Use of transcranial magnetic stimulation in the primary care setting for the treatment of resistant depression: Opinions of general practitioners and general practioners-in-training from Flanders, Belgium

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Samenvatting

Inleiding: Patiënten met therapieresistente depressie ervaren depressie ondanks psychologische en medicamenteuze behandeling. Transcraniële magnetische stimulatie (TMS) is goedgekeurd voor de behandeling van depressie, is effectief bij patiënten met een resistente depressie en is veilig. Het is echter onbekend of huisartsen in België TMS aanbevelen, erover leren of het gebruiken. We wilden de bekendheid met TMS bepalen en of huisartsen bereid zouden zijn om TMS aan te bevelen en aan te leren/toe te passen bij patiënten met een resistente depressie.

Methoden: We hebben een online enquête uitgevoerd onder huisartsen. Acht vragen verzamelden demografische gegevens en voorkeuren voor de behandeling van depressie. De overige vragen vormden vier schalen om te bepalen of huisartsen TMS kennen, of ze het effectief of veilig vinden, of ze het aanbevelen en of ze bereid zijn het te leren of toe te passen.

Resultaten: Alle vier de schalen toonden een acceptabele validiteit en betrouwbaarheid. De respondenten (n=113) beantwoordden meer dan 97% van de vragen. De bekendheid met TMS was significant hoger bij huisartsen in opleiding en huisartsen met minder ervaring. In totaal was 25% van de respondenten bereid om TMS aan te bevelen, maar ongeveer 80% was neutraal in hun geloof in de effectiviteit of veiligheid ervan en in hun bereidheid om het aan te bevelen, te leren of toe te passen. Hogere waargenomen effectiviteit, veiligheid van TMS en makkelijke beschikbaarheid van TMS waren de enige significante factoren die samenhingen met een potentiële aanbeveling voor TMS.

Conclusie: Onze bevindingen leveren het bewijs dat het gebruik van TMS bij resistente depressie kan worden verhoogd door huisartsen te trainen en het aantal instellingen dat TMS toedient te verhogen. Dit kan veel patiënten met depressie helpen die resistent zijn tegen zowel medicatie als niet-farmacologische behandelingen.

Sleutelwoorden: Transcraniële magnetische stimulatie, apparaatveiligheid, eerstelijnszorg, huisarts

Abstract

Introduction: Patients with treatment resistant depression experience depression despite psychological and medication treatment. Transcranial magnetic stimulation (TMS) is approved to treat depression, is effective patients with resistant depression, and is safe. However, it is unknown whether general practitioners (GPs) in Belgium recommend, learn about, or use TMS. We aimed to determine the awareness regarding TMS and whether GPs would be willing to recommend TMS and learn/administer TMS to patients with resistant depression.

Methods: We conducted an online survey of GPs. Eight questions collected demographic details and preferences for depression treatment. The remaining questions formed four scales designed to determine whether GPs know about TMS, feel it is effective or safe, recommend it, and are willing to learn or administer it.

Results: All four scales showed acceptable validity and reliability. Survey respondents (n=113) answered more than 97% of the questions. Awareness of TMS was significantly higher in GPs-in-training and GPs with less experience. In total, 25% of respondents were willing to recommend TMS, but approximately 80% were neutral in their belief in its effectiveness or safety and in their willingness to recommend, learn, or administer it. Higher perceived effectiveness, safety of TMS, and easy availability of TMS were the only significant factors associated with a potential recommendation for TMS.

Conclusion: Our findings provide evidence that the use of TMS in resistant depression can be increased by training GPs and increasing the number of facilities administering TMS. This may help many patients with depression who are resistant to both medication and non-pharmacological treatments.

Keywords: Transcranial magnetic stimulation, device safety, primary care, general practitioner

Introduction

With the evolution of the general practitioner (GP) specialty as the center and first line of care, GPs are the first point of contact for a person with depression. Previously, GPs preferentially used selective serotonin reuptake inhibitors (SSRIs) to treat major depressive disorder (MDD). However, GPs also use higher doses of SSRIs in treatment-resistant depression (TRD) [1], which occurs in about a third of people with depression who do not respond to more medication [2]. A change in medication, combining medications, and psychotherapy could be beneficial; however, when these methods fail or cause side effects, treatment with transcranial magnetic stimulation (TMS) can be an effective and safe alternative.

In 2016, the Clinical TMS Society published a consensus review and treatment recommendations for TMS in patients with MDD. Based on the evidence criteria used by the University of Oxford Center for Evidence-Based Medicine (cebm.net), they found Level 1 evidence, which is the highest level of evidence-based on large, prospective, randomized controlled trials, in favor of TMS to treat acute, relapsing, and chronic depression in patients who had failed to respond to or could not tolerate antidepressant medication [3]. However, no reports exist regarding whether GPs are aware that TMS can be an option to treat resistant depression, whether they recommend TMS to patients with resistant depression, or whether they would be interested in delivering TMS themselves to patients with resistant depression.

Depression is a common and severe condition that, if left untreated or undertreated, could lead to severe impairments that could limit the ability to carry out major life activities [4], and may lead to suicide. GPs are responsible for treating depression in most patients. Epidemiologically, approximately 5–10% of patients in primary care settings have depression [5], and in Belgium, approximately 9.4% of patients have depression [6]. Depression is more common among immigrant populations in Belgium [7]. In the UK, 40% of all GP appointments are related to mental health [8].

GPs have a good therapeutic relationship because they know the patient medically and personally, and are experienced in listening with empathy, respect, and without judgment [9]. However, treatment of depression by GPs adheres to guidelines in only one in five patients [10]. Although the combination of medication and psychological intervention is more beneficial than medication alone [11], the trend from 2009 to 2018 in over 300 primary care practices in Belgium showed an increasing use of medications, especially SSRIs [5]. Additionally, in Belgium, significant depression continues at 6 months in most patients, related to the infrequent use of non-pharmacological treatments by GPs [12]. When faced with TRD, GPs commonly increase

SSRI doses, with limited awareness that approximately half of patients with treatment-related depression do not respond to medication [13,14] or that high doses of medication can be harmful [15].

Approximately 30% of the patients with MDD fail to respond to antidepressant medications [16,17]. Stage 1 TRD is defined as a failure to achieve clinical response to at least one antidepressant medication, with adequate dose and duration [18]. Stage 2 TRD is defined as failure to respond to two adequate antidepressant trials. Antidepressant medication is useful in approximately 47% of patients with Stage 1 and 35% of Stage 2 patients with treatment-related depression [19]. Although treatment-related depression is difficult to treat, it affects many patients [20]. Alternative treatments are common [20,21]; however, these may result in side effects [22] and debilitating extrapyramidal symptoms of adjunctive antipsychotics [23,24]. An alternative treatment option is TMS [25,26].

TMS is used in the treatment of MDD in patients who do not respond to antidepressant medications. However, TMS may be underutilized [27]. TMS is beneficial in approximately 40% of patients with TRD [28,29]; however, common side effects include headache, local pain and discomfort, neck pain, toothache, and paresthesia; and rarer side effects, seizures, induced hypomania, decreased hearing, and skin burns from the TMS coil [30].

TMS has been approved for treatment-related depression in numerous countries, such as the United States, Canada, Australia, New Zealand, Brazil, Israel, as well as several member states of the European Union [31,32]. In 2018, a multidisciplinary advisory body of the Superior Health Council of Belgium [33] found Level A evidence that repetitive TMS (rTMS) is a "definite effective technique" to treat unipolar major depression and treatment-related depression. TMS should be performed either in a hospital or in an appropriately equipped outpatient clinic, by a certified healthcare professional (clinical psychologists and physiotherapists) [33]. Physicians and staff should receive formal peer-to-peer training and, at a minimum, should receive documented product training by the manufacturer, develop a standard operating procedure, determine the initial motor threshold and coil location in all new patients, and delegate subsequent treatments to trained non-physician staff [3].

Unlike ECT, TMS does not require anesthesia and can therefore be performed in an office setting. In TMS, a coil is placed on the scalp just above the left dorsolateral prefrontal cortex [34], and a powerful pulsed electrical current is delivered to the coil [35]. This current generates strong but short-lasting magnetic pulses [36] approximately 2–5 cm below the scalp and skull. To treat MDD or treatment-related depression, rTMS is applied, with the focal delivery of hundreds or thousands of magnetic pulses to the scalp area [37]. These

magnetic pulses, like those seen on MRI, produce secondary electrical fields [38] that depolarize axons and release neurotransmitters in the prefrontal cortex, an area that is involved in mood regulation, and which on imaging shows hypometabolism in patients with depression [29]. The amplitude of the generated action potential depends on the intensity, frequency, and pattern of the current delivered to the coil; the shape of the coil; its location; its angulation relative to the scalp; and patient-specific neuronal anatomy and responsiveness [39,40]. The response is monitored using an electromyogram or the twitch of the thumb on the opposite side [34].

