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CHARACTERIZING AND PREDICTING DRUG EFFECTS ON COGNITION
A DOUBLE-BLIND, RANDOMIZED, CROSSOVER STUDY OF THE EFFECT OF TOPIRAMATE AND LORAZEPAM ON LANGUAGE AND COGNITION (HEALTHY VOLUNTEERS)

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Study Product: *Topiramate (TOPAMAX)/ Lorazepam (ATIVAN)*

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CONFIDENTIAL

Revision #	Version Date	Summary of Changes	Consent Revision/Date
1	08/07/2012	Original to IRB	n/a
2	06/28/2013	#blood draws;compensation increase; transportation; #EEG sessions	06/28/2013
3	08/07/2013	Genetic testing; compensation	08/07/2013
4	08/23/2013	Add Postural Sway to test battery	n/a
5	10/29/13	Delete “into EDTA tubes”	10/29/13
6	07/15/2015	Addition of RTT to test battery;subject compensation	07/15/2015

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List of Abbreviations

(e.g.)

CFR	Code of Federal Regulations
ICH	International Conference on Harmonisation
CRF	Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IRB	Institutional Review Board

Study Summary

Title	**Characterizing and Predicting Drug Effects on Cognition**
Short Title	*Drug Effects on Cognition*
Protocol Number	
Phase	*R01*
Methodology	*Parallel group, randomized, double-blind, cross-over design with placebo*
Study Duration	*Five (5) years*
Study Center(s)	*Single-center*
Objectives	*Our primary objective is to elucidate the relationship among drug exposure as measured by plasma drug levels, its neurophysiological effects measured by EEG, and consequent effects on the cognitive processes observable in everyday language use. Using topiramate (TPM) as a prototype, we apply the tools of clinical pharmacology, computational linguistics, neuroscience, and engineering to the design and execution of parallel group, randomized, double blind, crossover studies using three (3) single, low doses of TPM and a placebo. In order to isolate the cognitive effects of TPM from those possibly arising from an underlying medical condition, subjects will be healthy adults. We will capitalize on an innovative system for automated language and speech analysis (SALSA) developed in our laboratory, to quantify the effects of TPM administration on effective language use, a crucial component of normal day-to-day functioning.*
Number of Subjects	*Three parallel groups of 24 (12 men; 12 women; total n=72; enrollment target = 84 to account for dropouts),*
Diagnosis and Main Inclusion Criteria	*Healthy volunteers native English-speaking (necessary for language analysis), ages 18-50*
Study Product, Dose, Route, Regimen	*Topiramate (TPM): 100mg, 150mg or 200mg, po, 1x; Lorazepam (LZP): 2mg, po, 1x;*
Duration of administration	*Only one (1) dose of each drug will be administered during the study (3 parallel groups)*
Reference therapy	*Placebo (PLA) (non-active)*

Statistical Methodology	*Neuropsychological and speech data will be analyzed on both the group and individual level. For each individual neuropsychological and speech measure, the two baseline scores will be averaged to correct for any practice effects associated with repeated testing across the entire study. This average is then used in a change score, for each measure for each participant, associated with drug conditions, computed as (drug session score - average baseline score)/average baseline score. Neuropsychological and speech change scores will each be summarized by drug group at each collection time (0.5, 2.5, 6 and either 24, 48, 72 or 96 hours post dose) with means and standard deviations. Change scores at 2.5 hours post dose are our primary outcome; change scores at 0.5 and 6 hours post dose will be used in exploratory analyses. Change scores will each be independently taken as the outcome in a repeated measures ANOVA with drug group (TPM, LZP, PLA) as the primary factor of interest. The Tukey-Kramer procedure will be used to adjust type I error rates for the multiple comparisons among the three drug groups. All ANOVAs will be adjusted for treatment order and session number, and include a random effect for participant to control for within-person correlation across the three sessions. Separate ANOVAs will examine the three TPM dose groups compared to each other. As exploratory work, we will also examine whether age or gender modify any of the drug effects.* *Each TPM dose will be used in a three-way crossover study with 24 participants. Detectable differences are based on pilot data estimates of within-person and between-person variability in each of the outcomes shown; in general, within-person correlation was weak, well below 0.5. Our budget allows for recruiting 4 extra participants per dose study in case of dropout.* *<u>Pharmacokinetic/Pharmacodynamic analyses</u>: Separately for the three TPM doses and for LZP, neuropsychological and speech data change scores will each be used as the outcome in a linear regression with the three pharmacokinetic parameters (AUC, trough, maximum) as the primary predictors of interest. If AUC, trough, and maximum are highly collinear, we will consider them one at a time. With 24 participants per drug/dose combination, and two-sided p=0.05, we will have power 75% to detect a correlation of size ≥0.5, 90% power to detect a correlation of size ≥0.6, and 98% to detect a correlation of size ≥0.7. All regressions will be adjusted for session number, age, and gender. We will also compare the R-square from the model with AUC as predictor to the R-square from the model with dose as predictor. Population pharmacokinetic modeling will be used to calculate individual measures of exposures.*

