Title.
How Neuromodulation using Zolpidem may Begin to Unravel Mechanisms for Faster Recovery in Comatose, Stroke, Parkinson's, and Traumatic Brain Injury Patients

Abstract:

While Neural Engineering has had breakthrough technologies including cochlear implants for hearing restoration and deep brain stimulation for a range of diseases including Parkinson's, engineering approaches to several neurological disorders following traumatic brain injury (TBI) have been largely unsuccessful [1]. The Brain is extraordinarily complex, and despite decades of research, remains poorly understood [1][3]. The pharmaceutical Zolpidem originally prescribed for sleep disorders, has gained attention due to its ability to paradoxically increase alertness in patients with TBI, temporarily reduce the symptoms of Parkinson's disease, and even transiently induce brief periods of consciousness in comatose patients. Zolpidem has been shown to manifest dramatic differences in mechanistic activity between healthy patients and patients with disorders of consciousness (DOC) or TBI. Only small subsets of patients with TBI's respond to this form of pharmaceutical intervention. It is a lack of understanding of this phenomenon that is causing schisms between researching its causal mechanisms of neural activity and leveraging neural engineering to treat targeted patients [2][3]. Due to EEG, MEG, and MRI comparisons, advances for neuromodulation using Zolpidem have been made to target specific disorders and TBI's. This review hopes to examine how Zolpidem is being investigated using neuromodulation to explain the vast differences in patient recovery following severe brain injuries and diseases.

Introduction:

Zolpidem is a common drug prescribed for sleep that acts within a small drug class of molecules called nonbenzodiazepines that, like benzodiazepines, modulate the activity of Gaba, the bodies' most common neurotransmitter. Zolpidem, originally marketed as Ambien, acts as a positive agonist of Gaba receptors, increasing GABAergic activity throughout the nervous system, with high affinity to receptors found primarily in the brain. It is within a relatively novel class of pharmaceuticals called imidazopyridines and is pharmacologically unique as a sleep medication when compared to other classes of sedatives and hypnotics, such as benzodiazepines, antihistamines, and barbiturates [3].

The first case reports for Zolpidem's paradoxical arousal effects were in 1997 when a patient with a 25-year history of Parkinson's showed reductions in akinesia and rigidity instead of drowsiness, and in 2000 when a 3-year TBI comatose patient was administered Zolpidem and subsequently began speaking and recognized those around them for the duration the drug was in their system [4][5]. Both cases saw patients return to baseline after the drug left their system, however, with repeated doses and similar results, both patients saw improvements in quality of life. Since then, thousands of case studies and dozens of clinical trials have yielded mixed results in treating patients with TBI or DOC. In a systematic review conducted by Bromalaski et al., researchers attempted to classify what disorders Zolpidem seemed effective in treating. In a well cited study, [6] less than 5% of patients responded to Zolpidem, however these researchers were

unable to find any trends or predictors for a pharmacological response. This and other larger clinical trials included patients with a variety of DOC and TBI with reporting respondent patients to be within a range of 5-7% [3]. Bromalaski et al. stated that pinpointing predictors in patient response and activity may be more arduous and less beneficial to patients given the minimal side effects and high efficacy in patients that respond to treatment. This review even went as far as to suggest that all patients with brain disorders, TBI, or DOC, be given a dose of Zolpidem.

After these systematic reviews highlighted the disparity in activity and efficacy, they called for evaluation of DOC and TBI with respect to a categorization and compartmentalization of both of these patient groups. It was posited that this be pursued through high level data collection and imaging of the neuropharmacological response to Zolpidem in these patients' groups. This need for high level data processing has produced more research mapping of the brain and modeling for motor diseases such as Parkinson's and TBI [7][8][9][10]. This is where neural engineering is beginning to change patient outcomes. Typically, data is collected from sensory or motor systems in order to influence these systems using artificial devices or pharmaceutical intervention. The fields of neuromechanics and neuromodulation also look into casual mechanisms within neurophysiology, evaluating regional dose response and mapping regional activity across a variety of TBI and DOC. These fields apply an engineering approach to pharmaceutical intervention creating a closed loop system. Just as the first patients' quality of life improved through repeat dosing of Zolpidem, continued evaluation of the ideal patient and continual dose response could maximize patient recovery. Pharmaceuticals in neural engineering have used this closed loop approach in the past to modulate chronic pain [11].