To appreciate how TMS works, it is important to understand the impact thereof on neurobiology. Intrinsic functional networks have consistently shown abnormalities in MDD, including the default mode network (DMN), the salience network (SN), and the central executive network (CEN), suggesting their crucial pathophysiological role [41] The DMN, which is involved with rumination, referential processing, and episodic memory processing, includes the medial prefrontal cortex, posterior cingulate cortex, and medial areas of the posterior parietal cortex [42]. In MDD, activity of the DMN is correlated with the subgenual cingulate cortex and other limbic areas [43]. The SN, which becomes engaged when detecting, integrating, and filtering pertinent interoceptive, autonomic, and emotional information, includes the dorsal anterior cingulate cortex (dACC) and frontoinsular cortex (FIC) [44]. The CEN, which is involved with regulating attention, working memory and decision making, includes the dorsolateral prefrontal cortex (DLPFC) and lateral areas of the posterior parietal cortex [45]. Abnormalities in the nodes of these networks have guided TMS targeting, such as hypoactivity of the left DLPFC [46,47].

Using resting state fMRI, TMS was found to alter the activity of distant structures within these networks as well as the connectivity between the DMN and CEN; particularly, connectivity between the DLPFC (a CEN structure) and the DMN increased, suggesting modulation of between-network interactions by TMS [47]. Hyperactivity of the subgenual cingulate (a DMN structure) was also reduced after TMS. A triple network theory of psychopathology incorporates the abnormal interconnectivity of the DMN, SN, and CEN in MDD [41], and provides a framework for understanding the mechanisms underlying the therapeutic application of TMS.

TMS is more effective than sham stimulation in patients with depression who failed to respond to a single antidepressant [48]. TMS is also beneficial in patients in whom more than one antidepressant medication failed [31,49]. In 2008, the FDA approved the use of rTMS with 10 Hz stimulation for the treatment of depression [50]. Furthermore, the intermittent theta burst stimulation (iTBS) technique was introduced to reduce the TMS

treatment time from 37.5 to 3 min [40]. Multiple treatment protocols for depression have been approved by the FDA [28,51], and TMS effectively ameliorates depression in 40–60% of patients [28]. The acute benefits of TMS for treatment-related depression have also been observed [52].

The long-term efficacy of TMS in depression lasts 5–12 months after treatment [53,54], and studies have evaluated the usefulness of TMS than sham treatment for depression, reporting a benefit thereof [50,55–57]. Some studies, however, reported no difference in benefits when either TMS or sham was used to treat acute depression [58], in the treatment of depression in veterans [59] or in adolescents [60].

Patients should be advised that TMS is generally well-tolerated [61]. The most serious adverse effect is seizure, occurring in approximately 60,000 sessions [63]. The most common side effects are transient local pain and headache [64]. Furthermore, cognition is not affected [65]; conversion to hypomania or mania is not a concern [66]; and hearing is unaffected if the ears are protected from loud sounds during treatment [61]. Similar to MRI, TMS should not be performed on patients with metallic pacemakers. With close attention to guidelines on patient selection, physician supervision, technique, and equipment [67], TMS can be provided by non-experts [68].

Further studies should address whether education and training can increase awareness, acceptance, and enthusiasm for TMS among GPs. Resistant depression is common, leads to suffering, and lacks effective treatments. Because TMS can help patients in this situation, its promotion through the use of GPs can help many patients.

We, therefore, aimed to conduct a questionnaire-based study to determine the awareness of GPs in Flanders, Belgium regarding TMS as a safe and effective treatment option for resistant depression. We also wanted to determine the willingness of GPs to recommend TMS as a treatment modality and administer TMS in their practices to treat patients who have resistant depression. We sent questionnaires to GPs and GPs-in-training in Flanders, Belgium, regarding their approach to treating major depression, with a focus on their awareness and attitudes toward the use of TMS in patients with TRD and their views on the potential for GPs to use TMS. Based on our survey, we aimed to elicit recommendations regarding the use of TMS to treat TRD by GPs in Belgium. We hypothesized that GPs and GPs-in-training in Flanders, Belgium are unaware that TMS can be an option for TRD, and that GPs and GPs-in-training will be willing to recommend and/or be willing to learn and administer TMS to treat patients who have TRD.

Materials and methods

Survey design

We surveyed GPs and GPs-in-training in Flanders, Belgium regarding their knowledge, attitude, and practice in using non-pharmacological options, especially TMS, in the treatment of TRD in patients in the primary care setting. We developed a survey that was substantiated by our literature review, involving extensive analysis of various expert literature sources. Our survey consisted of 20 self-administered questions and took approximately 5–10 minutes to complete online. All survey questions were followed by multiple-choice responses. Some questions allowed the selection of only one best answer, whereas others allow for the selection of multiple answers.

The questionnaire consisted of four scales: A, "Awareness of TMS" scale; B, "Effectiveness and Safety of TMS" scale; C, "Recommend TMS" scale; and D, "Willingness to learn TMS and/or Willingness to administer TMS" scale. To understand whether these four scales were appropriate for studying our aims, we examined their reliability and validity.

Reliability

A reliable scale has the same meaning as the respondent for the re-administration of the scale. Reliability can also be assessed by measuring the "internal consistency" of items on a scale; that is, a scale is internally consistent if its constituent items all measure the same common factor. This could be confirmed if the respondents answered the items on a similar scale. The measure of internal consistency is statistically calculated and expressed as a number (Cronbach Alpha). This primarily helps identify how closely related a set of Likert scale items are as a group, reflecting whether the responses are consistent across those items. To determine reliability, we calculated the Cronbach Alpha for each of the four scales. The alpha score should be ≥ 0.6 to ensure high internal consistency (i.e., reliability) [69].

Validity

A valid scale has items that are clear in their meaning and accurately ask what is intended to be asked. A valid scale has: "face validity," its items are written such that their meaning is clear and they ask what is intended to be asked; "content validity," its items ask the entirety of what is intended to be asked; and "construct validity," its items are focused on measuring the core essence of what is intended to be asked. To determine validity, we performed a principal components analysis (PCA) [70], followed by a confirmatory factor analysis (CFA) [71] on each of the four scales.

Survey items and scales

Through statistical analysis, we allocated the questions in our survey questionnaire to different groups such that each group as a whole was constructed to address a separate query. Some questions were common to the different groups. The questionnaire is detailed in Appendix 1. The words “resistant depression” were shortened to “depression.”

Survey administration

We surveyed GPs or GPs-in-training who were registered with the Orde der Artsen and were currently actively working in Flanders, Belgium. We required the GPs to speak Flemish because the questionnaire was in Flemish; however, there were no other exclusion criteria.

Our goal sample size was approximately 100 GPs or GPs-in-training with active registration. We intended to conduct the survey without obtaining any identification of participants, and in the email, we reassured the participants regarding this with a privacy statement, and provided them with contact email and phone numbers of the study investigators and of the Ethics Committee at KU Leuven. We were fully compliant with the GDPR data privacy and security regulations. The study design was approved by the ethics committees of UZ Leuven and KU Leuven, Commissie Medische Ethiek (referentienummer B143201524388/I/U, see bijlage 2 en 3).

We sent an online survey via email to GPs and GPs-in-training. In the email, we explained the reasons for the survey and included a hyperlink to the survey on the fully encrypted Survey Monkey website (https://nl.surveymonkey.com/). After completing the survey, participants were able to simultaneously submit the survey on the Survey Monkey website.

In addition to directly sending an email to potential participants, to recruit as many Flemish GPs as possible, we asked for the support of relevant agencies/intermediaries that would help in distribution of the online survey. Specifically, the various waiting posts in Flanders (‘wachtpost’) helped in this endeavor, as they have strict requirements for GPs and GPs-in-training to register with the particular wachtpost, and their requirements fitted our inclusion criteria. The primary mode of communication between these two organizations and their registered members was via email. These various wachtpost organizations were willing to send GPs-in-training emails containing our survey embedded in the SurveyMonkey hyperlink, as well as information about the survey and privacy.

After obtaining approval from the ethics committee of KU Leuven, the online questionnaire was sent in January 2024. We also sent reminder emails after 6 and 10 weeks in case of a lack of response. We stopped further recruitment after September 2024, since we were able to recruit more than our goal sample size of 100 participants.

