the medial prefrontal cortex and anterior cingulate cortex. The first published study on the use of this method [45] demonstrated its effectiveness (using a high frequency stimulation protocol) in the reduction of obsessive and compulsive symptoms in the group of patients refractory to pharmacotherapy. Donse et al. [46] hypothesized that one of the possible predictors of non-response to magnetic stimulation in OCD may be concomitant circadian rhythm disorder. In 2018, dTMS got FDA registration in OCD.

Post-traumatic stress disorder (PTSD)

The previously published data on the efficacy of rTMS in the treatment of PTSD are very limited, however, a number of protocols have demonstrated possible efficacy in alleviating the underlying symptoms of the disorder and the accompanying depressive and anxiety symptoms. In 2014, in the International Federation of Clinical Neurophysiology (IFCN) guidelines [9], the right-sided HF-rTMS of the DLPFC received a level C recommendation in the treatment of PTSD.

A systematic literature review of rTMS use in PTSD [47], which included 18 studies, was published in 2017. The authors analyzed data on applied stimulation protocols compared to placebo stimulation. The DLPFC areas in both hemispheres of the brain were subjected to magnetic stimulation, using high – and low-frequency protocols, achieving slightly higher efficacy in the right hemisphere. The best-described protocol is LF-DLPFC, which has been shown to be effective in reducing excessive arousal, avoidance and re-experiencing trauma. In addition, it reduces the severity of depressive symptoms, but not anxiety. However, the published research highlights the large heterogeneity of results, the small size of the tested groups, as well as selective reporting and high level of diversity in the range of used measurement scales. For this reason, rTMS in PTSD, despite promising results, still requires confirmation of efficacy in high-quality studies on larger groups with uniformly established stimulation protocols.

Alcohol and nicotine dependence syndromes

A systematic review with a meta-analysis [48], published in 2017, demonstrated the overall effectiveness of rTMS in reducing craving in the addiction syndrome. However, the analysis of subgroups showed only the reduction in the level of nicotine

craving and the amount of cigarettes consumption after HF-DLPFC. The most likely neurophysiological mechanism of this phenomenon is the inhibitory effect of the DLPFC on the reward system through the meso-fronto-limbic pathway. No beneficial rTMS effect was found in the alcohol addiction syndrome. However, the authors drew attention to the large diversity of protocols in the location of stimulation (left, right or bilateral) and the number of therapeutic sessions. Confirmation of the effectiveness of rTMS in these diagnoses undoubtedly requires further research, especially due to the debatable quality of the included publications.

In 2014, the IFCN guidelines recommended a C-level recommendation for HF-DLPFC in nicotine addiction syndrome [9]. In 2019, Zhang et al. [49] published a meta-analysis that showed quite good effectiveness of TMS in reducing craving, regardless of substance type, but probably the magnitude of this effect is dose-dependent. However, the achieved improvement is impermanent, which is why the authors paid special attention to the need to develop methods for prolonging the beneficial therapeutic effect of TMS.

Safety and side effects of TMS

TMS is a safe method and it is generally well tolerated by patients. The most common side effects include pain or discomfort in the scalp (40%) and transient headaches after TMS session (30%) [11]. Both of these symptoms gradually decrease during continuing therapy, usually respond well to commonly used analgesics and are not a significant reason for discontinuation of therapy. No impairment of cognitive function was observed [11].

Convulsive seizure is the most serious possible complication during the use of rTMS, but it is very rarely observed. The risk of seizure is estimated at 0.01–0.1%. High-frequency stimulation is definitely contraindicated in patients with seizure history, although in practice most clinicians consider epilepsy as a general contraindication to TMS [11]. Most of the reported seizure cases refer to patients with pre-existing epileptic risk or the use of stimulation parameters that exceed the recommended safe ranges. The risk is also higher in the group of patients taking drugs lowering the seizure threshold. Nevertheless, it should be remembered that a small risk of developing a seizure also exists in patients without recognized risk factors who use TMS parameters considered to be safe [50].

