Concomitant lorazepam use and antidepressive efficacy of repetitive transcranial magnetic stimulation in a naturalistic setting

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Abstract

Background/objectives: Repetitive transcranial magnetic stimulation (rTMS) has been established as an effective therapeutic intervention for the treatment of depression. Preliminary data suggest that the efficacy of rTMS is reduced in patients taking benzodiazepines (BZD). Here, we use real-world data from a large sample to investigate the influence of lorazepam on the effectiveness of rTMS.

Methods From a retrospective cohort of clinically depressed patients that were treated with rTMS, we compared 176 patients not taking any BZD with 73 patients taking lorazepam with respect to changes in the Hamilton Depression Rating Scale (HRDS).

Results Both groups improved during rTMS according to HRDS scores, but the amelioration of symptoms was significantly less pronounced in patients taking lorazepam (18% vs. 38% responders in the non-lorazepam group). We could not see any association of intake regimen of lorazepam with response in rTMS.

Conclusion Our observational study suggests that intake of lorazepam impedes the response to rTMS. The impact of lorazepam and other BZD on rTMS should receive more attention and be further investigated in prospective, hypothesis-based treatment studies to determine causal relationships between medication treatments and outcome. This could lead to specific recommendations for pharmacological treatment for depressed patients undergoing rTMS.

Keywords rTMS · Brain stimulation · Depression · Affective disorder · Lorazepam · Benzodiazepine

Introduction

Depression is a psychiatric illness of high prevalence and it is associated with a high level of individual suffering [1, 2] as well as socioeconomic burden [3–5]. Depressive disorders are a heterogeneous group [1] of different disease entities, whose neurobiological pathophysiology is not yet well understood and controversially discussed [6–8]. Despite new pharmacological [8–10] and non-pharmacological [11] approaches, treatment outcome remains unsatisfactorily in a substantial proportion of patients [12, 13]. Repetitive transcranial magnetic stimulation (rTMS) is becoming increasingly important as an effective treatment method for depression with a few side effects and good patient acceptance in everyday clinical practice [14–24].

To further increase effectiveness of rTMS, a better understanding of interaction between rTMS and drugs is important, especially as most depressed individuals that are treated with rTMS also receive psychotropic medication. Despite their unfavorable side effect profile, especially in long-term use [25, 26], benzodiazepines (BZD) are widely used in the treatment of depression due to their good efficacy and rapid onset of action [25] with lorazepam being one of the most commonly prescribed BZD [27, 28]. Therefore, the influence of lorazepam on the antidepressive efficacy of rTMS is of particular interest.

A few clinical studies have investigated the interaction of BZD and rTMS in the treatment of depression. Hunter et al. [29] analyzed in a retrospective study 181 patients with MDD who were treated with rTMS and medication for 6 weeks to examine potential relationships between categories of medication use and clinical outcome to
rTMS treatment for depression. Patients treated with a BZD showed a lower improvement at week 2 and a lower responder rate at week 6 compared to patients not treated with a BZD. In contrast, patients receiving psychostimulants showed a greater improvement at week 2 and over the entire 6 weeks, and a higher responder rate than patients not receiving psychostimulants. All other drug groups studied did not affect the effect of rTMS treatment [29].

Kaster and colleagues reported a secondary analysis of the THREE-D study, a big randomized, multicentre, non-inferiority clinical trial [30], and could demonstrate that treatment response to rTMS is reduced in patients taking BZD [31]. This analysis raised awareness of the importance of the investigation of rTMS–medication interactions [32].

Caulfield and Stern retrospectively examined 58 patients with depression who were treated with rTMS and medication. An attempt was made to differentiate between rTMS effects on depression and on anxiety. rTMS was effective in treating both depression and anxiety regardless of the medication given. BZD users were pre- and post-treatment significantly more anxious than non-BZD users. Only in patients using BZD, changes in mood and anxiety were correlated. The authors themselves discussed a floor effect for non-BZD users as they started from lower anxiety scores [33].

In sum, studies investigating influence of BZD on rTMS effects in depression are in controlled trials but not with the aim of the study to investigate the effects of BZD. Data were analyzed retrospectively. In this study, we analyzed a large real-world sample of clinically depressed individuals receiving rTMS treatment under naturalistic conditions (high ecological validity) with the question whether concomitant use of lorazepam, one of the most commonly used BZD [27, 28], influences the antidepressive effectiveness of rTMS.