Methods:

Bromalaski et al. reviewed 2314 articles published before 2015. Of the 67 articles that observed more than one patient, and only 11 that had more than10 participants, only 9 were randomized controlled trials. These trials included patients with the movement disorders of dystonia and Parkinson's, DOC such as comatose patients, with several neurological disorder groups with stroke, TBI, and dementia. Comparing these patient groups, it appeared as though the majority of respondents across all groups randomly responded to Zolpidem at a rate of 5-7%. Movement disorders however had respondent rates up to 24% for some Parkinson's groups, and above 10% for several stroke groups. Parkinson's patients that exhibited transient relief of symptoms of 30-80% of PD symptoms. The data collected lead these authors to suggest that damage to the Basal Ganglia regions of the brain.

Oh et al. tested this basal ganglion hypothesis within an ischemic stroke rat model. Within two weeks all 24 rats that received Zolpidem after the inducement of a stroke showed upregulation in neural plasticity, BDNF, and had significant improvements in behavioral function [12].

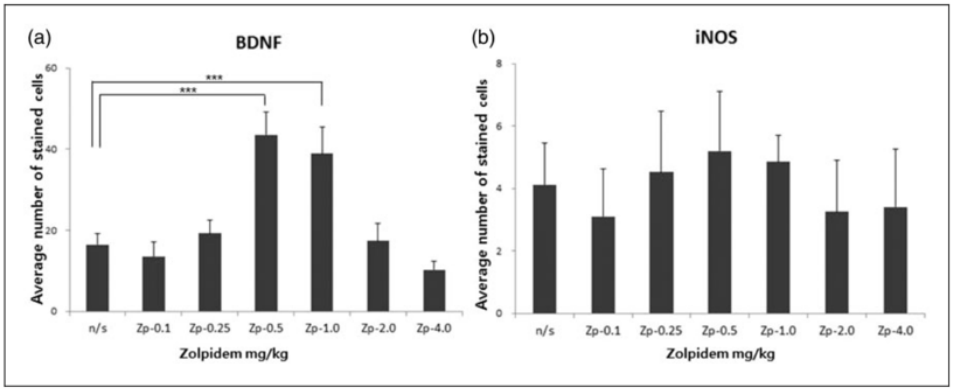

Figure 3. Immunohistochemistry at Day14.
(a) Immunostained sections using brain-derived neurotrophic factor (BDNF) showed that by comparison with the normal saline (n/s) group, the zolpidem 0.5 mg/kg and 1.0 mg/kg groups had statistically significantly (***$P < 0.001$) greater numbers of stained cells
(b) Immunostained sections using inducible nitric oxide synthase (iNOS) showed no difference in the number of stained cells among the groups.

Figure from Oh et al. showing large increases in BDNF for 0.5-1 mg/kg dose. [12]

Oh et al. discusses MRI imaging of the rats but doesn't comment on neurological changes while the drug is in the rodents system. These results contrast with the findings of Bromalaski et al. in that observations for immediate treatment with Zolpidem in stroke patients had less benefit immediately after a stroke, with larger improvements several weeks after onset. This means that the rat model likely is not comparable to the neurological mechanisms relating to stroke and Zolpidem, however, the awakening and alertness effect was clear, and there is now some evidence to suggest upregulating healing within the brain.

Khalili et al. provided a 2020 analysis of neuromodulation of the brain in respondent TBI patients using single photon emission computed tomography (SPECT). This study observed 12 patients with TBI of which 6 were found to be Zolpidem responders [10]. Of these 6 patients, 5 had focal cortical profusion defects suggesting that damage to the cortex may be a predictor of Zolpidem response in TBI and posited that cortical changes in profusion over a long-term period may relate to patients with Parkinson's that responded to Zolpidem. Sripad et al. observed focal cortical changes in MEG data collected from a Parkinson's respondent patient, however this effect and its symptom alleviation was described to vary based on how frequently the drug was administered [7].