Statistical analysis

The survey data were collected and automatically saved using SurveyMonkey. The data can be viewed as customizable tables and charts. They can also be exported to Excel, PDF, and PowerPoint files. The data can also be exported as csv files showing the words for each question and its answer choices, the number and percentage of each answer choice, and the number of respondents who did not answer the question.

In SurveyMonkey data, it is also possible to easily export the data for use in the Statistical Package for the Social Sciences (SPSS), which is a well-known computer program to help with statistical analysis. Statistical analyses were performed using SPSS 27 (IBM Corp., 2020).

The reliability and validity of the four scales were analyzed. We then used frequency analysis to define the respondents' demographic characteristics and other aspects related to how the GPs treat depression. We obtained means scores of the overall latent (composite) variables, which are the study outcomes as follows: awareness of TMS, effectiveness and safety of TMS, recommendation of TMS, and willingness to learn and administer TMS. We performed one-sample t-tests to determine whether the observed mean scores of the given constructs were significantly greater than the test values, that is, neutral or unsure about TMS.

Different tests of mean differences, like independent samples-test and one-way analysis of variance (ANOVA) were used to determine whether the demographic characteristics of the respondents contributed to the level of awareness they had about TMS, whether they considered it an effective or safe therapy, whether they would recommend TMS, and whether they were willing to learn or administer TMS. A regression analysis (Model 1) used a general linear model to examine whether GPs and GPs-in-training recommend non-pharmacological (non-medication) treatment for depression; then, they would also be more likely to recommend TMS, since TMS is also non-pharmacological. In Model 2, we examined the factors that influence respondents' decisions to recommend TMS. The results were obtained from one or more answers that respondents chose for Q15 (see the survey in Appendix a). In this question, the following factors influenced the decision to recommend TMS for resistant depression: efficacy and safety of TMS in the treatment of resistant depression, severity of depression and response to pharmacological and other non-pharmacological treatments, patient preference for

other non-pharmacological options instead of TMS; easy availability of TMS facilities/equipment, the patient did not have to pay for TMS himself, and the patient's willingness to receive TMS after the respondent had explained TMS to the patient.

Results

Reliability and validity of the four scales

The reliability results for the four scales are presented in Table 1, showing the following: awareness of TMS (α=0.670), effectiveness and safety of TMS (α=0.718), recommendation of TMS (α=0.618), and willingness to learn and administer TMS (α=0.707). All scales exhibited high reliability, with an alpha score above 0.6. This analysis shows that all scale items are reliable and can be used in the study.

The validity results for the four scales are presented in Tables 2–5. All four scales were found to be reliable and valid for use. Table 2 shows the component matrix of awareness of TMS items. All items were observed to load under one component and had factor loadings greater than 0.3. This analysis validates the construct of awareness of TMS, suggesting that it could be used for further analysis.

The items measuring effectiveness and safety Table 3 also loaded under a single component, showing a factor loading greater than 0.3. This analysis validates the effectiveness and safety of the scale, suggesting that it can be used for further analysis.

Table 4 shows that among the items measuring recommendation for TMS, the first item, "Have you recommended TMS in the past to some of your patients suffering from depression?" does not load under Component 1. This means that going forward, this item will be eliminated from the TMS recommendation and analysis scale. After removing this item, the analysis of the remaining seven items validates the recommended TMS scale, suggesting that it can be used for further analysis.

Table 5 shows that all items of the learning and administration TMS scale are loaded into a single component. This analysis validates the willingness to learn/administer the TMS scale, recommending that it be used for further analysis.

Frequency analysis of survey responses

We analyzed the frequency of the survey analysis, with the following results listed per question.

Q1: Of the 113 respondents, 93% (n=105) were GPs and 7% (n=8) were GPs-in-training. Answered by 113/113 respondents.

Q2: 69% (n=78) of respondents were females and 31% (n=34) were males. Answered by 112/113 respondents.

Q3: 9% (n=10) of respondents had <5 years of experience as a GP, 19% (n=21) had 5–10 years, and 72% (n=81) had experience of >10 years; 112/113 respondents answered this question.

Q4: 58% (n=65) of the respondents practiced in urban areas, and 45% (n=50) practiced in the countryside. Answered by 112 of the 113 respondents.

Q5: 72% (n=81) of respondents only start non-pharmacological therapy for newly diagnosed depression, 5% (n=6) start antidepressant medication, and 35% (n=39) start both. Answered by 113 of the 113 respondents.

Q6: In non-pharmacologic therapy, 78% (n=88) recommend cognitive behavioral therapy; 32% (n=36), interpersonal therapy (n=36); 74% (n=83), supporting therapy, 84% (n=95), physical activity; 0%, electroconvulsive therapy; and 0%, TMS. Answered by 113/113 respondents.

Q7: If they do not recommend non-pharmacological therapy, 2% (n=2) of respondents noted that this was because of its ineffectiveness; 1% (n=1), because of lack of safety; 1% (n=1), because of inconvenience; 1% (n=1), because of it being unneeded; 7% (n=6), because of the expense; and 3% (n=3), because of not knowing enough about non-pharmacological treatments; however, 88% (n=78) of respondents chose “not applicable,” since they did recommend non-pharmacological therapy. Answered by 89/113 respondents.

Q8: If depression persisted despite the use of antidepressant medication, 63% (n=71) of the respondents chose to increase the dose thereof; 59% (n=67), chose to change antidepressant medication; and 59% (n=67), added non-pharmacological therapy if patients were not already using such therapy. Answered by 112/113 respondents.

Q9: 23% (n=26) of respondents had read about or heard of TMS as a treatment option for resistant depression, 70% (n=78) had not read about or heard of it, and 7% (n=8) were unsure. Answered by 112/113 respondents.

Q10: Only 2% (n=2) of respondents had a good understanding of TMS, 21% (n=23) had less understanding, 11% (n=12) had even less understanding, and 67% (n=75) did not have any understanding of TMS. Answered by 112/113 respondents.

Q11: 97% (n=110) of respondents had never recommended TMS in the past, and 3% (n=3) had recommended it rarely or very rarely. Answered by 112/113 respondents.

Q12: 25% (n=28) of respondents would recommend TMS in the future, 66% (n=75) were unsure, and only 9% (n=10) would not recommend TMS in the future. Answered by 113/113 respondents.

Q13: 81% (n=91) of respondents were neutral in their belief in the effectiveness of TMS for the treatment of resistant depression in primary care, 11% (n=12) believed it was effective, and 7% (n=8) believed it was not effective. Answered by 112/113 respondents.

Q14: 82% (n=93) of respondents were neutral in their belief in the safety of TMS for the treatment of resistant depression in primary care, 12% (n=14) believed that TMS was safe, and 4% (n=5) did not believe it was safe. Answered by 113/113 respondents.

Q15: Effectiveness and safety of TMS was the most common factor (82% respondents, n=90) in influencing the recommendation for TMS. Other influential factors were the severity of depression and response to treatment (50% respondents, n=55), patient preference for non-pharmacological options other than TMS (31% respondents, n=34), availability of TMS equipment and facilities (64% respondents, n=71) if the patient did not have to pay for TMS (33% respondents, n=37), and the patient's willingness to receive TMS (54% respondents, n=60). Answered by 111/113 respondents.

Q16: 17% (n=19) of respondents did not believe that TMS can be used by GPs to treat resistant depression; 46% were unsure (n=52); 10% (n=13) believed that GPs could use TMS if they had completed approved training in TMS; 4% (n=5) believed they could use TMS if the institution had TMS equipment; and 21% (n=23), if the TMS treatment was fully paid by insurance. Answered by 112/113 respondents.

Q17: 10% (n=11) of the respondents were willing to do a TMS course, and 50% (n=55) were unwilling. Of the respondents, 2.7% (n=3) were willing if the course were available in the Netherlands, 0% if it were available in the UK, and 38% (n=42) were willing if available in Belgium. Answered by 111/113 respondents.

Q18: 77% (n=87) of respondents were neutral in the belief that TMS should be more widely implemented in primary care, 8% (n=9) believed it should be implemented, and 16% (n=15) believed it should not be implemented. Answered by 113/113 respondents.