Methods

From a retrospective cohort of 716 patients with depression who were treated with rTMS in the Center for Neuromodulation Regensburg (Germany) between 2002 and 2017, complete data of the Hamilton Depression Rating Scale (HDRS; 44) at begin and end of treatment were available for 299 patients [23].

Response was defined as reduction of the HDRS-17 score by 50% or more at the end of treatment as compared to baseline.

The inclusion criteria for this retrospective analysis were naïvity to rTMS (only the patient’s first treatment with rTMS was considered), clinical depression with diagnosis F31–F33 according to ICD-10 (single or recurrent episode of unipolar or bipolar depression, each with or without psychotic symptoms), a complete documented HDRS at beginning and at the end the rTMS treatment and absence of any serious somatic illness. Both in- and outpatients were included. Patients were grouped according to their intake of BZD and z-drugs (zopiclone or zolpidem). Seventy-three patients took only lorazepam (group lorazepam). Fifty patients took other BZD or z-drugs (30 with z-drugs, six with oxazepam, one with lorametazepam, two with bromazepam, and two with z-drugs and BZD) and 176 took no BZD or z-drug (group no BZD). For the analysis, we concentrated on the groups lorazepam and no BZD as the scope of the paper was BZD and not z-drugs (due to differences in use) and the number of other BZDs were too small for adequate analyses.

Patients were treated with different rTMS protocols including stimulation of the left, right, bilateral dorsolateral, and also dorsomedial prefrontal cortex [23, 34–36]. There were no significant differences in the antidepressant effect of rTMS between different treatment protocols ($\chi^2 = 8.569$; df = 7; $p = 0.285$). A typical treatment lasted two up to 6 weeks, whereas in individual cases, treatment duration was different. No accelerated protocols were applied.

All data were analyzed using SPSS (IBM Corp., USA; Version 24.0.0.0). The significance level was set at $p < 0.05$ for group contrasts. For group contrasts we used Student’s $t$ tests or Chi-square test of independence depending on the scales of measurement. Effect sizes for HDRS group contrasts were reported by Cohen’s $d$ [37]. To exclude an influence of the baseline HDRS values on the group differences evaluated with $T$ tests, we analyzed changes from pre- to post-treatment for the two groups by an analysis of covariance with the within-subjects factor rTMS (pre- and post-rTMS) and the between-subjects factor group (no BZD or z-drugs vs. lorazepam) and the covariate baseline HDRS score for the dependent variables HDRS-21 and HDRS-17. This affirmed the results of the group comparisons.

To evaluate the influence of dosage regimen of lorazepam on rTMS effects, we correlated the sum of taken lorazepam over all days, the number of days lorazepam was taken, the average daily dosage, the relative proportion of the number of days lorazepam was taken to the number of rTMS treatment days, and the relation of the sum of lorazepam to the number of rTMS treatment days using Pearson correlation coefficients. We also compared the groups with an average daily dosage of maximal 1 mg and above 1 mg by Student’s $t$ tests.

Results

Both groups did not differ with respect to age, sex, resting motor threshold, stimulation intensity, number of treatment sessions, number of pulses per session, type and severity of depression, and baseline depressive symptoms (HDRS) (Table 1). Overall patients showed an amelioration of symptoms with rTMS, which was significantly less pronounced

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in patients taking lorazepam as compared to those who did not take BZD (Table 1). 18% of the patients with lorazepam were responders (>50% decrease in symptoms in HDRS-17) in contrast to 38% of the patients without lorazepam. Effect sizes were small for group contrasts. We could not show an association of the absolute sum of lorazepam dosage over the course of treatment (all 0.114 ≤ r ≤ 0.193; all p values ≥ 0.102) and relative to the number of treatment days (all 0.055 ≤ r ≤ 0.140; all p values ≥ 0.237), the absolute (all 0.146 ≤ r ≤ 0.202; all p values ≥ 0.087) or relative number of days taking lorazepam (all 0.051 ≤ r ≤ 0.115; all p values ≥ 0.332) or the daily dosage of lorazepam with changes in HDRS scores (all 0.070 ≤ r ≤ 0.148; all p values ≥ 0.212). Dividing the group into patients with daily dosage over and below 1 mg did not show significant differences (all T values ≤ 1.534; df = 71; all p values ≥ 0.129). In sum, the fact that lorazepam is taken lowers the response to rTMS without association of intake regimen of lorazepam in relation to rTMS.

