Gabapentin for Alcohol Withdrawal Syndrome

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IRB Minimal Risk Protocol Template

General Study Information

Principal Investigator: Simon Kung, MD and Ruth Bates, MD

Study Title: A Prospective Randomized Controlled Open Label Trial of Symptom-triggered Benzodiazepine versus Fixed-dose Gabapentin for Alcohol Withdrawal Syndrome

Protocol version number and date: Version 5, 11/14/2018

Research Question and Aims

Hypothesis: A fixed-dose proactive gabapentin schedule for alcohol withdrawal syndrome will be superior or similar, and as safe, compared with a symptom-triggered benzodiazepine approach.

Aims

1. To demonstrate that fixed dose gabapentin will result in shorter duration of alcohol withdrawal compared to symptom-triggered benzodiazepines. (Primary outcome)
2. To demonstrate that fixed dose gabapentin is comparable to symptom-triggered benzodiazepines for secondary outcomes related to patient safety, including adverse outcomes such as seizure and delirium tremens.
3. To demonstrate that fixed dose gabapentin is comparable to symptom-triggered benzodiazepines for further secondary outcomes such as severity of withdrawal assessed by CIWA scores, alcohol cravings assessed by Penn alcohol craving score (PACS), sleepiness assessed by Epworth Sleepiness Scale (EPS), anxiety assessed by Generalized anxiety disorder score (GAD7) and total benzodiazepine use.

Background

Alcohol dependency affects up to 20% of men and 10% of women in their lifetime.(Schuckit MA 2014) Alcohol withdrawal syndrome (AWS) can be experienced by approximately 50% of patients with alcohol use disorder. These symptoms such as nausea, sweating, tremor, headache, and anxiety, can start about 8 hours after the last alcohol use, and can peak at 72 hours. About 5% of patients may experience severe withdrawal symptoms such as delirium tremens (DTs) or seizures.

The current standard at Mayo for alcohol withdrawal is the use of the CIWA-Ar (Clinical Institute Withdrawal Assessment for Alcohol – Revised, henceforth referred to as "CIWA") instrument to guide initiation and subsequent administration of a benzodiazepine, typically oral lorazepam. (Appendix) This symptom-triggered protocol requires repeated assessments of the patient's subjective signs and symptoms based on a 10 question

rating scale. If the score is 10 or greater, a benzodiazepine is given with subsequent dosing dependent upon sequential CIWA scores.

There are several deficiencies with the symptom-triggered benzodiazepine protocol. First, the majority of the items are subjective, based on patient report of symptoms such as anxiety, tremulousness, and headaches, such that patient can overstate their symptoms in order to receive more benzodiazepines. Second, larger-than-necessary benzodiazepine dosages can be given per protocol such that additional hospital days are needed to allow patients to detoxify from generous benzodiazepine dosing. Third, it is symptom-triggered and thus reactive; in effect, the provider is chasing rather than preventing symptoms. Fourth, benzodiazepines may contribute to recidivism and thereby perpetuate alcohol dependency, and typically chemical dependency treatment programs require a patient to have discontinued benzodiazepines before treatment.

Gabapentin is an anticonvulsant medication which has some evidence of benefit for alcohol withdrawal. (Leung 2015) There are several benefits of using gabapentin for alcohol withdrawal. First, it does not have the same addictive potential compared with lorazepam. Second, the fixed schedule dosing provides for immediate use rather than waiting for symptom triggers, thus potentially decreasing the duration and severity of alcohol withdrawal symptoms. Third, gabapentin has been shown to decrease alcohol intake and relapse into heavy drinking in patients with alcohol dependency. (Furieri FA 2007) Fourth, gabapentin has a small evidence base for improving anxiety, which is a frequent symptom in patients with alcohol use disorder (Berlin RK 2015) and, for some patients, is a trigger for relapse.

Clinical use of gabapentin for alcohol withdrawal has been presented by Maldonado at Stanford University Hospitals. (Academy of Psychosomatic Medicine Annual Meeting, 2013-2015) At Mayo Clinic, the Psychiatry Consultation-Liaison hospital service has been recommending the use of a modified gabapentin protocol since January 2015, which has been clinically accepted on medical, surgical, and psychiatric hospital services. Currently, a retrospective review of that experience is in progress. The purpose of this research is to investigate the reactive benzodiazepine versus proactive gabapentin approaches to AWS in a prospective, randomized, open-label study.

