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Principles of patients selection and safety of repetitive transcranial magnetic stimulation – position statement of the Section of Biological Psychiatry of the Polish Psychiatric Association

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Summary

Transcranial magnetic stimulation (TMS) is a method of noninvasive brain stimulation developed since the 1980s. Repetitive transcranial magnetic stimulation (rTMS) is one of the methods of noninvasive brain stimulation, which is increasingly used to treat psychiatric disorders. Recent years witnessed a dynamic growth in the number of sites offering therapy with rTMS and of the interest of patients in this method in Poland. This article presents the position statement of the working group of the Section of Biological Psychiatry of the Polish Psychiatric Association concerning the proper patients selection and safety of use of rTMS in the therapy of psychiatric conditions.

Before starting to use rTMS, the involved personnel should undergo a period of training in one of the centers with relevant experience. Equipment dedicated to perform rTMS should be appropriately certified. The main therapeutic indication is depression, including drug-resistant patients. rTMS may also be used in obsessive-compulsive disorder, negative symptoms and auditory hallucinations in schizophrenia, nicotine addiction, cognitive and behavioral disturbances in Alzheimer's disease, and post-traumatic stress disorder. The strength of magnetic

stimuli and the overall dosing of stimulation must be based on the recommendations of the International Federation of Clinical Neurophysiology. The main contraindications are the metal elements in the body, especially medical electronic devices near the stimulating coil, epilepsy, hearing loss, structural changes in the brain, which may be associated with epileptogenic foci, pharmacotherapy, which lowers the seizure threshold, and pregnancy. The main side effects are induction of epileptic seizure, syncope, pain and discomfort during stimulation, as well as induction of manic or hypomanic episodes. The respective management is described in the article.

Key words: TMS, rTMS, safety guidelines, side effects

Introduction

Transcranial magnetic stimulation (TMS) is a method of noninvasive stimulation of the nervous system, being developed since the 1980s [1]. TMS applies brief, time-varying pulses of magnetic field over the cerebral cortex and other superficial neural structures. According to Faraday's law, after penetrating into the neural tissue, the magnetic field induces the electric current, which depolarizes the targeted neurons. Due to very limited attenuation of the magnetic field by its passing through the skull and other layers, the required strength of magnetic stimuli usually does not exceed 2 T. Such stimuli are mostly well tolerated. Only a minor part of patients complain of mild to moderate headache or other unpleasant experiences resulting mostly from the contraction of the head musculature [2].

TMS with single stimuli is used in neurology, most often to excite the primary motor cortex and to record the motor evoked potentials (MEPs) from respective skeletal muscles, which then allows to assess the conduction in the central motor pathways [3]. In neurosurgery, single stimuli are used with neuronavigation to map the eloquent areas preoperatively, which optimizes the extent of surgical resection and helps to spare the area [4]. Stimulation with paired pulses allows multidimensional assessment of cortical excitability, which is increasingly used to differentiate between various types of dementias and other neurodegenerative processes [5].

The application of TMS in psychiatry is mainly for therapeutic purposes, which presumes stimulation with series of stimuli called the repetitive transcranial magnetic stimulation (rTMS). rTMS induces brain plasticity. Depending on the frequency and the pattern of the stimuli emission, the induced plasticity may be directed predominantly towards long term potentiation (LTP) with a local increase of metabolic rate and neural activity or long term depression (LTD) with the decrease of metabolic rate. In general, LTP is induced with high frequency (5–20 Hz) and with several more complex patterns of stimulation of which the most widely used is the intermittent theta burst stimulation (iTBS). LTD, in turn, occurs after low frequency, i.e., 1 Hz or less or after the continuous theta burst stimulation (cTBS) and several other patterns [6]. The effect of the single therapeutic session, containing usually several hundred to several thousand stimuli outlasts the session for minutes to hours. Depending on the

condition treated, the whole therapy consists of several to several dozens of sessions, which stabilizes and prolongs the therapeutic effect for weeks or months. In most cases, therapeutic sessions are done once a day, on weekdays and the entire therapy can last, e.g., four weeks. Recently, the new protocols termed "accelerated rTMS" gain clinical attention. These protocols involve performing several sessions a day, which shortens the time of therapy [7].