This is consistent with theoretical considerations [32] on the interaction between BZD and rTMS, based on the increasing knowledge of the biological basis of MDD [38–40] and the role of rTMS in its treatment [17, 40]. In MDD, clinically depressed individuals show complex dysfunction in gamma-aminobutyric acid (GABA) regulation, including lower GABA levels in cerebrospinal fluid [41] and different parts of the brain [43–47], and normalizing after treatment [48–51]. The therapeutic effect of rTMS is presumably based, among other factors, on the normalization of dysfunctional neural networks [38, 39]. More specifically, the rTMS effect seems not to be based primarily on the intranetwork modulation of the target structure itself, i.e., the left DLPFC [17] in MDD, but on an inter-network propagation of the effect to connected neurocircuits [52, 53], which subsequently influences downstream systems, i.e., neuroendocrine systems such as the hypothalamic–pituitary–adrenal axis [54]. GABA type A receptors (GABA$_A$R) seem to be significantly involved in the mediation of this large-scale communication [55]. BZD such as lorazepam are positive allosteric modulators (PAMs) at GABA$_A$R [56].

In rodents, down-regulatory effects on GABA signaling, caused by concurrent, chronic use of BZD, have well been studied [57–62] and could tend to mitigate the probable increases in cortical GABA signaling that appear with clinical effective rTMS [50], as it was suggested by Hunter and Minzenberg [29].

### Table 1 Characteristics of patients with depression taking vs. not-taking lorazepam

|                         | No BZD or Z-drug (n = 176) | Lorazepam (n = 73) | Statistics for group contrasts |
|-------------------------|-----------------------------|--------------------|--------------------------------|
| Age (years)             | 47.8 ± 12.3                 | 49.3 ± 13.3        | T = 0.809, df = 247, p = 0.420 |
| Sex (female/male)       | 91/85                       | 46/27              | χ$^2$ = 2.667, df = 1, p = 0.102 |
| Resting motor threshold (% stimulator output) | 43.0 ± 8.6                 | 44.14 ± 11.1       | T = 0.882, df = 247, p = 0.379 |
| Stimulation intensity (% stimulator output)      | 45.2 ± 8.0                 | 45.1 ± 9.0         | T = 0.068, df = 247, p = 0.946 |
| Number of pulses per session                        | 1989.8 ± 227.6             | 2002.7 ± 143.3     | T = 0.451, df = 247, p = 0.652 |
| Number of sessions per patient/treatment            | 17.0 ± 6.3                 | 17.8 ± 6.3         | T = 0.849, df = 247, p = 0.397 |
| HDRS-17 pre treatment                                  | 19.4 ± 5.4                 | 19.7 ± 5.8         | T = 0.518, df = 247, p = 0.605 |
| HDRS-21 pre treatment                                  | 22.7 ± 6.4                 | 23.3 ± 6.7         | T = 0.661, df = 247, p = 0.509 |
| ICD-10 type of depression (F31/F32/F33)               | 12/56/106                  | 8/15/50            | χ$^2$ = 3.937, df = 2, p = 0.140 |
| ICD-10 severity of depression (mild + moderate/severe/psychotic) | 35/106/6                   | 9/57/6             | χ$^2$ = 4.995, df = 2, p = 0.082 |
| HDRS-17 absolute change                                | − 7.1 ± 6.3                | − 4.5 ± 7.6        | T = 2.728, df = 247, p = 0.007, d = 0.372 |
| HDRS-21 absolute change                                | − 8.1 ± 7.5                | − 5.4 ± 8.7        | T = 2.476, df = 247, p = 0.014, d = 0.332 |
| HDRS-17 relative change (%)                            | − 35.7 ± 30.7              | − 18.9 ± 42.1      | T = 3.511, df = 247, p < 0.001, 0.456 |
| HDRS-21 relative change (%)                            | − 34.2 ± 31.2              | − 18.8 ± 41.0      | T = 3.214, df = 247, p = 0.001, 0.423 |
| HDRS-17 relative change > 50% (responder/non-responder) | 66/110                     | 13/60              | χ$^2$ = 9.237, df = 1, p = 0.002 |
| HDRS item 10 for psychic anxiety                        | 2.1 ± 1.2                  | 2.3 ± 1.1          | T = 1.313, df = 246, p = 0.190 |
| HDRS item 11 for somatic anxiety                        | 1.6 ± 1.0                  | 1.4 ± 1.1          | T = 1.268, df = 247, p = 0.206 |