References

Berlin RK et al. Gabapentin therapy in psychiatric disorders: a systematic review. Prim Care Companion CNS Disord 2015;17(5):10.4088.

Furieri FA et al. Gabapentin reduces alcohol consumption and craving: a randomized, double-blink, placebo-controlled trial. J Clin Psychiatry 2007;68:1691-700.

Leung JG et al. Role of rabapentin in the management of alcohol withdrawal and dependence. Ann Pharmacotherapy 2015;49:897-906.

Maldonado JR et al. Prospective validation study of the prediction of alcohol withdrawal severity scale (PAWSS) in medically ill inpatients: a new scale for the prediction of complicated alcohol withdrawal syndrome. Alcohol Alcohol 2015;50:509-18.

Schuckit MA et al. Recognition and management of withdrawal delirium (delirium tremens). N Engl J Med 2014;371:2109-13.

Study Design and Methods

Methods

Patients will be randomized to one of two clinical protocols – the benzodiazepine protocol or the gabapentin protocol. Both of these medications are "clinical medications" and not "study medications."

Randomization

Block randomization will assign the patient to either the benzodiazepine or gabapentin protocol.

Intervention Procedures

The "CIWA scale" a 10 item questionnaire to measure alcohol withdrawal symptoms.(Appendix) It is performed hourly by the patient's clinical nursing staff. A score between 0-67 is obtained. If the score is 10 or higher, the patient is felt to have significant alcohol withdrawal symptoms, and an intervention occurs. When the score is less than 10 for 3 consecutive hourly assessments, the frequency of assessments decreases to every 4 hours. If there is a score 10 or greater, the assessments return to every hour. Each time the nursing staff obtains the CIWA score, a blood pressure, heart rate, respiratory rate, and temperature are also obtained.
If the patient is randomized to the symptom-triggered variable benzodiazepine protocol, whenever the CIWA score is 10 or higher, lorazepam is administered; dose is dependent on the CIWA score. Refer to the CIWA orderset in the Appendix for details. This approach is currently a clinical standard of care.

If the patient is randomized to the gabapentin protocol, a fixed schedule of gabapentin will be given at the start of the protocol:

- If the patient has normal renal function (estimated CrCl > 60 mL/min), then gabapentin dosing will be: 900 mg three times a day (t.i.d.) for 4 days, then 600 mg t.i.d. for 3 days, then 300 mg t.i.d for 2 days, then discontinue.
- If the patient has moderate renal impairment (estimated CrCl 30-60 mL/min), then the gabapentin dosing will be: 600 mg t.i.d. for 4 days, then 300 mg t.i.d. for 3 days, then 100 mg t.i.d for 2 days, then discontinue.

CIWA monitoring is performed for patients receiving gabapentin in the same manner as for those receiving a benzodiazepine, but the dose administered is not contingent upon the CIWA score.

If patients are already taking gabapentin at a dose greater than 300 mg t.i.d. at baseline, they will not be eligible for this study. If their dose is 300 mg t.i.d. or less, their gabapentin will be replaced with the dosages above. This gabapentin protocol for alcohol withdrawal has been used clinically and with increasing frequency at Saint Marys Hospital since January 2015, but is not the clinical standard of care. However, a preliminary order set

has been developed for the clinical use of this protocol. (Appendix) In this order set, for patients who have a history of seizures, the clinician also has the option to add divalproex, another anti-seizure medication.

The current clinical practice is for the patient's primary treatment team to decide whether to utilize the traditional benzodiazepine or the newer gabapentin protocol for patients with alcohol withdrawal.

Patients in both arms of the interventions will receive folate, thiamine, and multivitamin per clinician preference.

The patient completes alcohol withdrawal when their CIWA scores are less than 10 for at least 36 hours, or are less than 10 and clinician judgement is that the patient is safe to discharge. Sometimes patients are not discharged when their alcohol withdrawal is completed, because of other medical or psychiatric or psychosocial issue.