The meta-analysis made by the Health Quality Ontario [51] presented the frequency of other, less common adverse effects like gastrointestinal problems (5–22%), eye problems such as eye pain, conjunctivitis or tearfulness (5.6–21%), and muscle twitching (0–20.6%). The rarest side effects reported by different studies are dizziness (0–16.7%), insomnia (4.5–7.6%), muscle pain (4–5.5%), fatigue (5–27.8%), difficulty concentrating (0–41.7%), anxiety/panic episode (5–10.5%), hypomania (5%), tinnitus (0–11%), skin pain (1–8.5%), facial pain (6.7%), depersonalization (25%), paranoid ideation (8%), crying (13%), subjective deterioration of mental state (8%), suicidal ideation (6.7%), fainting (1%).

Contraindications for TMS are presented in Table 1. Interestingly, some experienced centers undertake to perform TMS in patients with some of these contraindications, with a good effect.

It is suggested to provide the patient with a comfortable position during the session; manufacturers of stimulation equipment also offer specially designed armchairs, which are designed to improve the patient's comfort during the procedure and reduce the severity of head and neck pain. There was no increase in the risk of migraine headache; which is justified by the use of TMS in the treatment of such pain. During the treatment of a depressive episode, the risk of conversion to hypomania/mania is assessed as very low. Fainting is also a rare side effect, which in contrast to epileptic seizures is usually associated with rapid return of consciousness [50].

Recapitulation

Undoubtedly, the progress in medical sciences, and related basic sciences, broadens our knowledge about the brain functioning and, consequently, about the causes and pathomechanisms of mental disorders. This knowledge and technological progress enable the introduction of new methods to therapy, which require a number of studies in the field of safety, effectiveness and the development of optimal therapeutic protocols. The presented review of the latest reports on transcranial magnetic stimulation in mental disorders justifies the use of this therapeutic method in clinical practice. We still have to answer the question whether TMS will become equivalent to psychopharmacotherapy in some clinical situations or will it be used only as potentialization. Wide possibilities of modification and configuration of parameters and protocols of TMS management require further exploration in clinical trials among people diagnosed with various mental disorders.

Table 1. **Indications and contraindications for transcranial magnetic stimulation**

Indications [9] – detailed information in appropriate sections of the article:
Confirmed effect
Probable effect
Possible effect
Depressive disorders (FDA approval in 2008)
Negative symptoms in schizophrenia
Auditory hallucinations in schizophrenia
PTSD
Nicotine dependence
Since 2018 in bipolar disorder type I [28]:
depressive episode – 2nd line treatment, 2nd category of evidence
maniac episode – 3rd line of treatment, 3rd category of evidence

table continued on the next page

Contraindications [50]
ferromagnetic or magnetic objects within the head and neck
cardiac stimulator, deep brain stimulation
history of seizures or epilepsy, including family history
medications that lower the seizure threshold
previous head injury or stroke with neurological consequences
other factors that may lower the seizure threshold: sleep deprivation, electrolyte disturbances, discontinuation of psychoactive substances, increased intracranial pressure
pregnancy (however, there are more and more reports indicating a probable safe profile for the pregnant and fetus)

