Jan 25. PMID: 31995968; PMCID: PMC6992856. 2. Inserra A. Hypothesis: The Psychedelic Ayahuasca Heals Traumatic Memories via a Sigma 1 Receptor-Mediated Epigenetic-Mnemonic Process. Front Pharmacol. 2018 Apr 5;9:330. doi: 10.3389/fphar.2018.00330. PMID: 29674970; PMCID: PMC5895707. 3. Lawrence, D. W. (2022). Heart rate (HR) and heart rate variability (HRV) response to inhaled N, N-dimethyltryptamine (N, N-DMT): A case report. Journal of Psychedelic Studies, 6(1), 63-68. https://doi.org/10.1556/2054.2022.00178
No conflict of interest

https://doi.org/10.1016/j.nsa.2024.105142

P3433
NEUROSCIENCE APPLIED 3 (2024) 105141
EXPLORING THE COGNITIVE EFFECTS OF BENZODIAZEPINE UTILIZATION IN A SPANISH PARTIAL HOSPITALIZATION UNIT

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Background: Use of benzodiazepines is particularly high in Europe, with Spain leading consumption in the world, with a 11.1 % prevalence in general population and 40.4 % in people with a mental illness [1]. This last percentage is specially alarming considering that most of the prescribers are probably psychiatrists, who supposedly are aware of risks and side effects of this medication, being cognitive impairment one of the most relevant, usually mis-identified as a symptom.
Objective: To study benzodiazepine impact on cognition on patients admitted to Marqués de Valdecilla Hospital's Partial Hospitalization Unit (Santander, Spain) between 2020 and 2023.
Methods: Our sample consisted of 147 patients (52 men, 95 women), with a mean age of 45.11 (±14.8). Most patients had a depressive disorder (18.8 %) or a bipolar disorder (18.1 %). After those, the most frequent disorders were psychotic (13.9 %, plus 6,9 % of first episodes of psychosis with no diagnose yet) and adaptative disorders (12.5 %). The rest represented less than 8 % of the total. Only 1.4 % of the patients had dementia (revising this diagnose after hospitalization). For every patient, a Montreal cognitive assessment test (MOCA) [2] was done at the time of admission and at the time of discharge, and it was registered if there was benzodiazepine medication at admission and if there has been an adjustment on the dose (same, augmentation or reduction) during hospitalization. We created three variables for analysis through IBM® SPSS software, being benzodiazepine medication adjustment the independent (and qualitative) variable and MOCA's punctuation at admission and at discharge the dependent (and quantitative) variables. MOCA's punctuation did not follow a normal distribution (Kolmogorov-Smirnov test). We divided data into subgroups: same dose of benzodiazepines, reduction, and increase; for following analysis. We compared MOCA's punctuations at admission and at discharge in the different subgroups with the Wilcoxon Signed-Rank test. We also analyzed with chi-square test the association between groups of age and presence of cognitive impairment (qualitative variable created from MOCA punctuation) and between groups of age and benzodiazepine medication at admission and adjustment of it.
Results: All patients took benzodiazepine at admission. Benzodiazepine medication was reduced in 60.4 % and fully suppressed in 37.4 % of the patients and maintained on the rest. The dosage of benzodiazepines was not increased in any case. MOCA's punctuation increased after decrease of benzodiazepine medication (mean at admission: 24.2 ±4.34 versus mean at discharge: 25.8 ±3.89, Z-value: 4.73, $p<0.001$), while no significant differences were found in MOCA's punctuation in those patients who maintained the same benzodiazepine dose (Z-value: 1.22, p: 0,22). There was a significant association, as expected, between groups of age and presence of cognitive impairment but there was no significant association between presence of benzodiazepine medication at admission or between groups of age and adjustment during the hospitalization.
Conclusion: These results suggest that benzodiazepine reduction significantly improves cognitive function, regardless of age. It is important to make efforts in this direction, and to try to control anxiety and sleep problems with other effective treatments.
References
[1] Encuesta sobre alcohol y otras drogas en España (EDADES), 1995-2017. SOBRE DROGAS, Observatorio Español. [Survey on alcohol and other drugs in Spain (EDADES), 1995-2017]. Madrid: Ministerio de Sanidad, Servicios Sociales e Igualdad, 2017. [2] Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Geriatr Psychiatry Neurol. 2005;53(4):695–9.
No conflict of interest

https://doi.org/10.1016/j.nsa.2024.105141

P3434
NEUROSCIENCE APPLIED 3 (2024) 105142
ACCELERATING IN TRANSLATION: ENHANCING CLINICAL AND PRECLINICAL RECOVERY FROM TREATMENT-RESISTANT DEPRESSION WITH ACCELERATED NEUROMODULATION PROTOCOLS