rTMS is meanwhile a widely used, often refundable therapeutic option. In 2008, it has been cleared for treatment-resistant depression by Federal Drugs Administration (FDA) and in the previous year also for obsessive-compulsive disorder. In the last few years, we can observe a rapid increase in the number of medical centers which offer rTMS as well as growing interest of the patients in Poland. Moreover, there is a noticeable increase in the number of offered magnetic stimulators and coils on the domestic market. The reason for these changes is the well-documented effectiveness of rTMS as well as its noninvasive character. At the time of preparation of these guidelines, rTMS was used in seven psychiatric in-patients centers of public healthcare in Poland with several hundred patients already having undergone the therapy. The number of private facilities which offer rTMS is not known, but most likely it is growing rapidly. The present statement of the Section of Biological Psychiatry of the Polish Psychiatric Association addresses the need for the appropriate selection of the patients and for performing the therapy safely and effectively in Poland. The statement bases on the international guidelines and own experiences gained during work in Polish healthcare. In future, the present text may contribute to the issue of the legal regulations of the use of rTMS in Poland.

The process of preparation of these guidelines

The need of preparation of guidelines, specific for psychiatric healthcare in Poland, was identified by the Section of Biological Psychiatry of the Polish Psychiatric Association under presidency of prof. dr hab. n. med. A. Wichniak. He entrusted dr A. Poleszczyk, mgr W. Dębowska and dr. hab. J. Antczak with the task of preparation of the preliminary version of the guidelines. Professor A. Wichniak also invited the experts from leading Polish academic centers who have experience in using rTMS as collaborators. The preliminary version was prepared mainly on the basis of available, respective literature. It was then sent to invited experts, who proposed their additions and modifications: prof. dr hab. n. med. J. Rymaszewska precised the fragment about indications and performing rTMS in patients with depression. She also described in more details the principles of application of classic and new protocols of stimulation. Professor J. Kaźmierski enriched the chapter concerning the use of rTMS in patients with implanted metal elements and wrote additional recommendations for patients with dementia and mild cognitive impairment. Prof. dr hab. n. med. N. Waszkiewicz added the comments regarding therapy in patients

with many psychiatric comorbidities and with suicidal ideations. Moreover prof. J. Rymaszewska, prof. J. Kaźmierski and prof. N. Waszkiewicz, basing on their experiences, modified the preliminary version, adapting these guidelines to the psychiatric healthcare in Poland. The questionnaire before receiving rTMS was created by mgr. W. Dębowska. Dr hab. J. Antczak introduced additions and modifications sent by other authors to the preliminary version. The updated text was sent by prof. A. Wichniak to all other authors for final approval.

GUIDELINES

The location where rTMS is done and the personnel

rTMS should be done exclusively in healthcare institutions. Patients selection and the design of the stimulation protocol should be done by a physician. The rTMS procedure can be performed by a medical technician. Both technicians and physicians should do training in one of the centers with sufficient respective experience before starting rTMS.

The equipment dedicated to rTMS

The frequency of the side effects may vary concerning which type of magnetic stimulator and coil are used. The respective data is, however, sparse and the reliable comparison of safety levels between particular products marketed currently in Poland is not possible. It is recommended to use magnetic stimulators and coils labeled with the CE sign and registered in the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products. The vast majority of the equipment available in Poland fulfils these requirements. Devices used in a TMS laboratory should be inspected regularly and the respective documentation should be stored and updated.

Psychiatric indications for rTMS

The most common psychiatric indication for rTMS is major depression, including drug-resistant depression. Therapeutic efficacy is documented with several hundred publications and confirmed in the guidelines of psychiatric and neurophysiological associations [8–10]. According to the precise recommendations of the Canadian Network for Mood and Anxiety Treatments, developed by Milev et al. [11], rTMS is the first-line treatment in patients with a depressive episode who did not respond to at least one antidepressive agent. The majority of studies and guidelines recommend the continuation of pharmacotherapy during rTMS and the evidence exists that rTMS used complementary to the drugs has efficacy superior to rTMS alone [12].