**HDRS-17/21** Hamilton depression rating scale 17/21 items; negative values indicate amelioration in HDRS from pre- to post-treatment

**Discussion**

In our study, we were able to show that concomitant use of lorazepam significantly reduces the effectiveness of and response rate to rTMS in the treatment of clinical depression with small effect sizes.
In motor cortex studies in healthy individuals, it is well established that this modified behavior of BZD-modulated networks has a significant influence on the effect of rTMS. In experimental models simulating central nervous adaption to peripheral lesions [63] and practice-dependent plasticity [64], single dose of lorazepam reduced cortical plasticity, suggesting that an increase in GABA-related inhibition seems to impede plasticity in the human motor cortex.

In combined TMS-EEG studies, application of the BZD midazolam in anesthetic doses prevented GABA_A-controlled propagation of TMS-evoked potentials (TEPs) from the stimulation site at premotor cortex to a series of distant cortical areas, as it is normally seen [65]. Similar results were found for TMS stimulation at premotor and parietal cortex after application of anesthetic doses of GABA_A PAMs propofol [66]. Premoli found that GABA_A PAMs alprazolam and diazepam decrease TEP component N100 in the non-stimulated hemisphere [67], which is likely representing GABA_A-controlled, long-range interhemispheric neurotransmission [55, 65]. These findings suggest that PAMs at GABA_A impair the propagation of rTMS effects from the stimulation site to distant brain areas, which may be important for antidepressive efficacy [32, 55].

A clinical rTMS-MRS study showed a trend towards lower increase in medial prefrontal cortex GABA concentration in depressed individuals with chronic lorazepam use [50]. In pooled data with 185 depressed individuals receiving 4 weeks of TMS using different treatment protocols, Fitzgerald et al. found no relationship between benzodiazepine use and clinical response in 64 BZD users compared to 121 patients not taking BZD [68]. Our results are consistent with recent findings of two other large exploratory studies: Kaster et al. [31] found depressed BZD users treated with rTMS to be with reduced odds of membership in a “rapid response” trajectory and with increased odds of membership in a “nonresponse” trajectory and Hunter. Minzenberg et al. [29] found a lower response rate to HF-rTMS applied to the left DLPFC in BZD users. As discussed earlier [32, 69], these findings suggest that BZD may have a negative impact on the antidepressant mechanisms of rTMS, consistent with the results of our and other recently published [29, 31] clinical studies. With three large exploratory studies with 388 [31], 181 [29], and 249 participants in our study, which all arrive at comparable results, there is growing evidence that BZD use is associated with a poorer outcome of rTMS treatment.

There were several limitations to this study. First, it is a retrospective study in a naturalistic setting. Inpatients and outpatients were included. Many of our patients are chronically ill patients, often with multiple psychiatric comorbidities, psychiatric multi-medication and a broad medication history. Even if the two groups with and without BZD did not differ in demographic and clinical characteristics, we cannot exclude that there were differences between the two groups, as there might have been clinical reasons why some of the patients received BZD and others not. However, these reasons seem not to be reflected in the clinical data that are usually recorded even in randomized-controlled trials.

A further important limitation may be that medication, given regularly and on-demand, was recorded exclusively during the study period. This comes with two major limitations: First, the latency of many psychotropic drugs, especially antidepressants, could not be assessed. Second, it was also not possible to determine how long certain drugs, especially BZD were taken and in what doses before the treatment began. This may be especially important, as long-term BZD users tend to shift their use of medication from an as-prescribed to an as-needed pattern [26]. Assuming that several complex control loops with a certain inertia and capacity for self-regulation are involved in the development and chronicification as well as in the recovery from depression, the duration of influencing factors is also of decisive importance. Furthermore, medication was not kept stable during the study period and was being changed by the treating physicians in most patients, often to a considerable extent. The intake was not monitored as standard. Serum-level controls were not carried out as standard. Particularly in outpatients, there is still a lack of information regarding the demand-oriented use of (self-)medication or other substance intake, e.g., OTC drugs and/or alcohol. However, patients with indications of clinically relevant substance use disorders were excluded from the study. Multiple psychiatric medication was the rule rather than the exception, especially for patients receiving lorazepam. Further pharmacodynamic and pharmacokinetic interactions must, therefore, be expected. The evaluation of the patient files was carried out with the greatest care by clinical specialists. Nevertheless, there is naturally a certain diagnostic fuzziness in the differential diagnosis of affective disorders, especially depression, compared to other mental disorders, e.g., personality disorders [70] or psychoses [7]. Further limitations are due to high heterogeneity in our naturalistic sample (different types of depression and different treatment protocols).

