

20 cases, zolpidem was found to be useless or potentially detrimental, even delaying other more useful interventions. A successful "Zolpidem Test" to confirm diagnosis was reported in 11 cases.

**Conclusions:** Given its lack of significant side effects and short half-life, zolpidem emerges as a possible diagnostic tool for catatonia, in the so-called "Zolpidem Test". In selected cases of catatonia associated with a variety of etiologies, it may be a useful therapeutic option, with efficacy ranging from a few hours of lucidity to complete restoration of consciousness. Information on the effect of GABA-A PAMs in this area are lacking. Further research is needed to clarify the role of zolpidem in the treatment of catatonia, especially to identify clinical features of patients that could predict outcome.

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NEUROMODULATION IN A PRECLINICAL MODEL OF TREATMENT-RESISTANT DEPRESSION: NEUROBEHAVIOURAL EFFECTS OF A STANDARD PROTOCOL

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**Background.** Repetitive transcranial magnetic stimulation (rTMS), a focal neuromodulation technique, is currently recommended for treatment-resistant depression (TRD) [1]. rTMS preclinical application has long been problematic; however, recent optimization has laid the foundations for improved translational studies [2]. Nonetheless, available results have limited predictive value for TRD patients treated with TMS, as only antidepressant-sensitive preclinical models were used [3].

**Objective.** To overcome this issue, we evaluated rTMS effects on the recovery of the depressive-/anxiety-like phenotype and the expression of key genes in a recently validated rat model of TRD [4,5].

**Methods.** As a TRD model, we applied chronic mild stress (4 weeks) to socially-isolated Wistar-Kyoto rats, an endogenous MDD model [4,5]. An antidepressant-responsive model (prolonged social isolation in Wistar rats; SI) and a control group (socially-housed Wistar rats; CON) were also included in the study. TRD, SI, and CON animals were exposed to standard rTMS, targeting the frontal cortex bilaterally, for eight consecutive days (10 Hz, 40 pulses/train, 1600 pulses/session). Corresponding TRD, SI, and CON sham groups were exposed to the same manipulation and acoustic effect. We then evaluated the short-term (after the last rTMS session) and long-term (after two weeks) effects through behavioural tests investigating motivational/apathy-like state, helplessness, and altered emotionality. We also assessed plasma corticosterone as well as short- and long-term variations in the expression of genes encoding for BDNF and CB1 receptor. Statistical analyses were performed using t-test or rm-ANOVA, as appropriate.

**Results.** SI rats receiving active rTMS showed reduced helplessness in the short-term forced-swim test (model×treatment:  $F(2,92)=5.47$ ,  $p=0.005$ ,  $p<0.05$  in Tukey posthoc) and decreased anxiety-like behaviour in the short-term open-field (model×treatment:  $F(2,92)=2.72$ ,  $0=0.071$ ,  $p<0.05$  in Tukey posthoc) and

long-term plus-maze (model×treatment:  $F(2,70)=2.15$ ,  $p=0.124$ ,  $p<0.05$  in Tukey posthoc) tests than sham SI animals. They also showed reduced plasma corticosterone concentrations (model×treatment:  $F(2,70)=5.08$ ,  $p=0.008$ ,  $p<0.05$  in Tukey posthoc). By contrast, active (vs. sham) rTMS in TRD rats normalized the greater anxiogenic response in the novelty-suppressed feeding test (group×treatment:  $F(2,90)=3.16$ ,  $p=0.047$ ,  $p<0.05$  in Tukey posthoc) and contributed to the recovery of the motivational/apathy-like state in the splash test ( $\chi^2_{(1)}=4.51$ ,  $p=0.034$ ). No significant behavioural changes were observed in the CON group following active rTMS. In the long-term assessment, the TRD active group had significantly higher BDNF and CNR1 mRNA levels in the prefrontal cortex than the TRD sham group ( $p=0.024$  and  $p=0.042$ , respectively). A similar trend was evidenced for BDNF mRNA levels in active SI rats ( $p=0.07$ ). No significant changes were observed in the hippocampus or in the short-term assessment.

**Conclusion.** Results obtained in the SI model confirmed available evidence on the efficacy of standard rTMS in ameliorating the neurobehavioural phenotype in an antidepressant-responsive model. The marked rTMS-induced variations in gene expression also suggested responsiveness in TRD rats, although the effects on the behavioural profile were more circumscribed. In the TRD model, deep brain stimulation reversed anhedonic, anxiogenic, and dyscognitive effects [4,5], whilst rTMS, to our knowledge, has not been previously tested. Further pre-clinical investigations in this model are deemed necessary to help identify optimal stimulation protocols and shed light on new neurobiological-based rationales for rTMS use.

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Conflict of interest

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GALANTAMINE AND MEMANTINE FOR TREATMENT IN MILD COGNITIVE IMPAIRMENT: AN OBSERVATIONAL-PROSPECTIVE STUDY IN 824 PATIENTS FOR 3 YEARS

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**Introduction:** During the last decades, specialists in Alzheimer's Disease (AD) have begun to perceive the close relationship between the development of Mild Cognitive Disorder as an indicator of two aspects: on the one hand the progression to dementia and on the other as a "clue" which reveals a probably effective therapy that delays the evolution and progression to dementia. Galantamine is a competitive and reversible cholinesterase inhibitor and an allosteric modulator of nicotinic receptors. Reduced levels of acetylcholine in the brain are thought to be responsible for some of the symptoms of Alzheimer's disease. Galantamine increases the concentration of acetylcholine in the brain and this increase is believed to be responsible for improved thinking, along with memantine: a