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Background: Repetitive transcranial magnetic stimulation (rTMS) is currently recommended for treatment-resistant depression (TRD), though long treatment duration and high costs limit its use. Implementing accelerated protocols (arTMS) could mitigate these limitations [1]. The rationale for arTMS lies in evidence that suggests a dose (number of pulses)-response relationship, where rTMS shows increased cortical excitability when administered within 24 hours [2].
Objective: Using a translational approach, we explored whether arTMS is a more cost-effective intervention in TRD patients and in a validated TRD rat model [3,4].
Methods: In the clinical study, 46 unipolar TRD patients (mean age: 58.26±14.25; male/female: 24/22; previous failed antidepressant trials: 3.47±1.32) received a four-times-daily, five-day arTMS protocol (10Hz, 120% rMT, train=40 pulses, intersession interval=55 min, 3000 pulses/session, totalling 60000 pulses/patient) [5]. We assessed effectiveness by tracking changes in Montgomery-Åsberg Depression Rating Scale (MADRS) scores at baseline (T0), post-treatment (day 6, T1), one-month (T2), and three-month (T3) follow-ups. The response was defined by a ≥50% reduction in MADRS scores, while a score <10 indicated remission. We monitored for significant Treatment-related Side Effects (TrSEs) to assess safety. The TRD rat model consisted of Wistar-Kyoto rats, an endogenous MDD model, to which chronic mild stress were applied. Animals received a four-times-daily, two-day arTMS protocol (10Hz, train=40 pulses, intersession interval=55 min, 1600 pulses/session, total 12800 pulses/rat). A corresponding sham group experienced the same handling/acoustic effects. Behavioural phenotyping assessed both short- and long-term effects. In an independent batch, we analysed short-term arTMS-induced changes in rat brain metabolism through in-vivo quantitative MR spectroscopy in the prefrontal cortex (PFC) and hippocampus (Hip), and structural alterations via 30-gradient directions DTI (Pharmascan 7.0T Bruker). Statistical significance was determined by t-tests or rm-ANOVA, as applicable.
Results: In TRD patients, arTMS significantly reduced depressive symptoms ($F(2,86)=32.908$, $p<0.001$), with fast post-treatment antidepressant effects (T1 vs. T0: $p<0.001$, Cohen's $d=1.120$) and sustained improvements at follow-ups (T2 vs. T0: $p<0.001$, Cohen's $d=1.333$; T3 vs. T0: $p<0.001$, Cohen's $d=1.574$). Response and remission rates increased progressively from T1 (Response: 26%; Remission: 6.82%) to T2 (Response: 36.58%; Remission: 22.73%) and T3 (Response: 50%; Remission: 34.88%). Only 17.39% of patients experienced transient TrSEs. In TRD rats, active (vs. sham) arTMS normalized heightened anxiety in the novelty-suppressed feeding test ($F(1,28)=5.132$, $p=0.031$) and reduced motivational/apathy-like states in the splash test ($F(1,28)=3.844$, $p=0.059$), while diminishing anxiety-related behaviours in the open-field test

(F(1,22)=4.348, p=0.048) and boosting exploratory motivation in the plus-maze test (F(1,20)=3.702, p=0.068). We observed an arTMS-induced increase in creatine, myo-inositol, and branched-chain amino acids (BCAA) in the PFC and BCAA and other macromolecules in the Hip. DTI revealed increased mean diffusivity in the PFC.