Data collection

Refer to the appendix for the data collection form. Data collected as part of routine clinical care will be used during data analysis. Data elements include (but are not limited to) demographic information, alcohol use and alcohol withdrawal history, PAWSS score assessing risk of alcohol withdrawal, home medications, admission lab work and vital signs, and urine drug screen results. Outcome measures include total amount of benzodiazepines, use of adjuvant medications, symptom assessments (CIWA scores, rating scales for depression symptoms, anxiety symptoms, sleepiness, alcohol cravings).

Suicidal ideation

Patients with alcohol use disorders may express suicidal ideation when intoxicated or afterwards. If indicated, the clinical treatment team may call upon the appropriate psychiatric resources to assess self-harm issues, as per usual clinical procedures. For the Hospital Internal Medicine services, these procedures may include ordering a Psychiatry consult or ordering a one-to-one sitter with the patient. For the Generose services, these procedures will consist of notifying the primary psychiatry team. Because all Generose hospital services are on locked units and have standard suicide precautions, any concerns of suicide risk can be managed by the clinical inpatient team.

Resources

The co-PI's are from the Department of Internal Medicine, Division of Hospital Internal Medicine (R.B.) and the Department of Psychiatry and Psychology, Hospital Division (S.K.). The co-investigators are from these two departments, as well as from pharmacy. The Division of Hospital Internal Medicine has access to study coordinator and statistical resources. Ivana Croghan, PhD, will provide overall mentorship.

☐ (1a) This is a multisite study involving Mayo Clinic and non Mayo Clinic sites. *When checked, describe in detail the research procedures or activities that will be conducted by Mayo Clinic study staff.*

☐ (1b) Mayo Clinic study staff will be engaged in research activity at a non Mayo Clinic site. *When checked, provide a detailed description of the activity that will be conducted by Mayo Clinic study staff.*

Subject Information

Target accrual is the proposed total number of subjects to be included in this study at Mayo Clinic. A "Subject" may include medical records, images, or specimens generated at Mayo Clinic and/or received from external sources.

Target accrual: 400

Subject population (children, adults, groups): Adults

Patient population

Inpatients at risk of AWS on the Hospital Internal Medicine and Generose Psychiatry inpatient units will be eligible. The Prediction of Alcohol Withdrawal Severity Scale (PAWSS) will be used to screen potential patients.(Appendix; Maldonado 2014) The PAWSS is a 10 item scale of which a total score greater than or equal to 4 signifies high risk of AWS. These patients will be offered the research study. If the patient scores less than 4, no formal AWS protocol would be recommended.

To be as inclusive as possible, we plan to enroll a broad range of patient populations, to better study real world conditions. For example, patients with certain other comorbid substance use disorders and those with suicidal ideation will be allowed to enroll. The use of gabapentin is not expected to worsen these other conditions.

Inclusion criteria

1. PAWSS≥4.
2. Adults age 18 or older.
3. Sufficient understanding of English.
4. Hospitalized on Hospital Internal Medicine, Family Medicine or Generose.

Exclusion criteria

1. Severe renal impairment (estimated CrCl < 30).
2. Intensive Care Unit (ICU) level of care.
3. Not responsive due to alcohol intoxication or withdrawal.
4. Already taking gabapentin more than 300 mg three times a day.
5. Prescribed pregabalin.
6. Primary seizure disorder.
7. Acute benzodiazepine withdrawal.

8. Concurrent substance use disorders (such as opioid use disorder, stimulant use disorder) if the disorder is assessed to be clinically significant. Cannabis use disorder will be allowed.
9. Concurrent anticonvulsant medications for psychiatric indications (e.g. bipolar disorder) will be allowed.
10. Pregnancy.
11. Involuntary legal status (e.g., on court commitment).
12. Patients admitted greater than 16 hours prior to potential enrollment.
13. Patients receiving great than one therapeutic dose of gabapentin (rather than continuation of home dose) prior to enrollment.

Termination criteria

1. Seizure
2. Delirium tremens
3. Transfer to ICU
4. Patient leaves against medical advice
5. Any other situation in which the clinician feels it is the best interest of the patient to withdraw them from the study.

Consent

Our consent process aligns with the ideas presented by the National Institutes of Health (NIH) in their on-line document "Research Involving Individuals with Questionable Capacity to Consent" (http://grants.nih.gov/grants/policy/questionablecapacity.htm). Because alcohol intoxication or withdrawal can impair a person's "consent capacity," we must ensure that person understands the purpose and elements of the research study, the potential benefits and risks, and that the research is voluntary. As this study involves medications and protocols which are already in clinical practice (benzodiazepines versus gabapentin), it is considered "minimal risk."