The protocol of stimulation, most frequently used so far is the high-frequency stimulation (5–20Hz) over the left dorsolateral prefrontal cortex (DLPFC) using

a stimulating coil in the shape of the figure of eight or coils of H-type as well as other coils for the deep repetitive transcranial magnetic stimulation (dTMS). The strength of the therapeutic stimuli exceeds slightly the level of the motor threshold (MT). MT is the lowest intensity of the magnetic field which is capable to reliably evoke MEPs. The method of estimating MT and of localizing the area over the scalp where the DLPFC can be optimally stimulated is beyond the scope of this article. The interested reader is referred to the appropriate English language [3, 13] or Polish language [14, 15] publications.

The evidence of safety and efficacy of several other depression treatment protocols, though much smaller than that of the high frequency over the left DLPFC, is sufficient to use them in routine treatment. These protocols include low-frequency rTMS over the right DLPFC, rTMS over bilateral DLPFC (low frequency over the right and high frequency over the left hemisphere), cTBS and iTBS over the right and left DLPFC [10]. The low-frequency rTMS may be better tolerated. iTBS over the left DLPFC is the only protocol with documented noninferiority to the classic, 10 Hz protocol over the left DLPFC [16], despite a significant reduction in the duration of a single session. Despite these advantages, the doctor who discusses the treatment should inform his/her patient that the protocols other than the classic one have less proven efficacy. Accelerated rTMS seems to be safe and effective. To date, its efficacy has not been, however, compared with a traditional schedule with one rTMS session once a day [7].

Other psychiatric indications with documented therapeutic effects of rTMS include obsessive-compulsive disorder (OCD), where the protocols of choice are the low-frequency rTMS (1 Hz or less) over the right DLPFC or dTMS over the medial prefrontal and the anterior cingulate cortex [17]. The use of dTMS for OCD has been FDA cleared. Further indications are the negative symptoms of schizophrenia (high-frequency rTMS over the left DLPFC), auditory hallucinations in schizophrenia (low frequency rTMS over the temporo-parietal area), nicotine dependence (high-frequency stimulation over the left DLPFC), and post-traumatic stress disorder (high-frequency stimulation over the right DLPFC) [10]. Recently, the use of rTMS in patients with mild cognitive impairment and dementias, in particular Alzheimer's disease (AD) gained momentum and the randomized controlled trials, in which the control group consisted of patients subjected to sham therapy, documented improvement of global cognitive functions measured with the Mini-Mental State Examination (MMSE) and with the Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog). Similarly, improvement was seen in particular cognitive domains, including memory, attention, language, and visuo-spatial domain [18–21]. Moreover, the results indicate that rTMS improves behavioral and affective symptoms in AD [21, 22]. According to the last meta-analysis (n = 293), the size of the therapeutic effect of rTMS in AD is moderate to large (0.77) with respect to placebo [23]. A no-

table limitation is the lack of studies evaluating the therapeutic effect in a period longer than three months after therapy. Neither the effect of the maintenance rTMS to prolong the therapeutic gain from the main therapy cycle has been assessed. In the majority of trials conducted to improve the cognitive functions, the left DLPFC was stimulated with 1800 to 3000 magnetic pulses in one session. Frequently, the cognitive training was done simultaneously with rTMS [23]. Some studies investigated the effect on cognition after stimulation over several areas associated with various cognitive domains, which was effective and safe but not superior to one-site stimulation [24]. In general, rTMS in patients with cognitive impairment is not less safe than in other groups. Due to the age of the patients, it is more likely that a person with an implanted pacemaker or vascular lesions within the CNS may qualify for therapy. Considering the limited effectiveness and only symptomatic effect of drugs used in Alzheimer's disease and the high safety of non-invasive neuromodulation techniques, rTMS therapy combined with cognitive training may be recommended as the adjuvant therapy in patients diagnosed with cognitive and behavioral disorders in the course of Alzheimer's disease

In other psychiatric conditions, rTMS can be used within research projects and the approval of the appropriate ethics committee must be always obtained. The present article does not include the non-psychiatric indications for rTMS such as pain, migraine or post-stroke weakness. Beyond the scope are also the indications and safety issues in pediatric population.

Safety of magnetic field and the dosing of rTMS

The strength of the magnetic field and the dosing of stimulation should comply with the guidelines and recommendations of the International Federation of Clinical Neurophysiology (IFCN) published in 2009 [25] and updated in 2021 [26]. The classic protocol for depression cleared by FDA in 2008 and updated in 2018 includes the following parameter of stimulation over the left DLPFC:

- frequency: 10 Hz;
- stimulus strength: 120% MT;
- intervals: 4 sec. ON, 11 sec. OFF, 75 repeats / or according to terminology used by some manufacturers: trains of 4 sec. (40 pulses in train), with 11 sec. intertrain intervals, 75 trains in one session;
- duration of the session: 19 min;
- 5 sessions a week; 6 weeks = 30 sessions in total;
- 3,000 pulses per session = 90,000 pulses during the whole therapy.