Conflict of interest: Authors do not declare the conflict of interest

References

1. GBD 2013 DALYs and HALE Collaborators, Murray CJ, Barber RM, Foreman KJ, Abbasoglu Ozgoren A, Abd-Allah F, Abera SF et al. *Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990–2013: quantifying the epidemiological transition*. Lancet. 2015; 386 (10009): 2145–2191.
2. World Health Organization. *Depression and other common mental disorders*. Institutes Heal Natl. 2017: 1–22. Doi:CC BY-NC-SA 3.0 IGO.
3. Rahe C, Khil L, Wellmann J, Baune B, Arolt V, Berger K. *Impact of major depressive disorder, distinct subtypes, and symptom severity on lifestyle in the BiDirect Study*. Psychiatry Res. 2016; 245: 164–171.
4. Rush A, Trivedi M, Wisniewski S et al. *Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps*. Am. J. Psychiatry. 2006; 163(11): 1905–1917.
5. Trevino K, McClintock S, McDonald Fischer N, Vora A, Husain M. *Defining treatment-resistant depression*. Ann. Clin. Psychiatry. 2014; 26(3): 222–232.
6. Zyss T, Starzyński J, Krawczyk A. *Trójwymiarowy stereotaktyczny model głowy ludzkiej dla badań symulacyjnych nad techniką przezczaszkową stymulacją magnetyczną mózgu*. Ann. Acad. Med. Lodz. 1999;.40:.101–109.
7. Zyss T, Zięba A, Dudek D. *Najnowsze techniki neuromodulacyjne w terapii zaburzeń depresyjnych*. Krakow: Library of Polish Psychiatry Krakow: PPA Editorial and Publishing Committee; 2009.
8. Zyss T. *Nowe techniki stymulacji elektrycznej i magnetycznej w terapii depresji – Porównanie z elektrowstrząsami i farmakoterapią*. Psychiatr. Pol. 2010; 44: 853–869.
9. Lefaucheur J-P, André-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH et al. *Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS)*. Clin. Neurophysiol. 2014; 125: 2150–2206. Doi:10.1016/j.clinph.2014.05.021.
10. Brunoni AR, Chaimani A, Moffa AH, Razza LB, Gattaz WF, Daskalakis ZJ et al. *Repetitive transcranial magnetic stimulation for the acute treatment of major depressive episodes*. JAMA Psychiatry. 2017; 74: 143. Doi:10.1001/jamapsychiatry.2016.3644.

11. Milev RV, Giacobbe P, Kennedy SH, Blumberger DM, Daskalakis ZJ, Downar J, et al. *Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: Section 4. Neurostimulation treatments*. Can. J. Psychiatry. 2016; 61(9): 561–575. Doi:10.1177/0706743716660033.
12. Voigt J, Carpenter L, Leuchter A. *Cost effectiveness analysis comparing repetitive transcranial magnetic stimulation to antidepressant medications after a first treatment failure for major depressive disorder in newly diagnosed patients – A lifetime analysis.* PLoS One. 2017; 32: 1–15. Doi:10.1371/journal.pone.0186950.
13. Berlim M, Van den Eynde F, Daskalakis Z. *High-frequency repetitive transcranial magnetic stimulation accelerates and enhances the clinical response to antidepressants in major depression: a meta-analysis of randomized, double-blind, and sham-controlled trials*. J. Clin. Psychiatry. 2013; 74(2): 122–129.
14. Carpenter LL, Janicak PG, Aaronson ST, Boyadjis T, Brock DG, Cook IA et al. *Transcranial magnetic stimulation (TMS) for major depression: A multisite, naturalistic, observational study of acute treatment outcomes in clinical practice*. Depress. Anxiety. 2012; 29(7): 587–596. Doi:10.1002/da.21969.
15. Berlim MT, Van Den Eynde F, Jeff Daskalakis Z. *Clinically meaningful efficacy and acceptability of low-frequency repetitive transcranial magnetic stimulation (rTMS) for treating primary major depression: A meta-analysis of randomized, double-blind and sham-controlled trials*. Neuropsychopharmacology. 2013; 38(4): 543–551. Doi:10.1038/npp.2012.237.
16. Berlim MT, McGirr A, Rodrigues dos Santos N, Tremblay S, Martins R. *Efficacy of theta burst stimulation (TBS) for major depression: An exploratory meta-analysis of randomized and sham-controlled trials*. J. Psychiatr. Res. 2017;.90:.102–109. Doi:10.1016/j.jpsychires. 2017.02.015.
17. Blumberger DM, Vila-Rodriguez F, Thorpe KE, Feffer K, Noda Y, Giacobbe P et al. *Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial*. Lancet. 2018; 391(10131): 1683–1692. Doi:10.1016/S0140-6736(18)30295-2.
18. Mendlowitz AB, Shanbour A, Downar J, Vila-Rodriguez F, Daskalakis ZJ, Isaranuwatchai W et al. *Implementation of intermittent theta burst stimulation compared to conventional repetitive transcranial magnetic stimulation in patients with treatment resistant depression: A cost analysis*. PLoS One. 2019; 14: e0222546. Doi:10.1371/journal.pone.0222546.
19. Shen X, Liu M, Cheng Y, Jia C, Pan X, Gou Q et al. *Repetitive transcranial magnetic stimulation for the treatment of post-stroke depression: A systematic review and meta-analysis of randomized controlled clinical trials*. J. Affect. Disord. 2017; 211: 65–74. Doi:10.1016/j.jad.2016.12.058.
20. Sun X, Deng L, Qiu S, Tu X, Wang D, Liu M. *Pharmacological and psychotherapeutic interventions for management of poststroke depression: A Bayesian network meta-analysis of randomized controlled trials*. Med. 2017; 96(7): 1–11. Doi:10.1097/md.0000000000006100.
21. Zhou DD, Wang W, Wang GM, Li DQ, Kuang L. *An updated meta-analysis: Short-term therapeutic effects of repeated transcranial magnetic stimulation in treating obsessive-compulsive disorder*. J. Affect. Disord. 2017; 215: 187–196. Doi:10.1016/j.jad.2017.03.033.
22. Bauer M, Pfennig A, Severus E, Whybrow PC, Angst J, Möller HJ et al. *World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders, Part 1: Update 2013 on the acute and continuation treatment of unipolar depressive disorders*. World J. Biol. Psychiatry. 2013; 14(5): 334–385. Doi:10.3109/15622975.2013.804195.