In our naturalistic study, we found no correlation between lorazepam dose and efficacy of rTMS treatment, most likely due to limitations in study design. Whether such a correlation exists should be further investigated.

It was suggested that the negative influence of BZD on outcome of rTMS is most severe in the first weeks of rTMS treatment [69]. Analyzing improvement of symptom severity in weeks 2, 4, and 6, Hunter, Minzenberg et al. found the largest deficit in BZD users in week 2 [29], while Kaster et al. reported that BZD users were underrepresented in rapid response group during a 4 week course of rTMS treatment [31]. Due to study design, we cannot make any conclusions about trajectories.
Conclusion

Our results show a reduced effectiveness of rTMS treatment of depression when lorazepam is administered concomitantly. The impact of lorazepam and other BZD on rTMS should receive more attention and should be further investigated in prospective, hypothesis-based treatment studies to determine causal relationships between medication treatments and outcome. Given our results, one should investigate whether patients treated with rTMS for depression may benefit from discontinuation of BZD in controlled trials. Whether the results for lorazepam are also valid for other BZD and the influence of lorazepam dose on efficacy of rTMS should be further investigated. A better understanding of the interactions between rTMS and drugs is important for efforts in increasing the effectiveness of rTMS.

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Author contributions TP, PK, MS, MA, MD, and TH recorded the data. MS analyzed the data. MD, BL, and MS drafted the manuscript. All authors designed the study, interpreted the data, and approved the final version of the manuscript.

Data availability Not possible due to restrictions of the ethics committee.

Compliance with ethical standards

Conflicts of interest MD, MA, PK, TP, MS and BL declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. TH has had travel expenses paid for by Nexstim Plc.

Ethics approval The retrospective analysis of clinical data was approved by the local ethics committee of the University of Regensburg (16-104-0223).

Consent to participate Not necessary due to retrospective analysis.

Consent for publication Not necessary due to retrospective analysis.

Code availability Not relevant due missing availability of data.

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References

1. Belmaker RH, Agam G (2008) Major depressive disorder. New Engl J Med 358(1):55–68. https://doi.org/10.1056/NEJMoa073096
2. Nemeroff CB (2007) The burden of severe depression: a review of diagnostic challenges and treatment alternatives. J Psychiatry Res 41(3–4):189–206. https://doi.org/10.1016/j.jpsychires.2006.05.008
3. Lépine J-P, Briley M (2011) The increasing burden of depression. Neuropsychiatr Dis Treat 7(Suppl 1):3–7. https://doi.org/10.2147/NDT.S19617
4. Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde, Ärztliches Zentrum für Qualität in der Medizin (AZQ) (2015) S3-Leitlinie/Nationale VersorgungsLeitlinie Unipolare Depression—Langfassung, 2. Auflage. Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde (DGPPN); Bundesärztekammer (BÄK); Kassenärztliche Bundesvereinigung (KBV); Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
5. Kessler RC, Berglund P, Demler O et al (2003) The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA 289(23):3095–3105. https://doi.org/10.1001/jama.289.23.3095
6. Pehrson AL, Sanchez C (2015) Altered γ-aminobutyric acid neurotransmission in major depressive disorder: a critical review of the supporting evidence and the influence of serotonergic antidepressants. Drug Des Devel Ther 9:603–624. https://doi.org/10.2147/DDDT.S62912
7. Reininghaus U, Böhneke JR, Chavez-Baldini U et al (2019) Transdiagnostic dimensions of psychosis in the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP). World Psychiatry 18(1):67–76. https://doi.org/10.1002/wps.20607
8. Duman RS, Aghajanian GK, Sanacora G et al (2016) Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants. Nat Med 22(3):238–249. https://doi.org/10.1038/nm.4050
9. Daly EJ, Singh JB, Fedgchin M et al (2018) Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: a randomized clinical trial. JAMA Psychiatry 75(2):139–148. https://doi.org/10.1001/jamapsychiatry.2017.3739
10. Swainson J, Thomas RK, Archer S et al (2019) Esketamine for treatment resistant depression. Expert Rev Neurother 19(10):899–911. https://doi.org/10.1080/14737175.2019.1640604
11. Schatzberg AF, Rush AJ, Arnow BA et al (2005) Chronic depression: medication (nefazodone) or psychotherapy (CBASP) is effective when the other is not. Arch Gen Psychiatry 62(3):513–520. https://doi.org/10.1001/archpsyc.62.3.513
12. McIntyre RS, Filteau M-J, Martin L et al (2014) Treatment-resistant depression: definitions, review of the evidence, and algorithmic approach. J Affect Disord 156:1–7. https://doi.org/10.1016/j.jad.2013.10.043
13. George MS, Nahas Z, Li X et al (2002) Novel treatments of mood disorders based on brain circuitry (ECT, MST, TMS, VNS, DBS). Semin Clin neuropsychiatry 7(4):293–304
14. George MS, Lisanby SH, Avery D et al (2010) Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Arch Gen Psychiatry 67(5):507–516. https://doi.org/10.1001/archgenpsychiatry.2010.46
15. Levkovitz Y, Isserles M, Padberg F et al (2015) Efficacy and safety of deep transcranial magnetic stimulation for major depression: a prospective multicenter randomized controlled trial. World Psychiatry 14(1):64–73. https://doi.org/10.1002/wps.20199
16. O’Reardon JP, Solvason HB, Janicak PG et al (2007) Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatry 62(11):1208–1216. https://doi.org/10.1016/j.biopsych.2007.01.018