Conclusions: arTMS reduces depressive symptoms effectively and rapidly in TRD patients, without notable TrSEs, supporting the notion that increasing daily stimulation frequency to shorten treatment duration does not compromise the safety profile of rTMS. Current preclinical findings suggest that arTMS may alleviate anxiety and motivational deficits. Further preclinical and clinical investigations are necessary to address major gaps in linking diagnostic biotypes with treatment response predictions in TRD, aiming for tailored neuromodulation strategies.

References

[1] Sonmez, A.I., Camsari, D.D., Nandakumar, A.L., Voort, J.L.V., Kung, S., Lewis, C.P., Croarkin, P.E., 2019. Accelerated TMS for Depression: A systematic review and meta-analysis. Psychiatry Res. 273, 770-781. [2] Baeken, C., 2018. Accelerated rTMS: A Potential Treatment to Alleviate Refractory Depression. Front Psychol. 9, 2017. [3] Papp, M., Gruca, P., Lason, M., Niemczyk, M., Willner, P., 2019. The role of prefrontal cortex dopamine D2 and D3 receptors in the mechanism of action of venlafaxine and deep brain stimulation in animal models of treatment-responsive and treatment-resistant depression. J Psychopharmacol. 33(6), 748-756. [4] Willner, P., Gruca, P., Lason, M., Tota-Glowczyk, K., Litwa, E., Niemczyk, M., Papp, M., 2019. Validation of chronic mild stress in the Wistar-Kyoto rat as an animal model of treatment-resistant depression. Behav Pharmacol. 30(2-3), 239-250. [5] Pettorruso, M, d'Andrea, G., Di Carlo, F., De Risio, L., Zoratto, F., Miuli, A., Benatti, B., Vismara, M., Pompili, E., Nicolò, G., Niolu, C., Siracusano, A., Sensi, S.L., Dell'Osso, B., Di Lorenzo, G., Martinotti, G., ReModula Study Group, 2023. Comparing fast-acting interventions for treatment-resistant depression: An explorative study of accelerated HF-rTMS versus intranasal esketamine. Brain Stimul. 16(4), 1041-1043.

Conflict of interest

This abstract is financially supported by a "Ricerca Finalizzata, Young Researchers" grant from the Italian Ministry of Health (to MP, FZ, and LDR grant code GR-2019-12370173).

https://doi.org/10.1016/j.nsa.2024.105142

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NEUROSCIENCE APPLIED 3 (2024) 105143

SAFETY PHARMACOLOGY OF ACUTE MESCALINE ADMINISTRATION IN HEALTHY PARTICIPANTS

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Introduction: Mescaline is a classic psychedelic and naturally found in different cacti, such as Peyote (Lophophora williamsii) and San Pedro (Echinopsis pachanoi). Despite its long history, modern studies focus mainly on lysergic acid diethylamide (LSD) and psilocybin and their potential in psychotherapy [1, 2]. Little is known about the acute effects and safety aspects of mescaline.

Methods: This analysis included two double-blind, randomized, placebo-controlled, cross-over studies involving a total of 48 (24 female and 24 male) participants and 112 mescaline administrations. Seven conditions were pooled and compared: Single oral included mescaline 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 800 mg, and co-administration of mescaline 800 mg with 40 mg ketanserin, a selective 5-HT_{2A} receptor antagonist. Study 1 compared LSD, psilocybin and mescaline. Subjects 1-16 received mescaline 300 mg and subjects 17-32 received mescaline 500 mg. Study 2 compared different doses of mescaline 100 mg, 200 mg, 400 mg, 800 mg, and co-administration of mescaline 800 mg with 40 mg ketanserin. In both studies, each dose was administered to 16 subjects. Subjective effects, vital signs, acute and subacute adverse effects, liver and kidney function before and after the study, blood cell count, and, finally, "flashbacks" were documented.