Q19: Only 9% (n=10) of respondents did not think that TMS has a role in treating depression; 4% (n=5) did not intend to recommend TMS; 4% (n=5) chose that TMS should be used as a last resort, if ever used; 31% (n=35) did not plan to administer TMS; 13% (n=15) did not want to learn TMS; 31% (n=35) did not have the time to learn TMS or the resources to administer it at their practice or hospital; and only 25% (n=28) chose that if TMS is applied it should be done only by a psychiatrist or in a psychiatrist clinic by a psychiatrist or a psychologist, but not by a GP; 43% (n=48) chose none of the above questions. Answered by 112/113 respondents.

Q20: 12% (n=14) of the respondents were interested in using TMS in their practice if they were eligible for reimbursement in Belgium; 18% (n=20), if they also had approved training in TMS; 12% (n=14), if they were

financially viable; 27% (n=30) were not interested; and 31% (n=35) were unsure. Answered by 113/113 respondents.

Awareness, knowledge, recommendation of TMS and willingness to learn administer TMS

Table 6 shows the means scores of the overall latent (composite) variables: awareness of TMS, effectiveness and safety of TMS, recommendations of TMS, and willingness to learn and administer TMS. The results showed that awareness of TMS had a lower average (mean) score of 1.32, meaning that respondents were less aware (M=1.32, 2.00 was average on a 3-point Likert scale). Respondents were neutral/unsure on the other three scales: effectiveness/safety of TMS (M=3.00, neutral/unsure on a 5-point Likert scale), recommending TMS (M=2.04, 2.0 was the average on a 3-point Likert scale), and learning/administering TMS (M=2.03, 2.0 is average on a 3-point Likert scale). This analysis shows that respondents were not statistically aware of TMS, even though 25% of respondents said they had read or heard about TMS. While respondents were neutral/unsure of the effectiveness or safety of TMS, they were neutral/unsure if they were willing to recommend TMS, and they were neutral/unsure if they wanted to learn and administer TMS.

Awareness, knowledge, recommendation of TMS and willingness to learn to administer TMS

Tables 7–8 show the results of the one-sample t-tests performed to determine whether the observed mean scores of the given constructs were significantly greater than the test values, that is, being neutral or unsure about TMS. Table 7 shows that by keeping test values of 2 (neutral/unsure) for the factors of awareness of TMS, recommend TMS, and learn administration TMS, the one-sample test found that the awareness average score was significantly lower than the test value ($t=-15.307$, $p<0.01$). This analysis confirms that respondents have low awareness about TMS. This confirms our hypothesis that there is a lack of awareness of TMS among GPs. The recommended TMS and learning/administration of TMS had no significantly different mean scores than their test scores. This analysis confirms that respondents are neutral/unsure in recommending or learning/administering TMS for the treatment of resistant depression.

Table 8 shows that using the test value of 3 (neutral/unsure) for Effectiveness_Safety of TMS, the one-sample test found an insignificant difference between the mean score of Effectiveness_Safety and the test value ($t=0.078$, $p=0.938$). This analysis confirmed that respondents were neutral/unsure in the effectiveness or safety of TMS in treating resistant depression.

Contribution of demographic characteristics of the respondents to the four scales

GPs-in-training and TMS training

An independent sample t-test showed that being a GP or GP-in-training showed a marginally higher level of awareness in GPs-in-training than in GPs (t=-1.666, p<0.1). Mean awareness scores were lower for GPs than for GPs-in-training (1.29 vs 1.58). Insignificant mean differences were found for effectiveness and safety of TMS (t=-0.895, p=0.373), for recommendation of TMS (t=-0.983, p=0.350, and for learning or administration of TMS (t=-1.273, p=0.206). The mean scores are shown in Figure 1.

Gender and TMS aspects

Independent t-tests showed that men had no significant contribution to scores on the four scales: Awareness of TMS (t=0.212, p=0.832), effectiveness and safety of TMS (t=0.274, p=0.785), recommendation of TMS (t=-0.633, p=0.528), and learning or administration of TMS (t=-1.317, p=0.191). The mean scores are shown in Figure 2.

Practice location and TMS

Independent t-tests showed that the practice location (urban vs. countryside) had no significant contribution to the four scales: Awareness of TMS (t=-1.398, p=0.165), effectiveness and safety of TMS (t=-0.403, p=0.688), recommendation of TMS (t=-0.061, p=0.951), and learning or administration of TMS (t=0.374, p=0.709). The mean scores were also similar, respectively in Urban vs Countryside: for awareness of TMS (1.36 vs 1/39), effectiveness and safety of TMS (2.98 vs 3.03), Recommend TMS (2.04 vs 2.03), and learning/administering TMS (1.07 vs 1.99) (data not shown).

Years of practice experience and TMS

An ANOVA revealed a slight but significantly higher awareness of TMS in respondents with less experience (F=3.059, p<0.1). Years of experience had no effect on the perceived effectiveness and safety of TMS (F=0.214, p=0.807), recommended TMS (F=0.335, p=0.716), or learning or administration of TMS (F=1.032, p=0.360) (Figure 3).

Regression analysis Model 1

This analysis examined whether GPs (or GPs-in-training) who recommended non-pharmacological treatment (NPT) for resistant depression also recommended TMS (which is also non-pharmacological) for depression (Table 9). To measure NPT recommendations, multiple variables were used, including four types of non-pharmacological treatments, and the choice of therapy for both new and resistant depression. In the model, awareness of TMS and effectiveness of TMS were used as controls. The results showed an R^2 value of 0.469, suggesting that 46.9% of the variance was explained in the outcome, that is, recommending TMS. The predictors (recommendation of different non-pharmacological therapies) had no significant effect on the TMS recommendations. Only, a higher perceived effectiveness and safety of TMS significantly influenced toward an increase in TMS recommendation ($t=9.166$, $p<0.001$). This confirms our hypothesis that GPs would be willing to recommend TMS in patients with resistant depression, but this is contingent on GPs having more knowledge about the effectiveness and safety of TMS.

Regression analysis Model 2

This study examined the factors affecting TMS recommendations. The factors (asked in Q15) included the effectiveness and safety of TMS, severity of depression, response to pharmacological and other non-pharmacological treatments, patient preference for other non-pharmacological options instead of TMS, availability of TMS facilities/equipment, no need for the patient to pay for TMS, patient's willingness to receive TMS after gaining an understanding of TMS (Table 10). The results showed an R^2 value of 0.106, indicating that the model explained only 10.6% of the variance in TMS recommendations. Only a higher "Easy availability of TMS facilities/equipment" was significantly associated with a higher recommendation for TMS ($t=-2.188$, $p<0.05$). This confirms our hypothesis that GPs would be willing to recommend/administer TMS if there is easier availability of TMS. None of the other factors were significantly associated.

Discussion

Our findings confirmed our first hypothesis that awareness of TMS is low among GPs practicing in Flanders, Belgium. Approximately 80% of GPs in our study were unsure or neutral regarding the effectiveness and safety of TMS in treating resistant depression. Even though Level 1 evidence exists that shows that TMS is effective in treating about 40% of patients with resistant depression, multiple studies have also found TMS to be very safe. In our study, the lack of knowledge in GPs about the effectiveness and safety of TMS was the strongest reason for the neutral or unsure recommendation of GPs regarding the use of TMS to treat resistant depression.

In addition to the lack of knowledge regarding the effectiveness and safety of TMS, decreased availability of TMS was the only factor in our study related to a neutral/unsure recommendation for TMS. Thus, our findings also confirm our second hypothesis that GPs will recommend and learn/administer TMS, but this is contingent on their knowledge of the effectiveness and safety of TMS, as well as on the wider availability of TMS.

Depression imposes a heavy burden on suffering. Approximately 30% of patients with depression have remnant depression [16-18] after treatment with antidepressant medications and non-pharmacological treatments. These patients are not assisted by different medications or therapies and even experienced psychiatrists may not be able to offer satisfactory treatment. Consequently, depressed patients prefer to visit their GPs for help [1], even though GPs do not treat depression well, even in patients in whom depression is easier to treat [5,10,12–15]. These GPs increase the dose of antidepressant medications [5], which remains ineffective in over half of the patients [12–14] and is associated with increasing side effects [15,22–24]. GPs would likely welcome any treatment that could help treat patients with depression if that treatment is known to be effective and safe. In this context, we surveyed GPs to determine whether they knew about TMS as a means to treat resistant depression, whether they knew that TMS was effective and safe, whether they would recommend TMS, and whether they would be willing to learn and administer TMS themselves.

Through statistical tests, we found that our survey had four scales, each of which served as a measure of the four components of our inquiry: awareness of TMS; perceived effectiveness and safety of TMS; willingness to recommend TMS; and willingness to learn and administer it. Statistically, all four scales were reliable and valid for measuring the four components.

