pii: jc-00366-16 http://dx.doi.org/10.5664/jcsm.6178

JCSM
Journal of Clinical Sleep Medicine

COMMENTARY

What's Old is New Again: Fresh Hope for Treatment Refractory Hypersomnolence Patients

Commentary on Trotti et al. Flumazenil for the treatment of refractory hypersomnolence: clinical experience with 153 patients. *J Clin Sleep Med* 2016;12(10):1389–1394.

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Plato wrote in his Socratic dialogue *The Republic* in 380 B.C. "…let us begin and create in idea a State; and yet a true creator is necessity, which is the mother of our invention."[1] In the field of sleep medicine, this necessity has never been more urgent to address the challenge of alleviating the symptoms of patients with treatment refractory hypersomnolence. The hopelessness physicians face as we exhaust medication after medication for treating these severely affected and debilitated patients can be demoralizing. In this issue of the *Journal of Clinical Sleep Medicine*, Trotti et al. provide hope by revealing a potential new use for a previously overlooked medication.[2]

Flumazenil, a competitive antagonist of the $GABA_A$ receptor benzodiazepine binding domain, has been used for more than 25 years to reverse benzodiazepine overdoses and treat prolonged anesthesia recovery.[3] Absent any clear indication for use by sleep providers, this medication went largely unnoticed by the sleep medicine community. However, Dr. David Rye and his team at Emory University made a startling scientific breakthrough in 2012 when they demonstrated that CSF from hypersomnolent patients, in the presence of γ-aminobutyric acid (GABA), stimulated $GABA_A$ receptor function. This molecular effect was reversed by flumazenil which subsequently improved the hypersomnolence in some patients.[4] This work introduced the concept of "GABA-related hypersomnolence" to the sleep medicine vernacular[5] and provided both pathophysiological insight into the central disorders of hypersomnolence and a potential novel therapy. The Emory team used this information to begin off-label usage of flumazenil in treatment refractory patients with hypersomnolence.

The majority of patients in this case series had some $GABA_A$ receptor potentiation observed in their CSF, making it difficult to assess whether this factor influenced treatment response. This raises the question whether or not this soporific CSF constituent is commonly present in all sleep disorders patients, only patients with central disorders of hypersomnolence, or only those with treatment refractory hypersomnolence. Recently Trotti et al. assessed the efficacy of clarithromycin, a macrolide antibiotic exhibiting negative allosteric modulation of $GABA_A$ receptors, in GABA-related hypersomnolence to find that subjective—but not objective—sleepiness improved.[5] Future studies assessing flumazenil treatment response in hypersomnolent patients with and without this potentiation could determine whether routine CSF testing for this somnogenic CSF constituent is clinically important to treatment outcomes. Perhaps flumazenil has a meaningful treatment effect even in the absence of $GABA_A$ receptor potentiation?

On January 20, 2015, President Obama announced the creation of the Precision Medicine Initiative, a $215 million dollar National Institutes of Health investment focused on tailoring therapies to patients based on their unique genes, environments, and lifestyles.[6] One of the key goals of this Initiative is focused on pharmacogenomics, which is the ability to identify causes of individual differences in response to commonly used drugs. Trotti et al. reported an initial treatment effect in 62.8% of patients and sustained clinical benefit in 39% of patients—significant results considering the treatment refractory nature of these individuals. However, 37.2% of patients endured the cost, inconvenience, and side effects of flumazenil before discontinuation, mostly due to lack of efficacy. Female sex and sleep inertia were the only factors predicting flumazenil treatment success, leaving clinicians with little to indicate which patients would respond to therapy. This situation is likely due, in part, to the pathophysiological heterogeneity of this case series which included patients with five hypersomnolence-causing disease types ranging from obstructive sleep apnea to Kleine-Levin syndrome—diseases with little in common beyond the hypersomnolence symptom. Although flumazenil response was seen in at least one patient in each disease type, the effect seems to be greatest in patients with idiopathic hypersomnia and Kleine-Levin Syndrome. Severe morning sleep inertia is the calling card of idiopathic hypersomnia, which may explain why the medication seems to work best in these patients. As the sleep community moves forward with further research addressing flumazenil for hypersomnolence, precise disease phenotyping and implementation of pharmacogenomic principles will identify patients more likely to respond to treatment.

Beyond the clear research challenges necessary to establish flumazenil as a safe and effective medication for treatment refractory hypersomnolence, a number of practical considerations exist. Retrospective case series such as this foster

hypothesis development that leads to further advanced studies, but issues such as selection bias and the placebo effect can limit their generalizability.[7] Much like CSF-hypocretin-1 testing for narcolepsy diagnosis, widespread availability of CSF testing for $GABA_A$ receptor potentiation does not exist. In addition, flumazenil lozenges or creams are not widely available to sleep physicians. Indeed, Trotti et al. used a single compounding pharmacy, Pavilion Compounding in Atlanta, GA, to source their medication. Presumably, these challenges will be overcome with demonstration of the clinical importance of GABA-related hypersomnolence and flumazenil, but until then clinicians are limited in their ability to implement flumazenil therapy. The optimal formulation, route of administration and dosing is yet to be determined, but the up to four times a day dosing in this study would be difficult for even the most fastidious patient in typical clinical practice. An analogue or preparation with a longer half-life and reduced dosing regimen is required. Patients who were prescribed cream were more likely to respond, suggesting a topical preparation may have the best utility. Safety is always top of mind whenever experimenting with off-label use of a medication, particularly with a new formulation. Adverse events were common (n = 79, 52% of subjects) but did not typically result in discontinuation, which speaks to the subjective benefits of the therapy and the generally mild and transient nature of the adverse effects.

In conclusion, Trotti et al. use a retrospective chart review case series design to provide tantalizing evidence of a treatment effect of flumazenil for treatment refractory hypersomnolence. The Epworth Sleepiness Scale (ESS) was reduced by an average of 4.7 points in these challenging patients, a remarkable result when compared to the 5.7 point reduction in the ESS in narcolepsy patients treated with modafinil.[8] Consistent with any potential breakthrough in therapy, this work raises more questions than answers. Nevertheless, the emerging story of GABA-related hypersomnolence holds great promise in our understanding and treatment of central disorders of hypersomnolence. Continuation of this line of investigation, hopefully culminating in a randomized, double-blind, placebo-controlled clinical trial, has the potential to alleviate suffering in our challenging treatment refractory hypersomnolence patients.

CITATION

Watson NF. What's old is new again: fresh hope for treatment refractory hypersomnolence patients. *J Clin Sleep Med* 2016;12(10):1321–1322.

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SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication September, 2016
Accepted for publication September, 2016
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DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.