1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 or 812 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 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. This lack of understanding impedes 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, with increasing frequency, being prescribed for a range of conditions including migraine prophylaxis, obesity, and pain. Moreover, it 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. While the number and magnitude of adverse cognitive side effects have been attributed, in part, to the effects of titration rate and maintenance dose in both patients and healthy adults, these factors do not capture all inter-individual variability in the cognitive response to TPM. Our rationale for this project is that our investigations will offer insight into the mechanisms underlying drug-induced cognitive deficits. It will also lay the foundation for a new line of research that will further delineate these mechanisms and provide methods to predict individual patient response. In this study we compare the cognitive effects of TPM to that of the benzodiazepine, lorazepam, as well as to a non-active placebo. A majority of the preliminary data for this study were collected under UMN IRB Study # 0805M33321 and published in a peer reviewed journal (Marino et al, 2012).

1.2 Investigational Agent

Please refer to the attached "prescribing information" brochures for both topiramate (Topamax) and lorazepam (Ativan)

1.3 Preclinical Data

NA: both TPM and LZP are marketed drugs.

Clinical Data to Date

NA. *both TPM and LZP are marketed drugs.*

1.4 Dose Rationale and Risk/Benefits

A 2mg dose of lorazepam was chosen since that is the most common dose that has been used in studies of the cognitive/memory effects of this drug in healthy volunteers [9, 10]. The doses of 100mg, 150mg and 200 mg of topiramate chosen for this study are much lower than those used in the classical studies of the cognitive effects of this agent on cognition and language. In their EEG study, Salinsky et al (2007*) titrated healthy volunteers to a maximum dose of 400mg/day whereas Werz et al (2006) used a dose of 300 mg/day of topiramate in their study comparing the cognitive effects of TPM to lamotrigine in healthy volunteers. Since there is evidence that the titration rate of TPM is proportional to the cognitive complaints attributable to TPM use (Meador et al, 2001), we expect that even the relatively low doses used here will produce an effect since the subjects are receiving the entire dose all at once.*

2 Study Objectives

Primary Objective: *Our primary objective is to elucidate the relationship among drug exposure as measured by plasma drug levels, its neurophysiological effects measured by EEG, and consequent effects on the cognitive processes observable in everyday language use. We have three (3) Specific Aims:*

Specific Aim #1: Characterize TPM-induced effects on linguistic behavior. *Our working hypothesis is that TPM has distinct, measureable effects on the fluency and content of spontaneous speech. We will test this hypothesis by measuring speech and language characteristics with SALSA from speech audio-recorded during a neuropsychological assessment that includes tests of verbal, memory and executive functions.*

Specific Aim # 2: Determine the neurophysiological mechanisms of TPM's action on executive function. *Our working hypothesis is that TPM-induced effects on language use are partly attributable to disrupted frontal executive function. We will test this hypothesis by recording EEG during a verbal working memory task. We predict altered frontal lobe activity and frontotemporal interactions, manifesting as changes in event-related potentials (ERP) and EEG coherence.*

Specific Aim #3: Predict individual vulnerability to TPM-induced impairments in linguistic, memory, and executive functions. *Our working hypotheses are 1. The extent of drug-induced impairments in these functions is proportional to systemic drug exposure, as measured by plasma drug levels. The area under the time-concentration curve (AUC), trough, and maximum drug concentration will be explored. 2. Drug exposure is a better predictor than dose of the degree of individual impairment.*

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3 Study Design

3.1 General Design

This study uses a parallel group, double-blind, randomized, crossover design to test neurocognitive functioning including natural language comprehension and production in people exposed to TPM and LZP. Healthy volunteers will be exposed to one of three (100mg, 150mg or 200mg) single low doses of TPM. Healthy volunteers rather than

patients are used as subjects in order to isolate the effects of the medication from the effects of the underlying disorder. In order to explore the differentially sensitivity to the cognitive effects of drugs from different classes, we chose LZP as an active comparator since unlike TPM, it is a benzodiazepine and produces its cognitive effects via a mild generalized sedation versus the more focal frontal lobe dysfunction of TPM. Moreover, LZP is not associated word-finding or fluency difficulties.