Although 23% of the respondents had read or heard of TMS, 67% did not know much about it or how it worked, and their overall awareness of TMS was low (i.e., less than neutral). Therefore, our hypothesis is correct, in that there is a lack of awareness among GPs about TMS. Awareness was significantly higher in GPs-in-training than in GPs, and in respondents with 0–5 years of experience than in respondents with higher experience. However, our study sample had only eight GPs-in-training and only 10 GPs with <5 years of experience.

In contrast to low awareness of TMS (which was statistically lower than neutral), the perceived effectiveness/safety, willingness to recommend TMS, and willingness to learn/administer TMS were all neutral/do not know (neither in favor nor against). When asked about whether they could recommend TMS, 25% of the respondents were willing to recommend it, and 67% were unsure.

For 82% of respondents, knowing the effectiveness and safety of TMS was the highest factor in their recommendation thereof. In addition, respondents who had higher perceived effectiveness and safety of TMS

were statistically more likely to recommend TMS. The availability of TMS facilities was also significantly associated with recommendations for TMS.

Thus, GPs would be willing to recommend, learn, and administer TMS if they knew it was effective and safe in treating depression. In this context, we found that TMS is known to be effective and safe in treating resistant depression, and its administration by non-experts has been found to be acceptable.

The first TMS device was developed in 1985 [72], when it was found that than electrical stimulation, magnetic stimulation could pass more easily through high-resistance structures, and that reduced activity in the left DLPFC was related to the severity of depression [73]. Magnetic pulses in TMS are similar to those in MRI and produce tiny electrical fields [38] that depolarize axons and release neurotransmitters in the prefrontal cortex, thus ameliorating depression [28]. In the early 2000s, many clinical studies demonstrated the effectiveness of TMS in treating depression [49], which led to FDA approval in 2008. At that time, TMS was difficult for the patient, requiring 4–6 weeks of daily 1-hour treatments. Subsequently, theta burst TMS reduced the treatment duration to 5 days [74]. The FDA also approved the use of iTBS, which reduces the TMS treatment time from 37.5 to 3 minutes [40].

TMS is beneficial in approximately 40% of patients with treatment-related depression, with complete remission in one-third of patients, although a varying degree of placebo effect was initially reported in sham studies [28,29,75]. However, TMS is superior to sham treatment in treatment-related depression [76]. TMS is effective in ameliorating depression in 40–60% of patients resistant to ≥1 antidepressant medication(s) [28,31,49]. The Oxford Center for Evidence-Based Medicine (cebm.net) found Level 1 evidence for the effectiveness of TMS in treating acute, relapsing, and chronic depression in patients who failed to respond to or could not tolerate antidepressant medication [3]. After a single TMS treatment, the benefit of treating depression lasted for 1 year in approximately half of the patients [53]. These studies powerfully support to the belief that TMS is effective in treating resistant depression. However, in our study, the awareness of TMS was low among GPs, and GPs were likely unaware that there is evidence that TMS is effective in treating depression and resistant depression.

Another question concerns the ability of GPs in Belgium to administer TMS. With close attention to guidelines on patient selection, physician supervision, technique, and equipment [67], TMS can be provided by non-experts [68]. In Belgium, TMS was extensively evaluated in 2018 by a health council, which found Level A evidence that rTMS is an effective technique for treating depression and treatment-related depression. The report recommended that TMS should be done either in a hospital or in an appropriately equipped outpatient clinic, that it should be done by a certified healthcare professional, and that clinical psychologists and

physiotherapists may also be allowed to administer TMS. There was no specific mention of whether the GPs could administer TMS. In our study, 25% of respondents noted that TMS should be administered only by a psychiatrist or a psychologist, 46% were unsure if GPs could administer TMS, and 17% did not believe that GPs could administer TMS.

The enthusiasm to learn or administer TMS was not high, but this was also related to the perceived neutrality of the effectiveness and safety of TMS. We confirmed our hypothesis that GPs would be willing to recommend/administer TMS, but this is contingent on increased awareness in GPs about the effectiveness and safety of TMS, and on the increased availability of TMS.

Conclusion

Depression is a common problem among patients visiting their GP, and untreated depression can be debilitating for both patients and their families. Depression is usually treated with psychological therapies and antidepressant medications; however, these therapies are not effective in almost one-third of the patients with depression. The committee of the National Institute of Health and Care Excellence (NICE) established evidence-based guidelines for GPs and other medical professionals in the United Kingdom [77]. In the guidelines, the committee concluded that TMS had positive outcomes in many clinical studies on resistant depression and a favorable safety profile [78]. In addition, in 2018, TMS received a positive approval from the Superior Health Council of Belgium as a treatment modality for resistant depression [33].

We conclude that GPs and GPs-in-training need to be aware of the existing evidence regarding the already known good effectiveness and safety of TMS in treating resistant depression. With this knowledge, GPs may have greater confidence in recommending TMS to patients with resistant depression, and may be more willing to learn TMS and administer it themselves. Additionally, the increased availability of TMS training courses and facilities could encourage the wider use of TMS to treat resistant depression. This is particularly important because medications and other non-pharmacological treatments are unhelpful for most patients with TRD.

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Ethical approval

The Ethical Review Board of the University Hospitals/KU Leuven approved the study protocol under reference MP028897.

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APPENDIX 1

VRAGENLIJST

Studie: Use of Transcranial Magnetic Stimulation in the primary care setting in the treatment of resistant depression: opinions of General Practioner's and General-Practioner's-in-training in Flanders, Belgium

Onderzoeker: Abhishek Mohan, Huisarts-In-Opleiding KU Leuven

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1. Bent u een (**selecteer één antwoord)** :

A. Huisarts,

B. Huisarts-In-Opleiding

2. Wat is je geslacht? (**selecteer één antwoord**):

A. Mannelijk

B. Vrouwelijk

3. Hoeveel jaar beoefent u huisartsgeneeskunde? Voeg jaren opleiding toe (**selecteer één antwoord**)

A. 0 tot 5 jaar

B. 5 tot 10 jaar

C. Meer dan 10 jaar

4. Waar is uw praktijklocatie? (**selecteer een of meer antwoorden**):

A. Stedelijk

B. Platteland

5. Wanneer uw patiënten voor het eerst symptomen vertonen die voldoen aan de criteria voor een **nieuwe** diagnose van depressieve stoornis, behandelt u bij voorkeur als volgt (**selecteer één antwoord**):

A. Alleen niet-farmacologische therapie aanbevelen

B. Beginnen met een antidepressivum

C. Zowel A als B, tegelijkertijd beginnend

6. Welke van de volgende niet-farmacologische therapieën beveelt u aan? **(selecteer een of meer antwoorden**):

A. Cognitieve gedrags therapie

B. Interpersoonlijke therapie

C. Ondersteunende therapie

D. Fysieke activiteit

E. Elektro-Convulsie therapie (ECT)

F. Transcraniële Magnetische Stimulatie (TMS)

G. Niet van toepassing, ik raad niet-farmacologische therapie af

7. Als u niet-farmacologische therapie NIET AANBEVEELT,denkt u dan dat niet-farmacologische therapie dat wel is (**selecteer een of meer antwoorden**):

A. Niet effectief genoeg

B. Niet veilig genoeg

C. Ongemakkelijk

D. Onnodig

E. Te duur

F. Geen specifieke reden

G. Ik weet niet genoeg over niet-farmacologische therapieën

H. Niet van toepassing: ik raad niet-farmacologische therapie aan

I. Niet van toepassing: ik raad niet-farmacologische therapie aan, maar alleen als een patiënt daarom vraagt

8. Wanneer uw patiënten **depressief blijven** nadat ze ten minste één antidepressivum hebben ingenomen, welke van de behandelingen beveelt u dan aan (**selecteer een of meer antwoorden**):

A. Dee dosis verhogen van het medicijn tenzij er bijwerkingen zijn

B. Overstappen op een ander antidepressivum of een tweede antidepressivum toevoegen

C. Een niet-farmacologische therapie toevogen (als ze momenteel geen dergelijke therapie gebruiken)

Wat betreft transmagnetische stimulatietherapie (TMS) om depressie te behandelen:

9. Heeft u gehoord of gelezen over TMS als behandeling voor depressie bij patiënten die depressief blijven ondanks behandeling met een of meer antidepressiva? (**selecteer één antwoord**)

A. Ja

B. Nee

C. Onzeker

10. -Begrijpt u **hoe** TMS werkt en/of hoe het wordt toegediend? (**selecteer een of meer antwoorden**):