23. Cohen RB, Boggio PS, Fregni F. *Risk factors for relapse after remission with repetitive transcranial magnetic stimulation for the treatment of depression*. Depress. Anxiety. 2009; 26(7): 682–688. Doi:10.1002/da.20486.

24. Dunner DL, Aaronson ST, Sackeim HA, Janicak PG, Carpenter LL, Boyadjis T et al. *A multisite, naturalistic, observational study of transcranial magnetic stimulation for patients with pharmacoresistant major depressive disorder: Durability of benefit over a 1-year follow-up period*. J. Clin. Psychiatry. 2014; 75(12): 1394–1401. Doi:10.4088/JCP.13m08977.

25. Janicak PG, Nahas Z, Lisanby SH, Solvason HB, Sampson SM, McDonald WM et al. *Durability of clinical benefit with transcranial magnetic stimulation (TMS) in the treatment of pharmacoresistant major depression: Assessment of relapse during a 6-month, multisite, open-label study*. Brain Stimul. 2010; 3(4): 187–199. Doi:10.1016/j.brs.2010.07.003.

26. Sehatzadeh S, Daskalakis ZJ, Yap B, Tu HA, Palimaka S, Bowen JM et al. *Unilateral and bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression: A meta-analysis of randomized controlled trials over 2 decades*. J. Psychiatry Neurosci. 2019; 44(3): 151–163. Doi:10.1503/jpn.180056.

27. Hsu JH, Downar J, Vila-Rodriguez F, Daskalakis ZJ, Blumberger DM. *Impact of prior treatment on remission with intermittent theta burst versus high-frequency repetitive transcranial magnetic stimulation in treatment resistant depression*. Brain Stimul. 2019; 12(6): 1553–1555. Doi:10.1016/j.brs.2019.07.011.

28. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Bond DJ, Frey BN et al. *Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder*. Bipolar Disord. 2018; 20(2): 97–170. Doi:10.1111/bdi.12609.