Each crossover study (using one dose of TPM) will consist of five (5) sessions with at least a two-week washout period in between sessions. Sessions 2, 3, and 4 will each be followed up by a visit at approximately 24, 48, 72 or 96 hours post drug administration. First and last sessions are baseline sessions with no drug administered and no blood sample drawn during session 1. During both sessions 1 & 5, subjects will be administered a single brief neuropsychological assessment (see details below) (approximately 1 hour). However, during session 1, subjects will also be required to perform a verbal memory task while having their EEG recorded (approximately 2 hours).

For the treatment sessions (sessions 2, 3, and 4), the sequence in which TPM, LZP, and PLA will be assigned to the three middle sessions will be determined according to a Latin square design balanced for first-order carry-over effects (6 possible sequences). A neuropsychological battery consisting of tests of verbal working memory capacity including the reading span test (Session 1 only) (Daneman & Carpenter, 1980; sentence comprehension), tests of executive behaviors drawn from the NIH Common Data Elements for Epilepsy (www.commondataelements.ninds.nih.gov/Epilepsy.aspx), two discourse-level language/verbal tests and one discourse-level memory test (described in the next section), as well as an assessment of postural sway (AgiliSway System, Agile Medicine, Minneapolis MN: www.agilemedicine/agilisway.com) will be administered 0.5, 2.5, 6 and either 24, 48, 72 or 96 hours after dosing for each of the three treatments, as well as once during each of the two baseline sessions (sessions 1 & 5). Alternate versions of each test will used during each session to reduce practice effects. Each testing battery is expected to take approximately 45-60 minutes to complete. A portion of the test battery will be audio-recorded for speech analysis using SALSA. A single, trained examiner will administer all tests for one subject. Blood samples will be collected for pharmacokinetic-pharmacodynamics analysis.

Pharmacokinetic (PK)-pharmacodynamics(PD) analysis: Blood samples will be collected from all participants at all 3 treatment sessions in the three parallel three-way crossover studies (one for each TPM dose: 100, 150, and 200 mg). Blood samples will be collected immediately prior to drug administration (time 0), 5 additional times after dose and at 1 time in the post-absorption phase (at either approximately 24, 48, 72, or 96 hours - randomly assigned). Preliminary results that include intensive PK sampling in healthy volunteers during the whole dosing interval enables the use of sparse sampling in order to limit the burden of additional sampling on subjects. The time of drug administration and the time of each blood draw will be recorded. Samples will be immediately centrifuged and the plasma frozen until analysis. TPM plasma levels will be measured by a simultaneous LCMS assay, developed by Subramanian, Birnbaum

and Remmel (2008). LZP plasma levels will be measured by an assay validated in our laboratory.

In one session only, and with separate subject consent, a sample will be drawn from part of the collected blood samples for subsequent genetic testing with the primary hypothesis, related to Specific Aim 3, that inter-individual differences in plasma drug concentrations may be due to polymorphisms in metabolic genes.

EEG: EEG recording will immediately follow the completion of the neuropsychological testing battery in session 1 and after the battery administered approximately 2.5 hours after drug dose in sessions 2, 3, and 4. EEG recording will be conducted in an acoustically and electrically shielded chamber in the UMN Center for Neurobehavioral Development. Subjects will be seated in a comfortable non-metal chair in the chamber and instructed to attend to a CRT monitor during recording. EEG will be recorded using a 128-channel Sensor Net System. EEG will be recorded during the presentation of the working memory paradigm.

3.2 Primary Study Endpoints

Our **primary end point** is a composite measure of disfluency comprised of the following measurements:

a. spoken discourse fluency
    i. speaker normalized duration and frequency of silent and filled pauses
    ii. speaker normalized frequency of repetitions
    iii. speaker normalized frequency of false starts
    iv. speaker normalized speaking rate (syllables per second)

Our **secondary end points** will consist of the following characteristics:

For <u>spoken samples</u>, we will examine the following measures of linguistic fluency:

- Average fundamental frequency fluctuations/variability
- Average length of hesitations before noun phrases
- Total speech duration
- The ratio of speech to silence
- The ratio of hesitant to fluent speech
- Average speaker normalized length of rhythmic phrases
- Any other promising prosodic variables identified in Aim 1.