Conclusion:

These applied engineering practices may dramatically increase the efficacy rate for responders to Zolpidem following patient classification. The creation of a closed loop medical intervention for sustained awareness, recovery, and symptom management can be used to increase quality of life. Sustained drug intervention in the first historic patients with Zolpidem resulted in long term benefit. Using engineering techniques to parse out predictive characteristics of responder patients across a variety of TBI, DOC, and many other neurological conditions could reveal new mechanisms of healing and recovery in the brain. The use of MRI, SPECT,

MEG and other data collection techniques provide much needed insight into the mechanisms of Zolpidem within the brains of patients with a variety of disorders who demonstrate marked improvements in their conditions with continued administration. Collecting this data to maximize patient recovery based on its effects within the brain could create a closed loop recovery protocol for the administration of Zolpidem.

References

1. Tan HX, Borgo MPD, Aguilar MI, Forsythe JS, Taylor JM, Crack PJ. The use of bioactive matrices in regenerative therapies for traumatic brain injury. *Acta Biomater*. 2020;102:1-12. doi:10.1016/j.actbio.2019.11.032

2. Liepert, J. (2016). *Update on pharmacotherapy for stroke and traumatic brain injury recovery during rehabilitation. Current Opinion in Neurology, 29(6), 700–705.* doi:10.1097/wco.0000000000000381

3. Bomalaski, M. N., Claflin, E. S., Townsend, W., & Peterson, M. D. (2017). *Zolpidem for the Treatment of Neurologic Disorders. JAMA Neurology, 74(9), 1130.*doi:10.1001/jamaneurol.2017.1133

4. A. Daniele, A. Albanese, G. Gainotti, B. Gregori, and P. Bartolomeo, "Zolpidem in Parkinson's disease," *The Lancet*, vol. 349, no. 9060, pp. 1222-1223, 1997

5. R. P. Clauss, W. M. Gu¨ldenpfennig, H. W. Nel, M. M. Sathekge, and R. R. Venkannagari, "Extraordinary arousal from semi-comatose state on zolpidem. A case re- port," *South African Medical Journal*, vol. 90, no. 1, pp. 68–72, 2000.

6. Whyte J, Rajan R, Rosenbaum A, et al. Zolpidem and restoration of consciousness. Am J Phys Med Rehabil 2014; 93:101 – 113.

7. Sripad, P., Rosenberg, J., Boers, F., Filss, C. P., Galldiks, N., Langen, K.-J., … Dammers, J. (2020). *Effect of Zolpidem in the Aftermath of Traumatic Brain Injury: An MEG Study. Case Reports in Neurological Medicine, 2020, 1–8.*doi:10.1155/2020/8597062

8. Arnts H, van Erp WS, Boon LI, et al. Awakening after a sleeping pill: Restoring functional brain networks after severe brain injury. *Cortex*. 2020;132:135-146. doi:10.1016/j.cortex.2020.08.011
9. Delorme C, Adanyeguh I, Bendetowicz D, et al. Multimodal neurometabolic investigation of the effects of zolpidem on leukoencephalopathy-related apathy. *Eur J Neurol*. 2020;27(11):2297-2302. doi:10.1111/ene.14465

10. Khalili H, Rakhsha A, Ghaedian T, Niakan A, Masoudi N. Application of Brain Perfusion SPECT in the Evaluation of Response to Zolpidem Therapy in Consciousness Disorder Due to Traumatic Brain Injury. *Indian J Nucl Med*. 2020;35(4):315-320. doi:10.4103/ijnm.IJNM_97_20

11. Backonja M. Neuromodulating drugs for the symptomatic treatment of neuropathic pain. *Curr Pain Headache Rep*. 2004;8(3):212-216. doi:10.1007/s11916-004-0054-4

12. Oh, M.-K., Yoon, K. J., Lee, Y.-T., Chae, S. W., Choi, H. Y., Shin, H. S., … Park, Y. S. (2017). *Effect of zolpidem on functional recovery in a rat model of ischemic stroke. Journal of International Medical Research, 46(1), 249–257.*doi:10.1177/0300060517723799