29. Wang J, Zhou Y, Gan H, Pang J, Li H, Wang J et al. *Efficacy towards negative symptoms and safety of repetitive transcranial magnetic stimulation treatment for patients with schizophrenia: A systematic review*. Shanghai Arch. Psychiatry. 2017; 29(2): 61–76. Doi:10.11919/j.issn.1002-0829.217024.

30. Dlabac-de Lange JJ, Bais L, van Es FD, Visser BGJ, Reinink E, Bakker B et al. *Efficacy of bilateral repetitive transcranial magnetic stimulation for negative symptoms of schizophrenia: results of a multicenter double-blind randomized controlled trial*. Psychol. Med. 2015; 45:1263–1275. Doi:10.1017/S0033291714002360.

31. He H, Lu J, Yang L, Zheng J, Gao F, Zhai Y et al. *Repetitive transcranial magnetic stimulation for treating the symptoms of schizophrenia: A PRISMA compliant meta-analysis*. Clin. Neurophysiol. 2017; 128(5): 716–724. Doi:10.1016/j.clinph.2017.02.007.

32. Slotema CW, Blom JD, Hoek HW, Sommer IEC. *Should we expand the toolbox of psychiatric treatment methods to include repetitive transcranial magnetic stimulation (rTMS)? A meta-analysis of the efficacy of rTMS in psychiatric disorders*. J. Clin. Psychiatry. 2010; 71: 873–884. Doi:10.4088/JCP.08m04872gre.

33. Hsu WY, Ku Y, Zanto TP, Gazzaley A. *Effects of noninvasive brain stimulation on cognitive function in healthy aging and Alzheimer's disease: a systematic review and meta-analysis*. Neurobiol. Aging. 2015; 36(8): 2348–2359. Doi:10.1016/j.neurobiolaging.2015.04.016.

34. Lee J, Choi BH, Oh E, Sohn EH, Lee AY. *Treatment of Alzheimer's disease with repetitive transcranial magnetic stimulation combined with cognitive training: a prospective, randomized, double-blind, placebo-controlled study*. J. Clin. Neurol. 2016; 12(1): 57–64. Doi:10.3988/jcn.2016.12.1.57.

35. Zhao J, Li Z, Cong Y, Zhang J, Tan M, Zhang H et al. *Repetitive transcranial magnetic stimulation improves cognitive function of Alzheimer's disease patients*. Oncotarget. 2017; 8(20): 33864–33871. Doi:10.18632/oncotarget.13060.

36. Anderkova L, Rektorova I. *Cognitive effects of repetitive transcranial magnetic stimulation in patients with neurodegenerative diseases – Clinician's perspective*. J. Neurol. Sci. 2014; 339(1–2):.15–25. Doi:10.1016/j.jns.2014.01.037.

37. Liao X, Li G, Wang A, Liu T, Feng S, Guo Z et al. *Repetitive transcranial magnetic stimulation as an alternative therapy for cognitive impairment in Alzheimer's disease: a meta-analysis*. J. Alzheimer's Dis. 2015;.48:.463–472. Doi:10.3233/JAD-150346.

38. Birba A, Ibáñez A, Sedeño L, Ferrari J, García AM, Zimerman M. *Non-invasive brain stimulation: A new strategy in mild cognitive impairment?* Front. Aging Neurosci. 2017; 9: 1–13. Doi:10.3389/fnagi.2017.00016.

39. Trebbastoni A, Pichiorri F, D'Antonio F, Campanelli A, Onesti E, Ceccanti M et al. *Altered cortical synaptic plasticity in response to 5-Hz repetitive transcranial magnetic stimulation as a new electrophysiological finding in amnestic mild cognitive impairment converting to Alzheimer's disease: Results from a 4-year prospective cohorts*. Front. Aging Neurosci. 2016; 7: 1–10. Doi:10.3389/fnagi.2015.00253.