No minimal interval between sessions is established in accelerated protocols. It is only known that the intervals of several hours used so far were not associated with the

occurrence of epileptic seizures in subsequent sessions. Similarly, 50-min intervals in the SAINT protocol (one of the newest accelerated rTMS protocols) [27], which included ten sessions a day for 5 days, were not associated with seizures. According to available data, iTBS and cTBS protocols are safe with stimulation intensity up to 120% MT [16].

Any protocol deviating from above specified should comply with the IFCN guidelines [25]. These guidelines specify the maximal safe strength of magnetic stimuli, the highest safe frequency with which the stimuli follow each other in the train, the maximal safe duration of the train and the shortest safe intertrain interval. No precise limits are set regarding the number of trains and stimuli in a single therapeutic session as well as the number of sessions in the whole therapy. Usually in depression, 20 to 30 sessions are administered once a day, in the following week-days. The whole therapy then lasts four to six weeks.

rTMS not preceded by registration of meps

According to the traditional procedure, the strength of the therapeutic stimuli is derived from the value of MT, which in turn is estimated by measuring the MEPs recorded from skeletal muscles with electrophysiologic equipment. Since over a decade, some centers replace the recording of MEPs with the visual assessment of muscle twitches after magnetic stimuli over the motor cortex. Also some of the sets for rTMS offered in Poland are now marketed without the amplifier to record MEPs. MT estimated visually is usually higher than using MEPs [28]. In consequence, visually estimated MT increases the strength of therapeutic stimuli, which, however, does not lead to more frequent occurrence of serious side effects or worse therapeutic effectiveness [29]. For this reason, rTMS may be done safely without the registration of MEPs. The pain which may be associated with strong stimuli may, however, compromise the tolerance of the therapy. Therefore, in the case of poor tolerance of the therapy after determining MT with the visual method, it is worth considering the re-determination of the motor excitability threshold in the laboratory, where it can be done using the electrophysiological method.

Magnetic seizure therapy (MST)

MST is a technique used since nearly twenty years to treat severe depression and other severe psychiatric disorders [30]. This technique differs in protocol from standard rTMS. Similarly to electroconvulsive therapy (ECT), MST aims at induction of seizure under general anesthesia. The strength of stimuli is 100% of the maximal stimulator output and the frequency is between 25 to 100 Hz with the train duration of 10 seconds (such parameters exceed by far the safety limits for conventional rTMS). The trains are repeated every 20 seconds until the continuously recorded electroencephalogram

(EEG) shows the seizure activity. In comparison to ECT, the energy delivered to the brain as well as the stimulated brain area are markedly smaller. The patients selection, safety procedures and monitoring of vital functions and EEG are similar to ECT. At the moment none of the domestic centers does MST (according to the knowledge of the authors). We therefore recommend training in one of the experienced foreign laboratories before starting treatment with MST.

rTMS in subjects with metal elements in the body

Metal elements in the proximity of stimulating coil, such as aneurysm clips, orthopedic implants, shrapnel, residual fillings in the eye can be displaced or heated during stimulation. In the subcutaneous or superficial wires leading to EEG-electrodes, deep brain stimulation, spinal or vagal stimulator eddy currents may be induced during rTMS, especially if the wires are arranged in loops. In consequence, the tissues in the brain, eyeball and other body parts may be damaged. rTMS in patients with metal elements within the brain is therefore not advisable with several exceptions where additional precautions should be taken.

In patients with metal elements without attached wires (such as aneurysm clips or surgical sutures) stimulation is safe if elements are not a contraindication for magnetic resonance imaging (e.g., are made up of titanium). We emphasize here the importance of a reliable interview regarding the elements' composition. The optimal way to ensure that rTMS will be safe is to obtain the respective documentation or direct interview with a physician who implanted the metal. The next exception are the valves to treat hydrocephalus, which are safe as proved experimentally. It is, however, recommended to check the settings of the valve during and after rTMS [31]. If a suspicion arises that the metal element may pose a hazard we recommend referring the patient to one of the domestic or foreign centers with experience in such stimulation. rTMS in these patients should be rather an exception. It always requires meticulous procedures to assess potential risk. One of such procedures is the *ex vivo* stimulation of an element identical with the implanted one with the observation of its possible displacement or heating.