Informed consent will be obtained by study staff. Patients will also be administered a short questionnaire to assess their understanding of the research study and the general procedures, and should answer all 9 questions correctly.(Appendix) Study staff will assess the patient's consent capacity based on the comprehension assessment combined with clinical judgement and, if needed, team discussion.

Research Activity

Check all that apply and complete the appropriate sections as instructed.

1. ☐ **Drug & Device**: Drugs for which an investigational new drug application is not required. Device for which (i) an investigational device exemption application is not required; or the medical device is cleared/approved for marketing and being used in accordance with its cleared/approved labeling. (Specify in the Methods section)

2. ☐ **Blood**: Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture.

3. ☐ **Biological specimens other than blood**: Prospective collection of human biological specimens by noninvasive means that may include: urine, sweat, saliva, buccal scraping, oral/anal/vaginal swab, sputum, hair and nail clippings, etc.

4. ☐ **Tests & Procedures:** Collection of data through noninvasive tests and procedures routinely employed in clinical practice that may include: MRI, surface EEG, echo, ultrasound, moderate exercise, muscular strength & flexibility testing, biometrics, cognition testing, eye exam, etc. (Specify in the Methods section)

5. ☒ **Data** (medical record, images, or specimens): Research involving use of existing and/or prospectively collected data.

6. ☐ **Digital Record**: Collection of electronic data from voice, video, digital, or image recording. (Specify in the Methods section)

7. ☐ **Survey, Interview, Focus Group:** Research on individual or group characteristics or behavior, survey, interview, oral history, focus group, program evaluation, etc. (Specify in the Methods section)

☐ NIH has issued a *Certificate of Confidentiality* (COC). *When checked, provide the institution and investigator named on the COC and explain why one was requested*. _____

Biospecimens – Categories 2 and 3

(2) Collection of blood samples. When multiple groups are involved copy and paste the appropriate section below for example repeat section b when drawing blood from children and adults with cancer.

a. **From healthy, non-pregnant, adult subjects who weigh at least 110 pounds**. For a minimal risk application, the amount of blood drawn from these subjects may not exceed 550ml in an 8 week period and collection may not occur more frequently than 2 times per week.
   Volume per blood draw: _____ml
   Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____

b. **From other adults and children considering age, weight, and health of subject.** For a minimal risk application, the amount of blood drawn from these subjects may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period, and collection may not occur more frequently than 2 times per week.
   Volume per blood draw: _____ml
   Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____

(3) Prospective collection of biological specimens other than blood: _____

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Review of medical records, images, specimens – Category 5

Check all that apply (data includes medical records, images, specimens).

☐ (5a) No data will be collected beyond the IRB submission date.

☐ (5b) The study involves data that exist at the time of IRB submission **and** data that will be collected after IRB submission. Include this activity in the Methods section.
Examples

- The study plans to conduct a retrospective chart review and ask subjects to complete a questionnaire.
- The study plans to include subjects previously diagnosed with a specific disease and add newly diagnosed subjects in the future.

☐ (5c) The study will use data that have been collected under another IRB protocol. Include in the Methods section and enter the IRB number from which the research material will be obtained. *When appropriate, note when subjects have provided consent for future use of their data and/or specimens as described in this protocol*.

Enter one IRB number per line, add more lines as needed

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ (5d) This study will obtain data generated from other sources. Examples may include receiving data from participating sites or an external collaborator, accessing an external database or registry, etc. Explain the source and how the data will be used in the Methods section.

☐ (6) Video audio recording: *Describe the plan to maintain subject privacy and data confidentiality, transcription, store or destroy, etc.*


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HIPAA Identifiers and Protected Health Information (PHI)

Protected health information is medical data that can be linked to the subject directly or through a combination of indirect identifiers.

Recording identifiers (including a code) during the conduct of the study allows you to return to the medical record or data source to delete duplicate subjects, check a missing or questionable entry, add new data points, etc. De-identified data is medical information that has been stripped of all HIPAA identifiers so that it cannot be linked back to the subject. De-identified data is **rarely** used in the conduct of a research study involving a chart review.