We will examine the following linguistic measures computed based on the transcripts of the spoken and written samples:

- Language model entropy/perplexity computed from the discrepancies between the distribution of three-word sequences in the transcripts to the general English patterns as well as patterns obtained from baseline assessments.

- Number of verbs, nouns, adjectives and adverbs (separate counts for each part-of-speech)
- Ratio of content words (verbs, nouns, adjectives and adverbs) to function words (prepositions, pronouns, auxiliaries)
- Syntactic complexity scores
- Any other promising linguistic complexity variables identified in Aim 1

3.2 Primary Safety Endpoints

N/A

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

1. *Healthy men and women are ≥18 and ≤50 (post menopausal or using approved birth control methods)*
2. *Capable of giving informed consent obtained*
3. *Native English speakers (due to speech and language analysis)*

4.2 Exclusion Criteria

1. Presence of clinically significant cardiovascular, endocrine, hematopoietic, hepatic, renal, neurologic, psychiatric disease including suicidality
2. Presence or history of drug or alcohol abuse
3. Vision or hearing impairments
3. The use of concomitant medications which are known to affect topiramate, lorazepam, or the use of any concomitant medications that may alter cognitive function, including antidepressants, anxiolytics, psychostimulants such as Ritalin, prescribed analgesics, and antipsychotics.
4. Prior adverse reaction to or prior hypersensitivity to topiramate, lorazepam or to related compounds
5. A positive pregnancy test (administered to all women before enrollment, and prior to each study session).
5. Subjects who have received any investigational drug within the previous thirty days
6. Dominant left hand (Note: to control for brain lateralization of language functions, subjects need to have a dominant right hand.

Subject Recruitment and Screening

Subjects will be recruited from the general population using an IRB-approved advertisement. After responding to the ad, one of the researchers or study coordinator will screen each applicant for inclusion/exclusion criteria. If the applicant is suited for participation in the study, the researcher/coordinator will send a copy of the consent form to the potential subject in order to provide him or her with sufficient time to carefully

read the forms, to call the researcher if there are any questions, and make an informed decision as to whether or not to proceed with enrolling in the study. If the applicant chooses to enroll, a study date will be scheduled and on the morning of the first session, a researcher/study coordinator will consent the subject and procure the required signatures.

4.3 Early Withdrawal of Subjects

4.3.1 When and How to Withdraw Subjects

Subjects will be asked to withdraw from the study if they show any adverse reactions to the study drugs, including allergic reactions or greater than expected cognitive effects. Subjects who are noncompliant with study visits may be asked to withdraw from the study.

4.3.2 Data Collection and Follow-up for Withdrawn Subjects

Data collected from subjects who either withdraw from the study voluntarily or who are dismissed because of safety concerns will be analyzed and retained in the database. Subjects who had any serious adverse event will be followed up by the researcher(s).

5 Study Drug

5.1 Description

Both TPM and LZP are marketed agents and will be given orally in tablet form. See section 1.4 for dosage information and justification.

5.2 Treatment Regimen

Subjects will be given either a single 100 mg, 150mg OR 200 mg oral dose of topiramate (3 parallel groups – one for each dose of TPM). Each subject will also receive a single 2mg oral dose of lorazepam during a separate experimental session.

5.3 Method for Assigning Subjects to Treatment Groups

A randomization number and associated treatment assignment will be made by the University of Minnesota Investigational Pharmacy. The number will be associated with a treatment kit prepared for each subject.

5.4 Preparation and Administration of Study Drug

We have contracted with the University of Minnesota Investigational Pharmacy to overencapsulate the study drugs as well as prepare a matching, inactive placebo. All drug will be stored and dispensed to study staff by the pharmacy.

5.5 Subject Compliance Monitoring

NA

5.6 Prior and Concomitant Therapy

Subjects will be asked for a list of their current medications when they inquire about participating. We will inform them at that time if they are on any drugs that interact with either TPM or LZP.

5.7 Packaging

There is no packaging necessary since the pharmacy will deliver the appropriate study drug according to their randomization scheme on the morning of the test session.