In the case of subcutaneous and deep electrodes, the safety assessment should be done by personnel with the appropriate technical background. It includes analysis of possible induction of electric currents, switching off the stimulators for the TMS session, appropriate arrangement of superficial wires and electrodes as well as EEG-monitoring during TMS. EEG during magnetic stimulation can only be recorded using a dedicated set containing electrodes without magnetic elements. Similarly, rTMS done simultaneously with transcranial direct current stimulation, transcranial alternating current stimulation or transcranial random noise stimulation should be performed with materials and electrode arrangement which will not induce significant currents.

Batteries for cardiac pacemakers, vagus nerve stimulators or deep brain stimulation electrodes are not a contraindication for rTMS if their distance to the stimulating coil is more than 10 centimeters. Such distance should be carefully assessed before every treatment. In uncertain cases, the therapy should not be done. The cochlear implants are located in proximity to all cortical areas and therefore they are a contraindication for rTMS [26]. (The new generation implants, adapted to operate in a magnetic field, not contraindicated for MRI and TMS are in their testing phase [32], however, they will not be commonly used in the nearest future).

Dentures do not bring the risk of adverse events. Permanent make-up and tattoos can contain metal particles, which may be overheated and increase the discomfort of the stimulated person, however, without the risk of serious adverse events. Earrings and other jewelry on the head should be removed for the time of stimulation. The present article does not describe the safety issues during TMS performed simultaneously with the acquisition of MRI. This procedure is currently done only in research settings with dedicated equipment and specific safety rules.

TMS in patients with structural changes in the brain

Traumatic and postoperative changes in the brain, as well as post-stroke scars, brain tumors and structural changes related to infections, may predispose to epileptic seizures. For this reason, such patients should be stimulated with particular attention regarding their safety. Moreover, the structural changes in the CNS may displace the cortical areas, which may be the target for the planned rTMS. The coil placement in such patients should regard their current neuroimaging. If a possibility exists, the neuronavigation should be used to optimize the coil placement.

Possible adverse events and procedures to minimize them

Induction of epileptic seizure

The risk of seizure during stimulation does not resolve completely even when all the safety precautions are taken. It is, however, lower than one event per one thousand of the conducted sessions in the population at risk of the seizure induction and significantly lower when there is no risk [25]. The risk further declines when a person undergoes the first rTMS session without the seizure [33]. Of note, all events to date, were single, usually short and spontaneously resolving seizures. Cluster seizures, status epilepticus and TMS influence on the development of epilepsy were not observed [26].

According to evidence, pharmacotherapy including seizure threshold lowering drugs does not affect safety [33]. It is, however, recommended that the drug regimen is unchanged during the whole therapy. In accordance with the general practice, phar-

macological treatment is maintained unchanged also during stimulation in patients with drug-resistant depression. If the change becomes necessary during rTMS, the MT should be estimated anew after the pharmacotherapy has been changed and the possibly resulting change in the strength of therapeutic stimuli should be introduced. A similar procedure is recommended in all other circumstances where the seizure threshold is likely to change, such as significant consumption of alcohol or other psychoactive substances or significant sleep deprivation. In patients with multiple factors contributing to the lowering of the threshold, such as co-occurrence of neurodegenerative process, post-stroke structural changes, electrolyte imbalance, infection, antibiotic treatment, unstable blood glucose level, significant endocrine changes, family history of epilepsy, and others, the decision should be tailored for each patient individually. The risks and benefits should be weighted. The therapeutic team should also consider if the therapy can be postponed until the overall risk of seizure will decrease, for example, after an infection is cured or electrolytes return to normal levels. If appropriate equipment is available, the electroencephalographic activity should be monitored during rTMS in patients at risk of seizure. If epileptiform discharges appear, discontinuation of therapy should be considered. Regardless of the seizure risk and electroencephalographic monitoring, we recommend that all patients should be monitored visually for the occurrence of myoclonic jerks and other signs which may herald the seizure through the entire rTMS session. If such signs appear, the stimulation must be stopped immediately. Subsequently, the decision to terminate or to postpone the therapy, or to modify it (e.g., by a weakening of therapeutic stimuli) should be made. The exception is the occurrence of involuntary movements during rTMS over primary motor areas where it is not associated with the risk of seizure. Such stimulation, however, is not performed for psychiatric indications.