17. Lefaucheur J-P, Aleman A, Baeken C et al (2020) Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): an update (2014–2018). Clin Neurophysiol 131(2):474–528. https://doi.org/10.1016/j.clinph.2019.11.002

18. Gaynes BN, Lloyd SW, Lux L et al (2014) Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and meta-analysis. J Clin Psychiatry 75(5):477–489. https://doi.org/10.4088/JCP.13r08815 (quiz 489)

19. Baeken C, Brem A-K, Arms M et al (2019) Repetitive transcranial magnetic stimulation treatment for depressive disorders: current knowledge and future directions. Curr Opin Psychiatry 32(5):409–415. https://doi.org/10.1097/YCO.0000000000000533

20. Rasmussen KG (2011) Some considerations in choosing electroconvulsive therapy versus transcranial magnetic stimulation for depression. J ECT 27(1):51–54. https://doi.org/10.1097/YCT.0b013e318de46

21. Rossi S, Hallett M, Rossini PM et al (2009) Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 120(12):2008–2039. https://doi.org/10.1016/j.clinph.2009.08.016

22. Janicak PG, O’Reardon JP, Sampson SM et al (2008) Transcranial magnetic stimulation in the treatment of major depressive disorder: a comprehensive summary of safety experience from acute exposure, extended exposure, and during reintroduction treatment. J Clin Psychiatry 69(2):222–232. https://doi.org/10.4088/jcp.v69n0208

23. Abdelnaim MA, Langguth B, Deppe M et al (2019) Anti-suicidal efficacy of repetitive transcranial magnetic stimulation in depressive patients: a retrospective analysis of a large sample. Front Psychiatry 10:929. https://doi.org/10.3389/fpsyt.2019.00929

24. Mutz J, Vipulananthan V, Carter B et al (2019) Comparative efficacy and acceptability of non-surgical brain stimulation for the acute treatment of major depressive episodes in adults: systematic review and network meta-analysis. BMJ (Clinical research ed) 364:k1079. https://doi.org/10.1136/bmj.k1079

25. Olfson M, King M, Schoenbaum M (2015) Benzodiazepine use in mental health treatment with benzodiazepines in dementia patients: an analysis of German health insurance claims data. Int Clin Psychopharmacol 30(5):282–289. https://doi.org/10.1097/YIC.0000000000000230

26. Romach M, Busto U, Somer G et al (1995) Clinical aspects of chronic use of alprazolam and lorazepam. Am J Psychiatry 152(8):1161–1167. https://doi.org/10.1176/ajp.152.8.1161

27. Rowntree R, Sweeney J, Crumlish N et al (2018) How do we measure response to dorsolateral prefrontal rTMS in major depression: a three-D study. Am J Psychiatry 176(5):367–375. https://doi.org/10.1176/appi.ajp.2018.18091096