5.8 Blinding of Study Drug

Tablets will be overencapsulated using a gel capsule

Receiving, Storage, Dispensing and Return

5.8.1 Receipt of Drug Supplies

The study drugs will be purchased by the principal investigator and delivered to the pharmacy. Upon receipt of the of the study treatment supplies, an inventory will be performed and a drug receipt log filled out and signed by the person accepting the shipment. The designated study staff will count and verify that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files.

5.8.2 Storage

Both TPM and LZP will be stored in the University of Minnesota Investigational Pharmacy according to the stated FDA requirements.

5.8.3 Dispensing of Study Drug

Only one dose per subject per test session will be dispensed.

5.8.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

6 Study Procedures

6.1 Session 1 (Baseline)

After being consented for the study, a brief demographic, medical and medication history will be taken during the first session to assure that subjects are not currently on any drugs that can interact with either TPM or LZP or potentially interfere with cognitive

functioning. Each participant will be administered the entire test battery once only (see below) (Week 1-baseline) after which they will perform a working memory task while having their EEG recorded, and be randomly assigned to a study treatment sequence (TPM or LZP).

6.2 Session 2

The first drug testing session will be conducted approximately 14 days after the baseline testing. At that time, an intravenous catheter will be inserted (left arm) after which he or she will be given either one of three doses of TPM (depending on whether they have been assigned to thee 100mg, 150mg or 200mg group),OR 2mg LZP OR placebo. Six blood samples will be drawn between 0 – 6 hours after dose. Vitals signs will also be recorded. One (1) additional sample (using a single needle stick) will be drawn either at (approximately) 24, 48, 72, or 96 hours postdose(randomly assigned) to capture a sampling in the post-absorption phase as well as limiting the burden of additional sampling on subjects. Neurocognitive and postural sway assessments will be collected at times approximately 0.5, 2.5, 6 and either 24, 48, 72 or 96 hours after treatment administration. Alternate test forms will be used for each time point. After the 2.5 hr blood draw and assessment are complete, the subject will be fitted with electrodes for the EEG portion of the study, after which he or she will return to the CTSI for the remaining blood samples and another neuropsychological test administration. A separate visit is required for collection of the post-absorption blood sample and testing.

6.3 Session 3

Participants will return approximately two (2) weeks later in order to repeat the testing protocol after switching drugs.

6.4 Session 4

The fourth session will occur approximately two (2) weeks after the second drug administration for the third drug (or placebo) treatment.

6.5 Session 5 (Post baseline)

The last session will occur approximately two (2) weeks after the third drug or placebo administration. Participants will not be given any drug at this session. One blood sample will be drawn to determine if any drug from the previous session is still present. The entire test battery will be administered. The baseline and postbaseline scores will be averaged in order to correct for any practice effects that might have occurred across the four testing sessions. This average will be used to compute the change score of each test administered under drug conditions. Oral samples in all tests will be audiotaped.

Neuropsychological Battery

We will employ a battery of neuropsychological tests that includes measures from our cognitive Anti-Epileptic Drug (AED) protocol as well as additional language-specific measures:
<u>Verbal Working Memory</u>:

1. Reading Span: Subjects read aloud a set of unrelated sentences, and then at the end of the set they recall the last word of each sentence in the set (see Daneman & Carpenter, 1980, 1983). As in the speaking span test, subjects are presented with increasingly longer sets until all sentences have been presented. Reading span is the total number of correct sentence-final words recalled. This test will only be administered during the first baseline session (session 1).

Executive function, processing speed, and word-level language/verbal tests:
1. Phonemic generative verbal fluency will be evaluated using the COWA test. COWA requires the subject to generate words other than proper names or numbers beginning with a specific letter of the alphabet; three 60-second trials are obtained, using three different letters, usually F-A-S or B-H-R.
2. Semantic generative verbal fluency will be evaluated using the Animal Fluency test. Subjects are asked to generate as many different animal exemplars as they can within 60 seconds. The primary dependent measure for both phonemic and semantic generative fluency is the number of correct words meeting scoring criteria normalized to individual (averaged) baseline.
3. Trails A and B will be used to assess visual search, mental flexibility, and task alternation. The subject is required to draw lines between circles in ascending order ("connect the dots"). Trail Making Part A requires the patient to connect the numbers from 1-25. Trail Making B requires subjects to alternate between numbered and lettered circles in ascending numerical/alphabetical order (e.g., 1-A-2-B, etc.) The primary dependent measure is time of completion.
4. Digit span subtest from the WAIS-IV will be used to assess immediate attention. It tests forward and backward digit span, includes a sequencing trial in which the subject is the repeat back the digits in ascending order.
5. Symbol Digit Modalities Test will be used to generate the Processing Speed Index (primary dependent measure). These are timed tasks that measure the ability to rapidly transcribe symbols that are paired with numbers (Coding).