Every member of the personnel involved in rTMS should be trained in the management of epileptic seizures. In laboratories where a patient sits in the armchair, the place should be designed where he/she could be placed in a horizontal position. The physician does not need to stay in the room where rTMS is performed, but a pathway to call him and to his/her arrival within several minutes should be secured. A person performing TMS should be able to call other staff using his/her voice and not the telephone (when he/she will deal with a patient with a seizure, using the telephone may be difficult). A TMS laboratory should be equipped with life-support equipment. The management of the seizure includes placement of the patient in horizontal, side position, protection of the head and other vulnerable parts of the body against trauma and securing the airway patency. In all stimulation-induced seizures described so far no additional interventions were needed as the seizures were characterized by a short duration and spontaneous remission. In case of cluster seizures or status epilepticus, the management should be in accordance with the center's guidelines or the guidelines of the Polish Neurological Society [34].

Induction of a seizure is not an absolute indication to terminate the therapy. Safe continuation after the seizure with satisfying therapeutic effect has been described in several reports [35–37]. The decision whether rTMS must be stopped or can go on after the seizure should be made individually, including an assessment of potential benefits and risks as well as possible negative consequences if a second seizure was to occur.

Syncopes

Syncopes resulting mostly from anxiety occur before, during and after the stimulation with frequency which is probably comparable to other medical interventions [38]. In case of syncope, rTMS must be stopped and the patient must be placed in the horizontal side position. The airway patency must be secured. Therapy can be resumed after the patient is emotionally prepared. The use of an anxiolytic drug can be considered. The differentiation between seizure and syncope should be done carefully as the latter can be associated with the tongue bit and myoclonic jerks. If there is a possibility, the session can be videotaped. In unclear cases, the consultation of a specialist in epileptology is recommended.

Hearing loss

The deformation of the coil during the induction of the magnetic field produces noise in the direct proximity of the ears. The intensity of the noise can exceed the acoustic safety norms. Transient and persistent hearing loss have been described in patients and healthy subjects undergoing rTMS [39–41]. For this reason, ear protection in the form of plugs or muffs for persons being stimulated is mandatory. Although the noise reaches the TMS operator with much lower intensity, ear protection should be applied also to the staff which stays in the laboratory during the session. Every time the stimulated or stimulating person reports the subjective worsening of hearing, audiologic testing should be done. Hearing loss and tinnitus are among the relative contraindications for TMS. The decision about starting the therapy should be preceded with careful assessment of potential benefits and the risk of further hearing decline and worsening of tinnitus.

Psychiatric side effects

Few papers described the induction of manic or hypomanic episodes during rTMS, mainly among patients with depression. One of them is the study of Hu et al. [42] who observed conversion of the diagnosis from unipolar to bipolar affective disorder in as much as 37% of stimulated patients. On the other hand, according to the systematic review of Xia et al. [43] on rTMS efficacy in depression, there were only four cases

of transition to a manic or hypomanic phase in ten studies in which this change in the mood was documented. There was also no significant difference in the frequency of phase change in unipolar and bipolar patients between the active and placebo groups. In the subgroup of bipolar patients (n = 65), the frequency of change to mania was 3.1% and was comparable to such frequency seen among bipolar patients receiving normothymic medication [43]. In unipolar patients, mood transition frequency was 0.37%. In a recent review, which focused only on bipolar patients, the transition was observed only in 14 out of 611 patients [44]. In the study of Nedjad and Folkerts [45], evaluating the safety of rTMS in healthy volunteers, mood elevation (corresponding to hypomania in 3 out of 50 people) was observed within an hour of rTMS termination, but resolved spontaneously by the next day.