40. Lawrence BJ, Gasson N, Bucks RS, Troeung L, Loftus AM. *Cognitive training and noninvasive brain stimulation for cognition in Parkinson's disease: a meta-analysis*. Neurorehabil. Neural. Repair 2017; 31(7): 597–608. Doi:10.1177/1545968317712468.

41. Buard I, Sciacca DM, Martin CS, Rogers S, Sillau SH, Greher MR et al. *Transcranial magnetic stimulation does not improve mild cognitive impairment in Parkinson's disease*. Mov. Disord. 2017; 00:1–3. Doi:10.1002/mds.27246.

42. Morrin H, Fang T, Servant D, Aarsland D, Rajkumar AP. *Systematic review of the efficacy of non-pharmacological interventions in people with Lewy body dementia*. Int. Psychogeriatrics. 2018; 30(3): 395–407. Doi:10.1017/S1041610217002010.

43. Lanza G, Bramanti P, Cantone M, Pennisi M, Pennisi G, Bella R. *Vascular cognitive impairment through the looking glass of transcranial magnetic stimulation*. Behav. Neurol. 2017;2017. doi:10.1155/2017/1421326.

44. Kedzior KK, Gierke L, Gellersen HM, Berlim MT. *Cognitive functioning and deep transcranial magnetic stimulation (DTMS) in major psychiatric disorders: A systematic review*. J. Psychiatr. Res. 2016; 75: 107–115. Doi:10.1016/j.jpsychires.2015.12.019.

45. Carmi L, Alyagon U, Barnea-Ygael N, Zohar J, Dar R, Zangen A. *Clinical and electrophysiological outcomes of deep TMS over the medial prefrontal and anterior cingulate cortices in OCD patients*. Brain Stimul. 2018; 11(1): 158–165. Doi:10.1016/j.brs.2017.09.004.

46. Donse L, Sack AT, Fitzgerald PB, Arns M. *Sleep disturbances in obsessive-compulsive disorder: Association with non-response to repetitive transcranial magnetic stimulation (rTMS)*. J. Anxiety Disord. 2017; 49: 31–39. Doi:10.1016/j.janxdis.2017.03.006.

47. Yan T, Xie Q, Zheng Z, Zou K, Wang L. *Different frequency repetitive transcranial magnetic stimulation (rTMS) for posttraumatic stress disorder (PTSD): A systematic review and meta-analysis*. J. Psychiatr. Res. 2017; 89: 125–135. Doi:10.1016/j.jpsychires.2017.02.021.

48. Maiti R, Mishra BR, Hota D. *Effect of high-frequency transcranial magnetic stimulation on craving in substance use disorder: a meta-analysis.* J. Neuropsychiatry Clin. Neurosci. 2017; 29(2): 160–171. Doi:10.1176/appi.neuropsych.16040065.

49. Zhang JJQ, Fong KNK, Ouyang R, Siu AMH, Kranz GS. *Effects of repetitive transcranial magnetic stimulation (rTMS) on craving and substance consumption in patients with substance dependence: a systematic review and meta-analysis.* Addiction. 2019; 114(12): 2137–2149. Doi:10.1111/add.14753.

50. McClintock SM, Reti IM, Carpenter LL, McDonald WM, Dubin M, Taylor SF et al. *Consensus recommendations for the clinical application of repetitive transcranial magnetic stimulation (rTMS) in the treatment of depression*. J. Clin. Psychiatry. 2018; 79(1): 16cs10905. Doi:10.4088/JCP.16cs10905.

51. Health Quality Ontario. *Repetitive transcranial magnetic stimulation for treatment-resistant depression: A systematic review and meta-analysis of randomized controlled trials*. Ont. Health Technol. Assess. Ser. 2016; 16(5): 1–66.

Address: Agnieszka Kobyłko
Wroclaw Medical University
Department and Clinic of Psychiatry
50-367 Wrocław, Wybrzeże L. Pasteura Street 10
e-mail: agnieszka.kobylko@student.umed.wroc.pl