A. Ja, ik heb een goed inzicht

B. Ik weet wat TMS is bij de behandeling van depressie, maar ik heb het gevoel dat ik er niet veel over weet

C. Ik weet wat TMS is bij de behandeling van depressie, maar ik begrijp niet hoe het werkt of hoe het wordt toegediend

D. Niet van toepassing: Ik heb niets gehoord of gelezen over TMS als behandeling tegen depressie

11. Heeft u **in het verleden** TMS aanbevolen aan sommige van uw patiënten die aan een depressie lijden (**selecteer één antwoord**)

A. Ja, vaak

B. Ja, maar zelden

C. Zelden

D. Nee nooit

E. Onzeker

12. Zou u **in de toekomst** TMS willen aanbevelen als optie voor de behandeling van depressie bij sommige van uw patiënten (**selecteer één antwoord**)

A. Ja

B. Nee

C. Onzeker

13. Ik geloof dat TMS een effectieve behandelingsoptie is **in de eerstelijnszorg** voor de behandeling van **resistente** depressie (**selecteer één antwoord**) *(Dat is wanneer uw patiënten **depressief blijven** nadat ze ten minste één antidepressivum hebben ingenomen*)

    A. Sterk mee oneens

    B. Het oneens zijn

    C. Neutraal

    D. Mee eens

    E. Sterk mee eens

14. Ik heb vertrouwen in de veiligheid en verdraagbaarheid van TMS in de **eerste lijnzorg** voor de behandeling van **resistente** depressie **(selecteer één antwoord**) *(Dat is wanneer uw patiënten **depressief blijven** nadat ze ten minste één antidepressivum hebben ingenomen)*

    A. Sterk mee oneens

    B. OnMee eens

    C. Neutraal

    D. Mee eens

    E. Sterk mee eens

15. Welke factoren zullen van invloed zijn op uw beslissing om TMS aan te bevelen aan patiënten met resistente depressieve symptomen? (**Selecteer een of meer antwoorden**)

    A. Werkzaamheid en veiligheid van TMS bij de behandeling van resistente depressie

    B. Ernst van de depressie en reactie op farmacologische en andere niet-farmacologische behandelingen

    C. De voorkeur van de patiënt voor andere niet-farmacologische opties in plaats van TMS

    D. Gemakkelijke beschikbaarheid van TMS-faciliteiten/apparatuur

    E. de patiënt hoefde voor TMS niet zelf te betalen

    F. De bereidheid van de patiënt om TMS te krijgen nadat u de patiënt uitleg heeft gegeven over TMS

    G. Anders: schrijf hier:

16. Denkt u dat TMS **in de eerstelijnszorg door huisartsen** kan worden gebruikt voor de behandeling van patiënten die depressief blijven, zelfs nadat ze ten minste één antidepressivum hebben ingenomen: (**selecteer één antwoord)**

A. Mee eens

B. Alleen akkoord als de huisarts met succes een goedgekeurde opleiding in TMS heeft gevolgd, en als de eerstelijnszorginstelling over de benodigde ruimte en apparatuur beschikt

C. Alleen akkoord als de huisarts met succes een TMS-opleiding heeft gevolgd, als de eerstelijnszorginstelling over de benodigde ruimte en apparatuur beschikt en als de therapie volledig door de verzekering wordt betaald

D. Oneens

E. Onzeker

17. Momenteel zijn er goedgekeurde TMS cursussen in Verenigd Koninkrijk en Nederland voor geregistreerde artsen. Zou je overwegen om een van deze cursussen te volgen: (**selecteer één antwoord**)

A. Ja

B. Ja, maar alleen de cursus die in Nederland beschikbaar is

C. Ja, maar alleen de cursus die beschikbaar is in Vernenigd Koninkrijk

D. Ja, maar alleen als er een cursus beschikbaar is in België

E. Nee

18. Ik denk dat TMS op grotere schaal moet worden geïmplementeerd **in de eerstelijnszorg** voor de behandeling van resistente depressies. (**selecteer één antwoord**)

A. Sterk mee oneens

B. Oneens

C. Neutraal

D. Mee eens

E. Sterk mee eens

19. Het volgende is waar (**selecteer een of meer antwoorden**):

A. Ik denk dat TMS momenteel geen rol speelt bij de behandeling van depressie

B. Ik ben niet van plan TMS aan te bevelen

C. TMS mag alleen als laatste redmiddel worden gebruikt, als dat ooit gebeurt

D. Ik ben niet van plan zelf TMS-therapie toe te dienen

E. Ik wil niet leren hoe ik TMS moet toedienen

F. Ik heb geen tijd om TMS te leren of heb niet de middelen om TMS in mijn praktijk/ziekenhuis toe te dienen

G. Als TMS wordt toegepast, mag dit alleen worden gedaan in de kliniek van een psychiater door een psychiater of psychologen, maar niet door een huisarts.

H. Geen van bovenstaande

20. Sinds 2017 komt TMS in Nederland voor vergoeding in aanmerking. In België is dat tot op heden nog niet het geval. Zou u geïnteresseerd zijn om in uw praktijk een TMS te hebben als dit in België voor terugbetaling in aanmerking komt? (**selecteer één antwoord**)

A. Ja, ik zou geïnteresseerd zijn

B. Ja, alleen als ik ook een goedgekeurde opleiding TMS kan behalen

C. Ja, als het financieel rendabel zou zijn

D. Nee, ik ben niet geïnteresseerd

E. Onzeker

APPENDIX 2

KU LEUVEN
UZ LEUVEN
GROEP BIOMEDISCHE WETENSCHAPPEN
HERESTRAAT 49, CAN II – BUS 700
BE-3000 LEUVEN

English version below.

Ons kenmerk: MP028897
Uw kenmerk: Masterproef studie: Use of Transcranial Magnetic Stimulation in the primary care setting in the treatment of resistant depression: opinions of General Practioner's and General Practioner's in training
Leuven, 08-01-2024

GEEN BEZWAAR BRIEF

Geachte Professor Professor Geert Goderis
Geachte Abhishek Mohan

De Ethische Commissie Onderzoek UZ/KU Leuven bevestigt hierbij dat er geen bezwaren zijn tegen het uitvoeren van de voorgestelde studie, zoals ze werd beschreven in het protocol. De Commissie is van oordeel dat er vanuit ethisch standpunt geen bezwaren zijn bij de voorgestelde studie. De studie werd goedgekeurd op 08-01-2024

De Onderwijs-Begeleidings-Commissie voor Medische Ethiek (OBC) heeft in delegatie van het EC Onderzoek UZ/KU Leuven het vermeld protocol onderzocht en besproken op haar vergadering.

Het betreft een anonieme onlinebevraging bij een honderdtal huisartsen en huisartsen, opleiding betreffende hun kennis, attitude en toepassing in de praktijk van Transcraniële Magnetische Stimulatie (TMS) in de behandeling van therapieresistente depressie. Het protocol is gedetailleerd uitgewerkt en privacy van de deelnemers wordt voldoende gegarandeerd. De studie is goed ontwikkeld. Er zijn geen bezwaren.

EC Onderzoek heeft geen bezwaar tegen het project mits vertrouwelijke behandeling van de gegevens en naleving van de Belgische wetgeving omtrent privacy. EC wenst de hoofdonderzoeker/promotor van de studie te wijzen op zijn/haar verantwoordelijkheid betreft de privacy van de persoons-/patiëntgegevens bij contact met levende personen, patiënten en/of inzage in het elektronisch medisch dossier, inclusief de correcte implementatie hiervan door medewerkers en studenten.

Deze geen bezwaar brief betreft de indiening van 06-01-2024 en wordt gegeven voor de duur van de Masterproef van de betrokken student(en). Elke wijziging aan het protocol doet dit advies vervallen. U dient in dat geval tijdig een amendement voor advies voor te leggen aan de Onderwijs-Begeleidings-Commissie (OBC) die de initiële studie heeft geëvalueerd.

EC bevestigt dat ze werkt in overeenstemming met de ICH-GCP principes (International Conference on Harmonization Guidelines on Good Clinical Practice), met de meest recente versie van de Verklaring van Helsinki en met de van toepassing zijnde wetten en regelgeving.

EC bevestigt dat in geval van belangenconflict, de betrokken leden niet deelnemen aan de besluitvorming omtrent de studie.

Met vriendelijke groet,

Prof. dr. Minne Casteels
Voorzitter

APPENDIX 3

Beschrijving van de risico's en voordelen

Uw deelname aan dit onderzoek brengt geen enkel gezondheidsrisico met zich mee. U heeft geen baat bij deelname aan dit onderzoek; Door jouw kennis en/of ervaringen te delen, kun je bijdragen aan het in kaart brengen van deze kennis, zodat hier in de toekomst verder naar gehandeld kan worden.