In summary, there are many discrepancies regarding the data on the association of rTMS with induction of manic or hypomanic episodes. At the moment, it cannot be confirmed that rTMS contributes significantly to such transition in patients with depression. It is nonetheless recommended to check upon the mood of the patient after every few sessions. In patients at risk of induction of manic or hypomanic episodes a normothymic drug, starting before rTMS, can be considered. However, an individual approach should be taken when a patient develops hypomania or mania. Discontinuation of rTMS should then be considered, however, if symptoms are not severe, continuation of therapy may be attempted in patients with mild symptoms with reduced frequency of the sessions (e.g., every second day), reduced rTMS frequency (e.g., from 10 Hz to 5 Hz) and/or reduced strength of stimuli (e.g., from 120% to 100% MT). Another option is an administration of normothymic drug with checking on the possible MT change and respective adjustment of the strength of therapeutic stimuli.

Other side effects in the psychiatric population include anxiety or exacerbation of the preexisting anxiety, exacerbation of psychomotor agitation and sleep disorders [16, 27, 46]. Continuation of rTMS despite these symptoms was safe after reduction of the rTMS frequency from 10 Hz to 5 Hz [46]. Some reports described also the occurrence of psychotic symptoms [47] as well as the occurrence or exacerbation of suicidal ideations during rTMS [16, 47] and the exacerbation of depression itself, which required hospitalization [16]. According to IFCN, however, psychiatric side effects are not more frequent in the groups treated with real stimulation than in those with sham stimulation [25]. Psychiatric complications during rTMS are therefore likely to result from the illness itself. The occurrence of psychotic symptoms in patients with depression was, however, associated with worse rTMS efficacy [48]. For this reason, psychotic symptoms should be seen as the relative contraindication for rTMS. Regarding suicidal ideations, patients should be tightly controlled during and after stimulation. Suicidal ideations are, however, not a contraindication for rTMS since rTMS can improve them [49, 50].

Pain and discomfort

Pain and discomfort are relatively frequent side effects of rTMS, but only rarely they become severe enough to disrupt the therapy [25]. To alleviate the pain oral, nonsteroidal anti-inflammatory drugs can be administered, especially when the pain outlasts the stimulation. In some centers, local anesthetics in the form of a cream applied on the skin at the site of stimulation are used. Their efficacy, however, has not been confirmed. If the pain localizes in the neck or nuchal area, significant relief can be achieved with the adjustment of the armchair or the coil holding. (A frequent error is an excessive pressure exerted by the coil on the head of the stimulated person due to not optimal holding by the human hand but also by the dedicated mechanic arm).

Personnel performing rTMS

No side effects have been reported in the staff performing TMS. IFCN recommends, however, that the staff member should not stay closer than 40 cm to the stimulating coil for longer periods. Staff members who are pregnant should maintain the distance between fetus and coil not shorter than 60 cm. Earplugs or ear muffs should be worn [26].

Contraindications

An absolute contraindication is the presence of electronic medical hardware, vulnerable to the magnetic field, which is closer than 10 cm from the stimulating coil. This applies to, e.g., above-mentioned cochlear implants.

Relative contraindications

- History of epilepsy: according to data, the risk of seizure induction in patients with epilepsy is below two or three percent [51–53].
- Pregnancy: The distance separating an embryo or fetus from the stimulating coil is usually more than 60 cm. Such distance ensures that the magnetic field which reaches the child is too weak to bear any risk [54]. In a randomized, controlled trial with pregnant, depressive women, no negative impact of rTMS on pregnancy and the fetuses was shown. The study included, however, only 22 women [55]. A dangerous outcome may result from the induction of the seizure during rTMS. No evidence, however, exists regarding the negative impact of seizure on pregnancy. In this situation, pregnancy should be considered a relative contraindication to TMS. When making a therapeutic decision, numerous factors should be considered. The main of them include

the possible negative influence of pharmacotherapy on the child, significance of the possible contraindications for ECT (ECT is relatively safe for the child as the mother is anesthetized, ventilated and the muscles are paralyzed) or the possible consequences of deferring the therapy for the postpartum period. (Pregnancy is a contraindication for magnetic stimulation of spinal roots, especially of the lumbosacral segment, which is occasionally done for neurological indications).

- Structural changes in the brain due to trauma, surgery, infection or stroke, as the potential epileptogenic foci.
- Psychiatric disorders or behaviors resulting in excessive consumption of alcohol and other psychoactive substances, irregular intake of drugs, periods of sleep deprivation, as the factors lowering the seizure threshold.
- Infections, electrolyte imbalance and other somatic conditions which may lower the seizure threshold
- Therapy with drugs lowering seizure threshold, especially when changing frequently.
- Metal elements in the head (except dentures, makeup and tattoos).