28. Kaiser RH, Andrews-Hanna JR, Wager TD et al (2015) Large-scale network dysfunction in major depressive disorder: a meta-analysis of resting-state functional connectivity. JAMA Psychiatry 72(6):603–611. https://doi.org/10.1001/jamapsychiatry.2015.0071

29. Williams LM (2016) Precision psychiatry: a neural circuit taxonomy for depression and anxiety. Lancet Psychiatry 3(5):472–480. https://doi.org/10.1016/S2215-0366(15)00579-9

30. Drysdale AT, Grosenick L, Downar J et al (2017) Resting-state connectivity biomarkers define neurophysiological subtypes of depression. Nat Med 23(1):28–38. https://doi.org/10.1038/nm.4246

31. Gold BJ, Bowers MB, Roth RH et al (1980) GABA levels in CSF of patients with psychiatric disorders. Am J Psychiatry 137(3):362–364. https://doi.org/10.1176/ajp.137.3.362

32. Sanacora G, Mason GF, Rothman DL et al (1999) Reduced cortical gamma-aminobutyric acid levels in depressed patients determined by proton magnetic resonance spectroscopy. Arch Gen Psychiatry 56(11):1043–1047. https://doi.org/10.1001/archpsyc.56.11.1043

33. Waagepetersen HS, Sonnewald U, Schousboe A (1999) The GABA paradox: multiple roles as metabolite, neurotransmitter, and neurodifferentiative agent. J Neurochem 73(4):1335–1342. https://doi.org/10.1046/j.1471-4159.1999.7031335.x

34. Hasler G, van der Veen JW, Tumonis T et al (2007) Reduced prefrontal glutamate/glutamine and gamma-aminobutyric acid levels in major depression determined using proton magnetic resonance spectroscopy. Arch Gen Psychiatry 64(2):193–200. https://doi.org/10.1001/archpsyc.64.2.193

35. Kugaya A, Sanacora G, Verhoef NPLG et al (2003) Cerebral benzodiazepine receptors in depressed patients measured with [123I]iomazenil SPECT. Biol Psychiatry 54(8):792–799. https://doi.org/10.1016/S0006-3223(02)01788-2

36. Price RB, Shungu DC, Mao X et al (2009) Amino acid neurotransmitters assessed by proton magnetic resonance spectroscopy: relationship to treatment resistance in major depressive disorder.
Biol Psychiatry 65(9):792–800. https://doi.org/10.1016/j.biopsych.2008.10.025

47. Sanacora G, Gueorguieva R, Epperson CN et al (2004) Subtype-specific alterations of gamma-amino butyric acid and glutamate in patients with major depression. Arch Gen Psychiatry 61(7):705–713. https://doi.org/10.1001/archpsyc.61.7.705

48. Sanacora G, Mason GF, Rothman DL et al (2003) Increased cortical GABA concentrations in depressed patients receiving ECT. Am J Psychiatry 160(3):577–579. https://doi.org/10.1176/appi.ajp.160.3.577

49. Sanacora G, Mason GF, Rothman DL et al (2002) Increased occipital cortex GABA concentrations in depressed patients after therapy with selective serotonin reuptake inhibitors. Am J Psychiatry 159(4):663–665. https://doi.org/10.1176/appi.ajp.159.4.663

50. Dubin MJ, Mao X, Banerjee S et al (2016) Elevated prefrontal cortex GABA in patients with major depressive disorder after TMS treatment measured with proton magnetic resonance spectroscopy. J Psychiatry Neurosci 41(3):E37–45

51. Hasler G, Neumeister A, van der Veen JW et al (2005) Normal prefrontal gamma-aminobutyric acid levels in remitted depressed subjects determined by proton magnetic resonance spectroscopy. Biol Psychiatry 58(12):969–973. https://doi.org/10.1016/j.biopsych.2005.05.017

52. Philip NS, Barredo J, Aiken E et al (2018) Neuroimaging mechanisms of therapeutic transcranial magnetic stimulation for major depressive disorder. Biol psychiatry Cogn Neurosci Neuroimaging 3(3):211–222. https://doi.org/10.1016/j.bpsc.2017.10.007