Als u aan dit onderzoek deelneemt, moet u weten dat :

- Het ontwerp van deze studie werd geëvalueerd en goedgekeurd door de Ethische Commissie van de KU Leuven.
- Wij sturen u deze uitnodiging per e-mail. De e-mail wordt naar u verzonden door Inter Universitaire Centrum voor Huisartsopleiding (ICHO) of uw wachtpost, aangezien zij mogelijk uw e-mailadres hebben.
- U bepaalt zelf of u mee wilt doen aan het onderzoek. Uw deelname is vrijwillig; er kan op geen enkele manier sprake zijn van dwang. Zelfs nadat u bent begonnen met deelname, kunt u van gedachten veranderen en uw deelname aan het onderzoek stopzetten. U hoeft hiervoor geen reden op te geven.U hoeft hiervoor geen reden op te geven.
- De gegevens die worden verzameld als onderdeel van uw deelname zijn volledig anoniem. Er worden geen persoonlijke gegevens zoals naam, geboortedatum, adres, etc. verzameld. In het kader van een publicatie wordt uw identiteit niet bekendgemaakt. Wij zullen de verzamelde gegevens uitsluitend in het kader van dit onderzoek gebruiken.
- Uit uw antwoorden op de enquête blijkt op geen enkele wijze uw identiteit. Omdat wij uw identiteit niet kennen, weten wij ook niet of u aan het onderzoek heeft deelgenomen of niet.
- **Na 6 en 12 weken sturen wij u een herinneringsmail met de uitnodiging om deze enquête in te vullen. Negeer deze e-mails als u de enquête al heeft ingevuld.**
- U heeft het recht om aan de onderzoekers te vragen welke gegevens zij over u hebben verzameld en waarvoor deze in het kader van het onderzoek zullen worden gebruikt. U heeft het recht deze gegevens in te zien en te laten corrigeren als deze onjuist zijn
- Uw gegevens worden verwerkt in overeenstemming met de Europese Algemene Verordening Gegevensbescherming (AVG) en de Belgische Wetgeving betreffende de bescherming van natuurlijke personen in verband met de verwerking van persoonsgegevens. KU Leuven is de verwerkingsverantwoordelijke voor jouw gegevens.

- U ontvangt geen vergoeding voor uw deelname aan dit onderzoek. Uw deelname brengt voor u echter geen extra kosten met zich mee.
- Als u bijkomende informatie wenst over hoe wij uw anonieme gegevens gebruiken, maar ook in geval van problemen, bijkomende vragen of bezorgdheden, kunt u contact opnemen met de onderzoeker Abhishek Mohan via e-mail (abhishek.mohan@student.kuleuven.be) en de belangrijkste onderzoeker professor Geert Goderis via telefoonnummer +32 0497 54 47 03 of via e-mail (geert.goderis@kuleuven.be). Ook de functionaris voor gegevensbescherming van het onderzoekscentrum staat tot uw beschikking. De contactgegevens van laatstgenoemde zijn als volgt:
- DPO – KU Leuven, e-mail dpo@kuleuven.be
- Als u vragen heeft over uw rechten als deelnemer aan de studie, kunt u contact opnemen met de **Ethische Commissie Onderzoek UZ/KU Leuven (ec@uzleuven.be ; 016 34 86 00 (werkdagen tussen 10.00 en 11.00 uur))**
- Als u ten slotte een klacht heeft over de verwerking van uw gegevens, kunt u contact opnemen met de Belgische toezichthoudende autoriteit die toezicht houdt op de naleving van de basisprincipes van de bescherming van persoonsgegevens. De Belgische toezichthoudende autoriteit heet Gegevensbeschermingsautoriteit (GBA). **U kunt hen contacteren op: Drukpersstraat 35,1000 Brussel, Tel. +32 2 274 48 00, e-mail: contact(at)apd-gba.be. Hun website is toegankelijk op: www.gegevensbeschermingsautoriteit.be**

Alvast bedankt.

Met Vriendelijke Groeten,

Abhishek Mohan

(HAIO, KU Leuven)

Geachte collega,

In deze mail heb ik een vragenlijst toegevoegd over het gebruik van transcraniale magnetische stimulatie (TMS) bij de behandeling van resistente depressie. Deze vragenlijst is een onderdeel van mijn thesis voor mijn HAIO opleiding. De details staan hieronder.

Ik verzoek u de vragenlijst, die 20 vragen bevat en ongeveer 5 minuten in beslag neemt, in te vullen. Hartelijk dank voor uw deelname.

Abhishek Mohan

HAIO, KU Leuven

Inleiding : Ongeveer een derde van patiënten met een depressie heeft een behandeling-resistente depressie, dat wil zeggen dat ze niet goed reageren op antidepressiva. Bij deze patiënten kan een verscheidenheid aan niet-farmacologische opties nuttig zijn. Eén van deze mogelijkheden is Transcraniële Magnetische Stimulatie (TMS). TMS is in veel landen, waaronder België, goedgekeurd voor de behandeling van resistente depressie. Het is echter niet bekend of huisartsen zich ervan bewust zijn dat TMS een optie kan zijn bij de behandeling van resistente depressies, of zij TMS aanbevelen en of zij zelf TMS willen toedienen aan patiënten met resistente depressie.

Doel van het onderzoek : Dit onderzoek heeft tot doel de kennis, houding en praktijk van huisartsen te evalueren met betrekking tot het gebruik van TMS voor de behandeling van depressie bij patiënten bij wie de depressie niet is verbeterd door het gebruik van een of meer antidepressiva.

Methode: Om dit doel te bereiken, verzoeken wij u een anonieme online vragenlijst in te vullen over uw mening over TMS. U kunt de vragenlijst volledig online invullen op het Survey Monkey-platform.

Om aan dit onderzoek deel te nemen, moet u een huisarts of huisarts in opleiding zijn, momenteel werkzaam in Vlaanderen.

Beschrijving van de risico's en voordelen

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- Uw gegevens worden verwerkt in overeenstemming met de Europese Algemene Verordening Gegevensbescherming (AVG) en de Belgische Wetgeving betreffende de bescherming van natuurlijke personen in verband met de verwerking van persoonsgegevens. KU Leuven is de verwerkingsverantwoordelijke voor jouw gegevens.
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*** Dit onderzoek werd goedgekeurd door het ethisch comité van UZ/KU Leuven.**

Tables

Table 1. Reliability of the scales

Name of latent variable (in each scale)	Cronbach Alpha Score	No. of Items
Awareness of TMS	0.670	3
Effectiveness and safety of TMS	0.718	3
Recommending TMS	0.618	8
Learning and administration of TMS	0.707	5

Table 2. Validity of the awareness of TMS scale

Component Matrix[a]	Component 1
Have you heard or read about transcranial magnetic stimulation (TMS) as a treatment for depression in patients who remain depressed despite treatment with one or more antidepressants? (select one answer) (Q9)	0.941
Do you understand how TMS works and/or how it is administered? (Q10)	0.929
Have you recommended TMS in the past to some of your patients suffering from depression (select one answer) (Q11)	0.410

Extraction Method: Principal Component Analysis; [a]1 component extracted

Table 3. Validity of the effectiveness and safety of TMS scale

Component Matrix[a]	Component 1
I believe TMS is an effective treatment option in primary care for the treatment of resistant depression (select one answer) (patients remain depressed after taking at least one antidepressant) (Q13)	0.837
I am confident in the safety and tolerability of TMS in primary care for the treatment of resistant depression (select one answer) (patients remain depressed after taking at least one antidepressant (Q14)	0.849
I think TMS should be more widely implemented in primary care for the treatment of resistant depression. (Q18)	0.734

Extraction Method: Principal Component Analysis; [a]1 component extracted

Table 4. Validity of the Recommend TMS scale

Component Matrix[a]	Component 1
Have you recommended TMS in the past to some of your patients suffering from depression (select one answer) (Q11)	
In the future, would you recommend TMS as an option for treating depression in some of your patients (select one answer) (Q12)	0.461
I believe TMS is an effective treatment option in primary care for the treatment of resistant depression (select one answer) (patients remain depressed after taking at least one antidepressant) (Q13)	0.710
I am confident in the safety and tolerability of TMS in primary care for the treatment of resistant depression (select one answer) (patients remain depressed after taking at least one antidepressant (Q14)	0.649
I think TMS should be more widely implemented in primary care for the treatment of resistant depression. (Q18)	0.685
Do you think TMS could be used in primary care by general practitioners to treat patients who remain depressed even after taking at least one antidepressant (Q16)	0.494
There are currently approved TMS courses in the United Kingdom and the Netherlands for registered doctors. Would you consider taking one of these courses (Q17)	0.641
The following is true: None of the above (Q19) i.e., the other 6 choices in this question are against recommendation of TMS, or against learning or administering TMS	0.385

