

Gabapentin Treatment for Alcohol Dependence: A Randomized Clinical Trial

BACKGROUND

- Approved medications for alcohol dependence are prescribed for less than 9% of US alcoholics
- Previous studies of gabapentin and alcohol dependence was limited by small sample size, methodological issues, or dosing issues

OBJECTIVE

- The main objective was to determine if gabapentin increases rates of sustained abstinence and no heavy drinking and decreases alcohol-related insomnia, dysphoria and craving, in a dose-dependent manner.

METHODS

- **Design:** 12-week, randomized, single-centered, parallel, double-blind, placebo-controlled, clinical trial
- **Inclusion criteria:** greater than 18 years, meet DSM-IV criteria for current alcohol dependence, and be abstinent from alcohol for at least 3-days prior to randomization
- **Exclusion criteria:** A CIWA-Ar risk for withdrawal score > 9, > 1 month of abstinence, other substance dependence (besides nicotine), positive UDS, clinically significant medical or psych disorders, treatment with medications that can affect data, and legally mandated treatment
- **Primary outcome:** Rates of complete abstinence and no heavy drinking (coprimary) over the 12-week study.
- **Secondary outcome:** Changes in mood, sleep, and craving over the 12-week study.
- **Patients/groups:**
150 participants randomized to receive either
 Placebo (49) + offered counseling
 OR
 Gabapentin 900mg/day (54) + offered counseling
 OR
 Gabapentin 1800mg/day (47) + offered counseling
Power 80% with an alpha level of 0.05 to detect “medium” effect size from a previous trial finding an OR of 2.96 for complete abstinence between drug and placebo
Data handling method was intent-to-treat

RESULTS

- 85 of 150 patients completed the study
- **Primary outcome** – Significant linear dose effect in increasing the rates of complete abstinence ($X^2 = 4.19$; $p = 0.04$) and no heavy drinking ($X^2 = 5.39$; $p = 0.02$) over 12 weeks vs placebo. The rate of sustained 12-week abstinence was 4.1% (95% CI, 1.1-

13.7%) in the placebo group, 11.1% (95% CI, 5.2-22.2%) in the 900mg group, and 17.0% (95% CI, 8.9-30.1%) in the 1800mg group.

- 1800mg group - NNT 8 (95% CI, 6-∞) and an OR = 4.8 (95% CI, 0.9-35.0) indicating a large effect size
- Significant linear decreases in the average number of drinks per week ($t = -5.32$; $p < 0.001$; 900mg group: -2.2 [95% CI, -5.3 to 1.0]; $t = -1.3$; $p = 0.20$; 1800mg group: -6.7 [95% CI, -9.8 to -3.5]; $t = -4.13$; $p < 0.001$)
- **Co-primary outcome** – The rate of no heavy drinking was 22.5% (95% CI, 13.6-37.2%) in the placebo group, 29.6% (95% CI, 19.1-42.8%) in the 900mg group, and 44.7 (95% CI, 31.4-58.8%) in the 1800mg group.
 - 1800mg group - NNT 5 (95% CI, 3-78) and OR = 2.8 (95% CI, 1.1-7.5) indicating a medium effect size
 - Significant linear decreases in the average number of days of heavy-drinking days per week ($t = -13.2$; $p < 0.001$; 900mg group: -1.8 [95% CI, -2.2 to -1.3]; $t = -7.22$; $p < 0.001$; 1800mg group: -2.0 [95% CI, -2.5 to -1.5]; $t = -8.14$; $p < 0.001$)
- **Secondary outcome** - significant linear dose effects on craving, mood, and sleep. Significant dose-dependent reductions were obtained on the ACQ ($F_2 = 3.56$; $p = 0.03$ 1800mg vs placebo: -6.8 [95% CI, -1.5 to -12.1]; $t = -2.52$; $p = 0.01$), the Beck Depression Inventory II ($F_2 = 7.37$; $p = 0.01$; 1800mg vs placebo: -1.1 [95% CI, -2.0 to -0.3]; $t = -.257$; $p = 0.01$) and the Pittsburgh Sleep Quality Index total score ($F_2 = 136$; $p < 0.001$; 1800mg vs placebo: -1.5 [95% CI, -2.1 to -0.8]; $t = 4.46$; $p < 0.001$).

STRENGTHS

Study objective current and relevant to society

Appropriate randomized controlled trial design

Appropriate dosing of gabapentin compared relative to other studies on substance abuse

Study length consistent with other substance abuse trials

Washout period 3 days before randomization into trial to standardize groups

Multiple measures to analyze alcohol intake in patients (diary, interview, breathalyzer, GGT)

Adverse events reported as number of events and severity of events to prove non-significance

LIMITATIONS

Exclusion of high-risk alcoholics (CIWA-Ar score > 9)

Single study site makes it difficult to extrapolate results to entire population

Large number of dropouts

Values from previous studies used for arbitrary effect sizes

Significant unblinding

Possibly unequal baseline values (age, sex, weekly drinks) between groups

Study drug compliance measures

Short duration of treatment

CONCLUSION

Although it seemed that blinding was appropriate, there was a large amount of unblinding due to the fact that the patients could correctly identify which study medication they were receiving and validity of the data could be compromised.

- Difficult to tell if there was an actual study benefit from the drug itself, or due to a possible change in motivation due to the patient's knowledge of their medication
- Difficult to tell if knowledge of the study medications had any impact on rates of counseling attendance or other tools used to prevent weekly drinking
- Patients could have been discouraged from abstaining if they could identify one pill over the other.

Gabapentin may be effective in maintaining abstinence, lowering weekly alcohol intake, and reducing cravings and improving mood and sleep in patients with moderate-risk alcohol dependence; however, extrapolation of these results to the entire population may be difficult.

- Investigators excluded those with a CIWA-Ar score > 9 making it difficult to relate the data to high-risk alcoholics who may truly benefit from a drug that may aid in reducing their weekly alcohol intake
- The study population was sampled only from the greater San Diego area from paper and internet advertisements
- Investigators excluded those possible abusing substances other than alcohol. A majority of alcoholics abuse substances along with alcohol.

Further research:

- Doses up to 3200mg/day have been used in other studies and should be investigated to find a more appropriate dosing range for the possible treatment of alcohol dependence with gabapentin
- Large number of dropouts, significant unblinding, and possible inequalities at baseline in this study require more structured research focusing on minimizing these limitations is needed to prove a major benefit vs placebo
- In order to show a benefit in more long-term situations, more research is necessary for periods of time exceeding 12 weeks

Reference: Mason BK, Quello S, Goodell V, Shadan F, Kyle M et al. Gabapentin Treatment for Alcohol Dependence: A Randomized Clinical Trial. JAMA Intern Med 2014;174(1):70-77.

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