Results: Duration of acute subjective effects increased from 6.4 to 14 h with doses of mescaline 100-800 mg. No ceiling effects were observed for acute subjective effects. Positive subjective effects increased dose dependently and were higher than negative subjective effects for all doses. "Anxiety" was only significantly different with mescaline 800 mg compared with placebo Autonomic effects increased only moderately. In none of the participants systolic blood pressure was >180 mmHg. Diastolic blood pressure >100 mmHg was measured in 6% of all mescaline administrations. A heart rate >100 beats/min was observed in 3% of all mescaline administrations. Body temperature >38°C was reported in 4% of all mescaline administrations. The total scores of acute adverse effects were 51, 12, 179, 143, 165, 180, and 130 at 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 800 mg, and 800 mg of mescaline co-administered with 40 mg ketanserin, respectively. Kidney and liver function remained unchanged before and after the studies, as did blood cell counts. "Flashbacks" were reported in 4% of all mescaline administrations. These findings suggest that the administration of single-doses up to 800 mg of mescaline is safe in a controlled-clinical setting regarding acute psychological and physical harm in healthy participants.

Conclusion: These findings suggest that single-dose administration of mescaline up to 800 mg were safe regarding psychological and physiological harm in a controlled clinical setting. Acute subjective effects were mainly positive, transient anxiety and "bad drug effects" occurred, but rather with doses higher than mescaline 400 mg. Cardiovascular stimulation induced by mescaline were mild.

References

[1] Glass-Coffin B (2010). Shamanism and San Pedro through Time: Some Notes on the Archaeology, History, and Continued Use of an Entheogen in Northern Peru. Anthropology of Consciousness 21: 58-82. [2] Nayak, S., & Johnson, M. W. (2021). Psychedelics and psychotherapy. Pharmacopsychiatry, 54(04), 167-175.

Conflict of interest

MEL is a consultant for Mind Medicine, Inc. The other authors declare no conflicts of interest.

https://doi.org/10.1016/j.nsa.2024.105143

P3437

NEUROSCIENCE APPLIED 3 (2024) 105144

THE EFFECT OF GABA-A α1-SUBTYPE SELECTIVE POSITIVE ALLOSTERIC MODULATORS IN CATATONIA: PRELIMINARY RESULTS FROM A SYSTEMATIC REVIEW

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Background: Catatonia is a relatively rare condition characterized by psychopathological, behavioral and motor signs and symptoms. It is defined by a lack of movement and/or communication, coupled with restlessness, anguish or confusion[1]. Previously considered as a Schizophrenia subtype[2], it has now been established in the context of a variety of psychiatric (Schizophrenia, Bipolar Disorder, Depressive Disorders, Post-traumatic Stress Disorder), neurodevelopmental (e.g. Autism Spectrum Disorder) or organic (e.g. tumors, autoimmune diseases and cerebrovascular diseases) conditions, and it may also be drug or substance-related (e.g. benzodiazepines [BDZ]/zolpidem/clozapine/alcohol/cannabis withdrawal or intoxications). The severity of this syndrome ranges from mild episodes to life-threatening situations posing the need for a rapid diagnosis and intensive medical care[3]. Although GABA-A α1-subtype Selective Positive Allosteric Modulators (PAMs) such as zolpidem or other so-called Z-drugs have been proposed both as a therapeutic option and as a test to further define the diagnosis, systematic reviews to clarify their role are still lacking.

Methods: The protocol for this systematic review was published in PROSPERO [CRD42024514081][4]. Four widely used databases (PubMed, Web of Science, Embase and Scopus) were searched between inception and March 1st, 2024. Any study reporting on humans of any age diagnosed with catatonia (any etiology) was considered, regardless of the design. A total of 361 abstracts were blindly screened by three reviewers (GB, MM, AM) to assess their eligibility for inclusion in the review, and 115 references were identified. Only 100 full-text articles/abstracts were retrieved for the subsequent screening phase. Rigorous efforts to obtain unfound articles are ongoing, and quality check using standardized appraisal tools will be performed.

Results: A total of 52 studies matching our inclusion and exclusion criteria were identified, the vast majority of which reported on single cases or case series. They comprehensively described 66 patients affected by catatonia that had been treated with zolpidem, 1 with zopiclone without improvement and 1 with zolpidem after an ineffective attempt with zopiclone. Clinical and demographic characteristics of zolpidem responders and non-responders will be reported when available.

Zolpidem, prescribed alone or in combination with other therapeutic options for catatonia, was effective in 33 patients; notably, 5 patients were affected by a disorder of consciousness, while outcome was not clearly stated for 14. Only in