RESEARCH/PROJECT NAME: Characterizing and Predicting Drug Effects on Cognition

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BACKGROUND: Cognitive impairment is a widely reported side effect of many commonly used drugs. Even a mild, untoward effect on an essential function such as linguistic behavior, a directly observable product of complex cognitive processes, is disruptive to daily life. Nevertheless, the mechanisms underlying a drug's impact on cognition are poorly understood, impeding our ability to predict both the effects of drugs in development and the degree to which an individual is vulnerable to the cognitive impact of a particular agent. Topiramate (TPM), a second-generation antiepilepsy drug (AED) is a prime example of a drug that causes speech and language problems severe enough in some patients to result in discontinuation of therapy. However, unlike many newer AEDs, and for reasons not well understood, TPM has a poorer cognitive profile than many of the older AEDs.

OBJECTIVE: Development of a multi-system approach to account for, and eventually predict, how a drug's mechanism(s) of action in the brain and its disposition in the body affect an individual's cognitive functioning.

METHODS: Three parallel groups of 24, native English-speaking, healthy volunteers, ages 18-50, receive one of three single oral doses (100, 150, or 200 mg) of TPM, an inactive placebo (PLA) or 2mg lorazepam (LZP) in three randomized, double-blind, placebo-controlled, three-way crossover studies, each consisting of five (5) sessions. First and last sessions are baseline sessions with no drug administered and no blood sample drawn. A neuropsychological battery consisting of tests of verbal working memory, executive function, discourse-level language and verbal fluency, as well as an assessment of postural sway, are administered 0.5, 2.5, 6 and either 24, 48, 72 or 96 hours after dosing for each of the three treatments, and once during each of the two baseline sessions (sessions 1 & 5). Blood samples for pharmacokinetic-pharmacodynamic analysis are collected immediately prior to drug administration (time 0), five (5) additional times after dose and at one (1) time in the post-absorption phase. High density EEG recording during a verbal working memory paradigm immediately follows the completion of the neuropsychological testing battery in session 1 and approximately 2.5 hours after drug dose in sessions 2, 3, and 4.

RESULTS: This study is currently enrolling subjects. However, previous studies as well as preliminary data from our lab demonstrate that TPM impairs both generative (phonemic) and discourse level fluency, as well as verbal working memory processes, reflecting a widespread disruption of a network that includes regions within the frontal and parietal cortices and cerebellum. Moreover, findings from preliminary analysis of our EEG data suggest that the brain employs a compensation mechanism by recruiting more neural resources to cope with the TPM-induced impairment under increasing cognitive demand.

FUTURE DIRECTIONS: Our next steps will be to extend our studies to patients with epilepsy and/or migraine and to incorporate advanced imaging technologies to further probe the neural underpinnings of TPM-induced cognitive impairment.