53. Hadas I, Sun Y, Lioumis P et al (2019) Association of repetitive transcranial magnetic stimulation treatment with subgenual cingulate hyperactivity in patients with major depressive disorder: a secondary analysis of a randomized clinical trial. JAMA Neuropat Open 2(6):e195578. https://doi.org/10.1001/jamanetworkopen.2019.5578

54. Baeken C, De Raedt R (2011) Neurobiological mechanisms of repetitive transcranial magnetic stimulation on the underlying neurocircuity in unipolar depression. Dialogues Clin Neurosci 13(1):139–145

55. Darmani G, Ziemann U (2019) Pharmacophysiology of TMS-evoked EEG potentials: a mini-review. Brain Stimul 12(3):829–831. https://doi.org/10.1016/j.brs.2019.02.021

56. Olsen RW (2018) GABAergic receptor: Positive and negative allosteric modulators. Neuropharmacology 136(Pt A):10–22. https://doi.org/10.1016/j.neuropharm.2018.01.036

57. Chen S, Huang X, Zeng XJ et al (1999) Benzodiazepine-mediated regulation of α1, α2, β1–3 and y2 GABA receptor subunit proteins in the rat brain hippocampus and cortex. Neuroscience 93(1):33–44. https://doi.org/10.1016/S0306-4522(99)00118-9

58. Galpern WR, Miller LG, Greenblatt DJ et al (1990) Differential effects of chronic lorazepam and alprazolam on benzodiazepine binding and GABAA-receptor function. Br J Pharmacol 101(4):839–842. https://doi.org/10.1111/j.1476-5381.1990.tb14167.x

59. Gouzer G, Specht CG, Allain L et al (2014) Benzodiazepine-dependent stabilization of GABA(A) receptors at synapses. Mol Cell Neurosci 63:101–113. https://doi.org/10.1016/j.mcn.2014.10.004

60. Impagnatiello F, Pesold C, Longone P et al (1996) Modifications of gamma-aminobutyric acid(A receptor subunit expression in rat neocortex during tolerance to diazepam. Mol Pharmacol 49(5):822–831

61. Pesold C, Caruncho HJ, Impagnatiello F et al (1997) Tolerance to diazepam and changes in GABA(A) receptor subunit expression in rat neocortical areas. Neuroscience 79(2):477–487. https://doi.org/10.1016/S0306-4522(96)00609-4

62. Uusi-Oukari M, Korpi ER (2010) Regulation of GABA(A) receptor subunit expression by pharmacological agents. Pharmacol Rev 62(1):97–135. https://doi.org/10.1124/pr.109.002063

63. Ziemann U, Hallett M, Cohen LG (1998) Mechanisms of deafferentation-induced plasticity in human motor cortex. J Neurosci 18(17):7000–7007. https://doi.org/10.1523/JNEUROSCI.18-17-07000.1998

64. Ziemann U, Muehlbacher W, Hallett M et al (2001) Modulation of practice-dependent plasticity in human motor cortex. Brain 124( Pt 6):1171–1181. https://doi.org/10.1093/brain/124.6.1171

65. Ferrarelli F, Massimini M, Sarasso S et al (2010) Breakdown in cortical effective connectivity during midazolam-induced loss of consciousness. Proc Natl Acad Sci USA 107(6):2681–2686. https://doi.org/10.1073/pnas.0913008107

66. Sarasso S, Boly M, Napolitani M et al (2015) Consciousness and complexity during unresponsiveness induced by propofol, xenon, and ketamine. Curr Biol 25(23):3099–3105. https://doi.org/10.1016/j.cub.2015.10.014

67. Premoli I, Castellanos N, Rivolta D et al (2014) TMS-EEG signatures of GABAergic neurotransmission in the human cortex. J Neurosci 34(16):5603–5612. https://doi.org/10.1523/JNEUROSCI.5089-13.2014

68. Fitzgerald PB, Daskalakis ZJ, Hoy KE (2020) Benzodiazepine use and response to repetitive transcranial magnetic stimulation in major depressive disorder. Brain Stimul 13(3):694–695. https://doi.org/10.1016/j.brs.2020.02.022

69. Hunter AM, Leuchter AF (2020) Benzodiazepine Use and rTMS Outcome. Am J Psychiatry 177(2):172. https://doi.org/10.1176/appi.ajp.2019.19060603

70. Gunderson JG, Elliott GR (1985) The interface between borderline personality disorder and affective disorder. Am J Psychiatry 142(3):277–288. https://doi.org/10.1176/ajp.142.3.277