Review the list of subject identifiers below and, if applicable, check the box next to each HIPAA identifier being recorded at the time of data collection or abstraction. Identifiers apply to any subject enrolled in the study including Mayo Clinic staff, patients and their relatives and household members.

Internal refers to the subject's identifier that will be recorded at Mayo Clinic by the study staff.
External refers to the subject's identifier that will be shared outside of Mayo Clinic.

Check all that apply:	INTERNAL	EXTERNAL
Name	x	
Mayo Clinic medical record or patient registration number, lab accession, specimen or radiologic image number	x	
Subject ID, subject code or any other person-specific unique identifying number, characteristic or code that can link the subject to their medical data	x	
Dates: All elements of dates [month, day, and year] directly related to an individual, their birth date, date of death, date of diagnosis, etc. **Note:** Recording a year only is not a unique identifier.		
Social Security number		
Medical device identifiers and serial numbers		
Biometric identifiers, including finger and voice prints, full face photographic images and any comparable images		
Web Universal Resource Locators (URLs), Internet Protocol (IP) address numbers, email address		
Street address, city, county, precinct, zip code, and their equivalent geocodes		
Phone or fax numbers		
Account, member, certificate or professional license numbers, health beneficiary numbers		
Vehicle identifiers and serial numbers, including license plate numbers		
Check 'None' when none of the identifiers listed above will be recorded, maintained, or shared during the conduct of this study. (exempt category 4)	☐ None	☐ None

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Data Analysis

Power analyses and study endpoints are not required for minimal risk research, pilot or feasibility studies.

☐ No statistical information. *If checked, please explain*:

Power Statement: Patients will be randomized 1:1 between the two treatments. The primary objective will be testing for noninferiority of the two treatments on the primary endpoint, but it is assumed the gabapentin arm will have a superior (shorter) time to outcome. Following Freidlin, Korn, George, and Gray (2007), we assume the median time to outcome is 48 hours for larazepam and 40 hours for gabapentin, and a noninferiority margin of 8 hours, corresponding to a hazard ratio less than 1.167. Using a one-sided type I error rate of 0.05 and with 90% power, the total required sample size is 303.

Data Analysis Plan: The primary endpoint will be analyzed using the Log-Rank test between the treatment arms, using the intention to treat analysis. The noninferiority margin for the primary outcome is 8 hours, corresponding to a hazard ratio less than 1.167.

Interim monitoring for feasibility will be performed when 50% (N = 150) of the patients have been accrued and followed for the primary outcome. If the hazard ratio is greater than 1.5, then the study will be stopped and we will fail to demonstrate that gabapentin is noninferior to larazepam for the primary outcome. With this stopping rule, there is a 50% chance to stop early if the true hazard ratio is 1.5, and only a 1% chance to stop early if the hazard ratio is 1.0.

For the analysis of the adverse events, events rates will be estimated within each treatment group and tested using a two-sample binomial test for differences in rates. No adjustment for multiple testing will be applied for the adverse event rates.

Trends in CIWA scores between treatment groups will be assessed using non-linear mixed effects models with random intercepts for each patient. The CIWA scores will be transformed so the empirical distribution of the residual terms is approximately normally distributed. We will test for time by treatment arm interaction effects within the regression model. Other pre-treatment variables will be assessed for significant interaction with the time trend both within and between treatment groups.

Symptom assessment scores will be analyzed using a difference-in-differences model for differential pre-post intervention scores between the treatment groups.

Endpoints

The primary outcome will be the patient's length of stay, defined as admission time to either:

1. **time of discharge**; or,
2. **CIWA score < 10 for 36 hours** (as a proxy for when patients are clinically stable for release because actual discharge may be delayed for non-medical reasons).

Secondary outcomes include: (assessment scales attached in the Appendix)

1. Safety: adverse events such as delirium tremens or seizures
2. Alcohol withdrawal severity: trends as measured by CIWA scores
3. Validated symptoms assessment scores at baseline (within 24 hours of admission) and 48 hours later:
    a. Sleepiness as assessed by the Epworth Sleepiness Scale
    b. Depressive symptoms as measured by the PHQ-9 (Patient Health Questionnaire-9)
    c. Anxiety symptoms as measured by the GAD-7 (Generalized Anxiety Disorder-7)
    d. Cravings as assessed by the Penn Alcohol Craving Scale
4. Total amount of benzodiazepines given