Computerized psycholinguistic assessment. Spontaneous speech will be elicited using two discourse level verbal tasks:

1. *In the picture description task, the subjects will be asked to describe a simple picture (e.g., The "Cookie Theft" stimulus from the Boston Diagnostic Aphasia Examination (Goodglass & Kaplan 1983).*
2. *Memory will be tested using a third discourse level task, the MCG Story Recall task, where subjects will recall a short but detailed description of a situation verbally presented to them (Meador et al 1993; Meador et al 1995).*
3. *Spontaneous narrative. Subject will be asked to speak on one of four (4) themes (adapted from the Trier Test) for two minutes.*

Working Memory Paradigm: A modified Sternberg working memory task (Sternberg, 1969) will be presented to each subject during EEG recording to test the effect of TPM on verbal and executive brain functions. A set of English (nonsense) syllables of comparable length will be presented on a CRT monitor for 1.5 seconds, followed by a 5s retention period, followed by the probe syllable. Subjects will be instructed to press a "Yes" or "No" button to indicate whether or not the probe stimulus belonged to the

previously viewed set. Memory-load is a function of the size of the syllable set. The paradigm consists of six blocks of 60 trials/block (360 trials in total). Presentation of the syllables and the memory loads will be randomized (120 trials/memory load). A practice block of 60 trials will be presented prior to testing and a one-minute break will be provided between each block to reduce fatigue effects. The main advantage of this paradigm over the classical Sternberg task, where the items are presented sequentially rather than all at once, as was done in our preliminary studies, is that the periods of encoding, retention, and recall are all well separated in time to permit the study of both the temporal and spatial development of neural activity during the different stages of the working memory process.

Postural Sway Assessment: Postural sway: Sway will be measured by the AgiliSway System (Agile Medicine, Minneapolis MN: www.agilemedicine/agilisway.com)
The dependent measures are total distance, medial/lateral distance, and anterior/posterior distance swayed.

A patient's center of pressure is measured using a force platform, in this case a modified Wii balance board, that records the pressure on each of four sensors once every 100 milliseconds. Prior to recording the patient data, 10 seconds of calibration data are recorded. After obtaining these readings, subjects are asked to stand on the board for 10 sec in each of three positions: with 1. feet together, 2. one foot raised and 3. in a tandem position, while several different measures of sway are calculated, including total distance, medial/lateral distance, and anterior/posterior distance swayed (all in centimeters). With additional computation, other measures such as average/maximum velocity of sway can also be calculated.
The calculations for measuring distance swayed are:

P(tl) = Pressure top left (TopLeft - CalAvgTopLeft)
P(tr) = Pressure top right (TopRight - CalAvgTopRight)
P(bl) = Pressure bottom left (BottomLeft - CalAvgBottomLeft)
P(br) = Pressure bottom right (BottomRight - CalAvgBottomRight)

Total (T) = P(tl) + P(tr) + P(bl) + P(br)

7 Statistical Plan

7.1 Sample Size Determination

Each TPM dose will be used in a three-way crossover study with 24 participants. Table 1 below shows the magnitude of group differences that will be detectable for 24 participants with 90% power, two-sided alpha =0.05, using Tukey-Kramer adjustment for multiple comparisons among the three drug groups. Detectable differences are based on pilot data (collected as part of IRB study # 0805M33321) estimates of within-person and between-person variability in each of the outcomes shown; in general, within-person correlation was weak, well below 0.5. Our budget allows for recruiting 4 extra participants per dose study in case of dropout.

MCG outcomes	Smallest detectable group difference	Pilot observed smallest / biggest group difference		Picture Description outcomes	Smallest detectable group difference	Pilot observed smallest / biggest group difference
Disfluency rate	0.31	0.20 / 0.43		Disfluency rate	0.18	0.02 / 0.50
Words correctly recalled	0.22	0.10 / 0.45		Mean pause duration	0.02	0.01 / 0.14
Mean pause duration	0.24	0.03/0.28		Correct units of information	0.09	0.02 / 0.13
Speaking rate	0.04	0.01/0.08		Speaking rate	0.03	0.06 / 0.12
				Word count	0.15	0.001 / 0.02