It is advisable to use a questionnaire which helps to assess the possible contraindications for TMS. Such questionnaire was published by IFCN [56]. The questionnaire in the Polish language recommended by the Section of Biological Psychiatry of the Polish Psychiatric Association is included at the end of this article (Annex).

One should remember that the positive responses to particular questions do not need to result in the exclusion of the patient from rTMS. The questionnaire is intended to be only help in identifying and assessing the importance of possible risk factors. The final therapeutic decision should be taken by the physician experienced in rTMS after taking into consideration all significant circumstances. Additionally to the questionnaire, every patient should read the information and sign the consent before therapy.

The new protocols of stimulation and the new devices

Stimulation with a protocol or with equipment which has never been used before should always be done in research settings, after the approval of the proper bioethics committee has been obtained. We recommend monitoring of the vital parameters and EEG after every session. If possible, the EEG monitoring should be done also during the sessions. Similarly, multi-channel electromyographic monitoring with superficial electrodes placed on different extremities should be performed (recording the possible spread of myoclonic jerks, heralding a seizure). Moreover, after every few sessions the patient should undergo a general psychiatric examination and the assessment of cogni-

tive functions. These recommendations are of particular importance if the investigated protocol exceeds the safety parameters published by IFCN [25].

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ANNEX

The questionnaire before receiving therapy with rTMS

Kwestionariusz dla osób kwalifikowanych do terapii z użyciem przezczaszkowej stymulacji magnetycznej (TMS)	
Proszę o zapoznanie się z listą potencjalnych przeciwwskazań do odbycia badania/sesji terapii z wykorzystaniem przezczaszkowej stymulacji magnetycznej (TMS). W przypadku punktów od 1 do 17 proszę o zaznaczenie, czy dane przeciwwskazanie Pani/Pana dotyczy:	

1. Schorzenia neurologiczne	**TAK**	**NIE**
2. Padaczka lub wystąpienie w przeszłości napadu padaczkowego	**TAK**	**NIE**
3. Występowanie padaczki w rodzinie	**TAK**	**NIE**
4. Występowanie w przeszłości omdleń, okresów utraty świadomości	**TAK**	**NIE**
5. Wystąpienie w przeszłości poważnych urazów głowy	**TAK**	**NIE**
6. Występowanie w przeszłości napadów migrenowych	**TAK**	**NIE**
7. Problemy ze słuchem, dzwonienie w uszach	**TAK**	**NIE**
8. Wszczepiony implant ślimakowy	**TAK**	**NIE**
9. Metalowe implanty w mózgu, czaszce bądź innych częściach ciała	**TAK**	**NIE**
10. Wszczepiony jakikolwiek typ stymulatora biologicznego, np. neurostymulator	**TAK**	**NIE**
11. Wszczepiony rozrusznik serca	**TAK**	**NIE**
12. Implantowana pompa insulinowa lub implantowane urządzenie infuzyjne	**TAK**	**NIE**
13. Spożycie więcej niż 2 jednostek alkoholu w ciągu ostatnich 24 h	**TAK**	**NIE**
14. Spożycie dużej ilości kofeiny w ciągu ostatniej godziny	**TAK**	**NIE**
15. Brak snu ostatniej nocy (np. spanie o 3 h krócej niż zazwyczaj)	**TAK**	**NIE**
16. DOTYCZY KOBIET: czy jest/może być Pani w ciąży	**TAK**	**NIE**
17. Przyjmowanie leków Jeśli tak, proszę wymienić jakich: …… ……..	**TAK**	**NIE**
18. Czy to pierwsze Pani/Pana badanie z zastosowaniem TMS	**TAK**	**NIE**

OŚWIADCZENIE

Ja niżej podpisana/podpisany oświadczam, że przeczytałam/przeczytałem, zrozumiałam/zrozumiałem i podałam/podałem powyższe informacje, które są zgodne ze stanem faktycznym. Oświadczam również, że biorę pełną odpowiedzialność za podane przez siebie informacje i świadomie wyrażam zgodę na terapię z użyciem przezczaszkowej stymulacji magnetycznej.

…….. ……

czytelny podpis data i miejsce