Extraction Method: Principal Component Analysis; [a]1 component extracted

Table 5. Validity of the Willingness to learn/ administer TMS scale

Component Matrix[a]	Component 1
I think TMS should be more widely implemented in primary care for the treatment of resistant depression. (Q18)	0.602
Do you think TMS could be used in primary care by general practitioners to treat patients who remain depressed even after taking at least one antidepressant (Q16)	0.604
There are currently approved TMS courses in the United Kingdom and the Netherlands for registered doctors. Would you consider taking one of these courses (Q17)	0.834
The following is true: None of the above i.e., the other 6 choices in this question are against recommendation of TMS, or against learning or administering TMS (Q19)	0.585
Would you be interested in having TMS in your practice if it was eligible for reimbursement: Yes, I would be interested, **or** Yes, only if I can also obtain approved TMS training, **or** Yes, if it was financially viable (Q20)	0.780

Extraction Method: Principal Component Analysis; [a]1 component extracted

Table 6. Means scores of the overall latent (composite) variables: awareness of TMS, effectiveness and safety of TMS, recommendations of TMS, and willingness to learn and administer TMS

Statistics					
		Awareness	Effectiveness_Safety	Recommend_TMS	Learn_Administer
N	Valid	113	113	113	113
	Missing	0	0	0	0
Mean		1.32	3.00	2.04	2.03
Median		1.00	3.00	2.00	2.20
Mode		1.00	3.00	1.71[a]	2.40
Std. Deviation		0.475	0.400	0.385	0.557
Skewness		1.224	-0.492	-0.075	-0.261
Std. Error of Skewness		0.227	0.227	0.227	0.227
Kurtosis		0.463	6.803	-0.295	-1.032
Std. Error of Kurtosis		0.451	0.451	0.451	0.451
Minimum		1.00	1.00	1.00	1.00
Maximum		3.00	4.33	3.00	3.00

[a]Multiple modes exist. The smallest value is shown

Table 7. Results of the one-sample t-tests: neutral or unsure about TMS

One-Sample Test						
	Test Value=2					
	t	Df	Sig. (2-tailed)	Mean Difference	95% CI of the difference	
					Lower	Upper
Awareness	-15.307	112	0.000	-0.68437	-0.7730	-0.5958
Recommend_TMS	1.035	112	0.303	0.03751	-0.0343	0.1093
Learn_Administer	0.650	112	0.517	0.03407	-0.0698	0.1379

CI, confidence interval

Table 8. Respondents neutral/unsure in the effectiveness or safety of TMS in treating resistant depression

One-Sample Test

	Test Value=3					
	T	Df	Sig. (2-tailed)	Mean Difference	95% CI of the Difference Lower	Upper
Effectiveness_Safety	0.078	112	0.938	0.00295	-0.0715	0.0774

CI, confidence interval

Table 9. Parameter estimates of Regression Model 1

Dependent Variable	Recommend TMS					
Parameter	B	Std. Error	t	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Intercept	0.117	0.235	0.498	0.620	-0.349	0.582
Recommend NPT=No	0.071	0.063	1.137	0.258	-0.053	0.196
Recommend NPT=Yes	0[a]					
Cognitive behavioral therapy=No	0.052	0.071	0.740	0.461	-0.088	0.193
Cognitive behavioral therapy=Yes	0[a]					
Interpersonal therapy=No	-0.042	0.062	-0.679	0.499	-0.164	0.080
Interpersonal therapy=Yes	0[a]					
Supportive therapy=No	0.039	0.067	0.578	0.565	-0.094	0.172
Supportive therapy=Yes	0[a]					
Physical activity=No	0.031	0.078	0.399	0.691	-0.123	0.185
Physical activity=Yes	0[a]					
Add NPT=No	0.023	0.059	0.393	0.695	-0.093	0.139
Add NPT=Yes	0[a]					
NPT for new diagnosis=No	-0.005	0.063	-0.081	0.936	-0.130	0.120
NPT for new diagnosis=Yes	0[a]					
Awareness	-0.051	0.059	-0.859	0.392	-0.168	0.067
Effectiveness and safety	0.653	0.071	9.166	0.000	0.512	0.794

[a]Reference category

Table 10. Parameter estimates of Regression Model 2

Dependent Variable	**Recommend TMS**					
Parameter	B	Std. Error	t	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Intercept	2.157	0.140	15.397	0.000	1.879	2.435
Efficacy Safety=No	-0.076	0.109	-0.692	0.491	-0.293	0.141
Efficacy Safety=Yes	0[a]					
Severity Depression=No	0.081	0.083	0.976	0.331	-0.083	0.245
Severity Depression=Yes	0[a]					
Patient Pref=No	0.027	0.105	0.260	0.795	-0.181	0.236
Patient Pref=Yes	0[a]					
Availability=No	-0.207	0.094	-2.188	0.031	-0.394	-0.019
Availability=Yes	0[a]					
Free=No	-0.027	0.090	-0.294	0.769	-0.206	0.153
Free=Yes	0[a]					
PatientWillingTMS=No	-0.064	0.084	-0.760	0.449	-0.229	0.102
PatientWillingTMS=Yes	0[a]					
Other=No	-0.046	0.130	-0.354	0.724	-0.303	0.211
Other=Yes	0[a]					

[a]Reference category

Figure legends

Figure 1. Mean of TMS aspects by GPs

Figure 2. Mean of TMS aspects by gender

Figure 3. TMS and years of practice

Figure 1

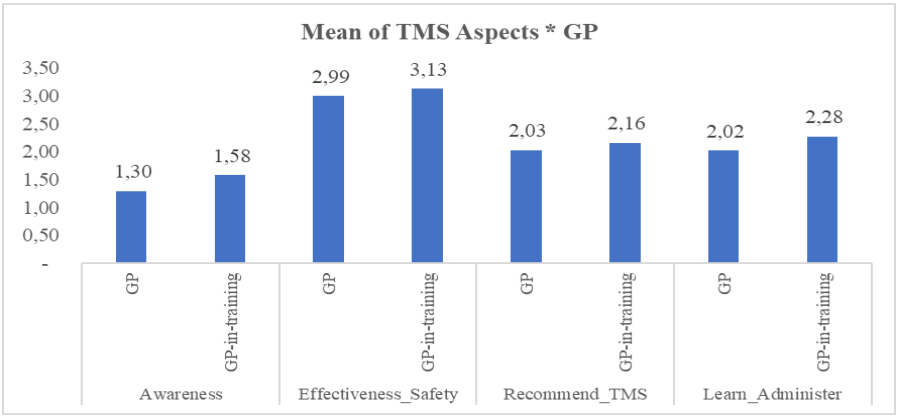


Figure 2

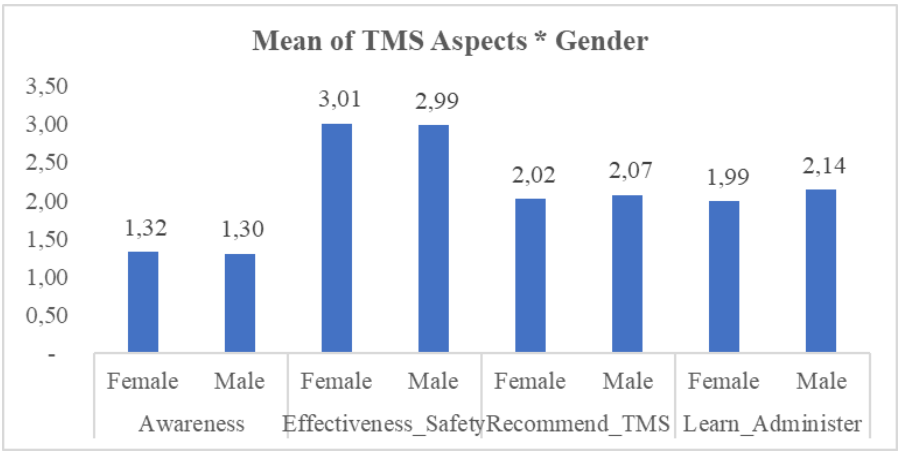


Figure 3