7.2 Statistical Methods

Statistical Analysis

Aim 1 Statistical considerations: *Neuropsychological and speech data will be analyzed on both the group and individual level. For each individual neuropsychological and speech measure, the two baseline scores will be averaged to correct for any practice effects associated with repeated testing across the entire study. This average is then used in a change score, for each measure for each participant, associated with drug conditions, computed as (drug session score - average baseline score)/average baseline score. Neuropsychological and speech change scores will each be summarized by drug group at each collection time (0.5, 2.5, and 6 hours post dose) with means and standard deviations. Change scores at 2.5 hours post dose are our primary outcome; change scores at 0.5 and 6 hours post dose will be used in exploratory analyses. Change scores will each be independently taken as the outcome in a repeated measures ANOVA with drug group (TPM, LZP, PLA) as the primary factor of interest. The Tukey-Kramer procedure will be used to adjust type I error rates for the multiple comparisons among the three drug groups. All ANOVAs will be adjusted for treatment order and session number, and include a random effect for participant to control for within-person correlation across the three sessions. Separate ANOVAs will examine the three TPM dose groups compared to each other. As exploratory work, we will also examine whether age or gender modify any of the drug effects.*

Aim 2 (EEG) Statistical considerations: *Behavioral data (error rate) and electrophysiological summary data will be analyzed in a repeated measures ANOVA with a 3x5 factorial for memory load (1, 3, 5 syllables) by drug (TPM, LZP, PLA, two baselines). The Tukey-Kramer procedure will be used to adjust type I error rates for the multiple comparisons among the drug groups at specific memory loads, and across memory loads. ANOVAs will adjust for treatment order and session number, and include a random effect for participant to control for within-person correlation across the three sessions. Electrophysiological measures (amplitudes, peak latency, will be analyzed separately with repeated measures multivariate analyses of variance (RM-MANOVA;*

maximum-likelihood analogs may be used if missing data are non-trivial) with factors and adjusting variables as above. Correlations between ERP difference (e.g., TPM vs PLA) and drug concentration (collected as part of Aim 3, below) will be computed. With 24 participants per drug/dose combination, and two-sided α=0.05, we will have power 75% to detect a correlation of size ≥0.5, 90% power to detect a correlation of size ≥0.6, and 98% to detect a correlation of size ≥0.7.

***Aim 3 (Pk/PD) Statistical considerations**: For PK analyses, variables are added and a model chosen using a forward selection process (cutoff of p<.005), followed by a backward elimination process (cutoff of p<.001) to avoid type I errors due to multiple statistical tests. The estimation step of a Nonlinear Mixed Effects Model (NONMEM) will be implemented using first order conditional estimation with an interaction term. Maximum a posteriori (MAP) Bayesian post-hoc estimates of each individual's PK parameter will be used to derive measures of drug exposure (e.g., AUC, steady-state concentrations) using standard PK equations. PD modeling will investigate if a relationship exists between outcomes of interest contained in the neuropsychological battery.*

Separately for the three TPM doses and for LZP, neuropsychological and speech data change scores will each be used as the outcome in a linear regression with the three pharmacokinetic parameters (AUC, trough, maximum) as the primary predictors of interest. If AUC, trough, and maximum are highly collinear, we will consider them one at a time. With 24 participants per drug/dose combination, and two-sided p=0.05, we will have power 75% to detect a correlation of size ≥0.5, 90% power to detect a correlation of size ≥0.6, and 98% to detect a correlation of size ≥0.7. All regressions will be adjusted for session number, age, and gender. We will also compare the R-square from the model with AUC as predictor to the R-square from the model with dose as predictor. Population pharmacokinetic modeling will be used to calculate individual measures of exposures (i.e., AUC, trough, and maximum drug concentration) to be used in the analyses above.

7.3 Subject Population(s) for Analysis

- *We will be using a protocol-compliant population consisting of healthy volunteers, 18-50 years of age.*

Safety and Adverse Events

7.4 Definitions

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or

injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct

each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

7.5 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has

been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

7.6 Reporting of Serious Adverse Events

7.6.1 Study Sponsor Notification by Investigator

A serious adverse event must be reported to the study sponsor by telephone within 24 hours of the event. A Serious Adverse Event (SAE) form must be completed by the investigator and faxed to the study sponsor within 24 hours. The investigator will keep a copy of this SAE form on file at the study site. Report serious adverse events by phone and facsimile to:

Susan E Marino PhD *612-501-8626 (cell)* *612-626-0148 (fax)*
John Rarick *612-626-2170 (phone)*
Ilo Leppik MD *612-625-7139 (phone)*

At the time of the initial report, the following information should be provided:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

Within the following 48 hours, the investigator must provide further information on the serious adverse event in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to the study sponsor

7.6.2 IRB Notification by Investigator

Reports of all serious adverse events (including follow-up information) must be submitted to the IRB within 10 working days if it falls under the UPIRTSO guidelines. Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's binder.

7.6.3 FDA Notification by Sponsor

The study sponsor shall notify the FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of

the drug as soon as possible but no later than 7 calendar days from the sponsor's original receipt of the information.

If a previous adverse event that was not initially deemed reportable is later found to fit the criteria for reporting, the study sponsor will submit the adverse event in a written report to the FDA as soon as possible, but no later than 15 calendar days from the time the determination is made.

7.7 Unblinding Procedures

Subjects who experience any serious adverse event, including what appears to be an allergic reaction or an expected, negative cognitive effect will be unblinded by the researcher who will call the Investigational Pharmacy for the necessary information. This information will be noted in the documents and the subject will be withdrawn from the study. Any necessary medical treatment will be delivered and subject will be followed up for at least 24 hours to make sure there are no continuing medical problems.

7.8 Stopping Rules

If there are any adverse effects reported by the subject or detected by the nurse or study coordinator, subjects will be asked to supply details regarding the nature of the adverse effect and its severity. Dr. Leppik (see 7.9) will determine the course of follow-up and whether or not the subject requires further medical care or should be discontinued from further participation in the study. Participation in the study would also be discontinued if, during the course of the study, the subject develops a significant medical condition or is initiated on medication that can be expected to interact with any of the study drugs. The subject has the option of discontinuing their participation at any time for any reason. Any adverse effects not commonly associated with the drugs under study or any serious adverse events will be reported to the IRB.

7.9 Medical Monitoring

Dr. Leppik, who is a co-investigator and Medical Director of this project, will be responsible or monitoring adverse events. At each visit subjects will be asked whether they are experiencing any side effects. Vital signs are also monitored before and after drug administration. Dr. Leppik is an epileptologist with first hand knowledge of TPM in epilepsy patients. He is also the study physician on the preliminary TPM/LZP/PLA studies performed by this research group. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 9 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

8 Data Handling and Record Keeping

8.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

8.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

Data generated by the methods described in the protocol will be recorded in the subjects' medical records and/or study progress notes. Data may be transcribed legibly on CRFs supplied for each subject or directly inputted into an electronic system or any combination thereof.

8.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO

NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

8.4 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

9 Study Monitoring, Auditing, and Inspecting

9.1 Study Monitoring Plan

This study will be monitored according to FDA/GCP guidelines. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

9.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

10 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB

concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

11 Study Finances

11.1 Funding Source

This study is funded from an R01 grant from the NIH/NINDS 1 R01NS076665-01A1.

11.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must refer to the Regents Policies on Individual Conflict of Interest Policy or Institutional Conflict of Interest Policy. These policies require University Faculty and staff to report external professional activities and business and significant financial interests related to his or her University activities by submitting a REPA (Report of External Professional Activities) at least once per year. Faculty and staff should also file a REPA when substantial changes in business or financial interests occur, when an activity that presents a potential conflict of interest is anticipated, or when submitting an application for research support or technology transfer, submitting research protocols to the IRB, or receiving financial contributions. All University of Minnesota investigators will follow the University conflict of interest policy.

None of the investigators have a conflict of interest with this study.

11.3 Subject Stipends or Payments

Subjects will not incur any costs as a result of participation in the study. Compensation will be $75.00 for each of the two baseline sessions and $150.00 for each of the three drug (2 study drugs and 1 placebo) test sessions, and $50.00 for each of three visits at either 24, 48, 72 or 96 hours following sessions 2, 3, and 4, for a total of $750.00 for completing all 5 sessions to compensate them for their time and inconvenience. If a

subject cannot continue or chooses to drop out of the study, their payment will be prorated for the sessions completed. Compensation will be paid by check issued from the University of Minnesota.

Lunch will be provided at sessions 2, 3, and 4 and snacks will be available at all visits. Transportation by taxi will be provided for free at all visits.

12 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the co-principal investigators. Any investigator involved with this study is obligated to provide the co-principal investigators with complete test results and all data derived from the study.

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