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# Is Rimonabant a Safe and Effective Treatment for Patients with Alcohol Dependence?

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# Is Rimonabant a safe and effective treatment for patients with alcohol dependence?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not Rimonabant is a safe and effective treatment for patients with alcohol dependence.

Study Design: Systematic review of three English language randomized control trials published in 2005, 2008 and 2010.

Data Sources: Three double-blind, placebo controlled randomized trials comparing Rimonabant or Naltrexone to placebo were found using PubMed, OVID, Medline and Cochrane.

Outcomes Measured: Outcomes measured include event rate of heavy drinking days using the timeline follow back method, which facilitates self-reporting of drinking habits by utilizing calendars and personal recall. Other outcomes measured include the number of self-reported drinks/day using daily call ins from study participants and number of days until first alcoholic drink and number of days until first heavy drinking (as measured by timeline follow back method).

Results: In a study by George et.al, there was no significant difference found in the number of alcoholic drinks consumed by non-treatment seeking heavy alcohol drinkers when comparing the Rimonabant and placebo groups during the 14 day study. A study by Soyka et.al. discovered that participants treated with once daily Rimonabant showed a marked, but not statistically significant, reduction in relapse to heavy drinking when compared to placebo after 12 weeks oif treatment: 27.7% versus 35.6%, respectfully. Finally, another study included in this review investigated the efficacy of intramuscular naltrexone as a treatment for alcohol dependence by measuring the event rate of heavy drinking days. Results of this study showed that long-acting IM naltrexone resulted in 25% reduction in heavy drinking days among treatment-seeking alcohol dependent patients when compared to placebo. The compiled data also demonstrates that both Rimonabant and Naltrexone are relatively safe to use in adult alcoholics, however patients receiving Rimonabant were more likely to have treatment emergent adverse events such as nausea, insomnia, headache, etc.

Conclusions: The results of two double-blind placebo controlled randomized control trials showed no statistical treatment effect of Rimonabant versus placebo in reducing the number of drinks per day, number of heavy drinking days, or time to heavy drinking relapse. Both Naltrexone and Rimonabant are considered safe for use in adults, despite a modest amount of mild adverse reactions associated with treatment.

Key Words: Rimonabant, Naltrexone, Alcohol dependence

INTRODUCTION

Alcohol dependence is a serious medical health problem in the U.S., and has recently become the 4th leading cause of disability in America[5]. Alcohol dependence, also known as alcoholism, is a syndrome consisting of two phases: at risk drinking and alcohol addiction. At risk drinking is typically defined as more than 4 drinks per day or 14 drinks per week for men and more than 3 drinks per day or 7 drinks per week for women[4]. People affected by alcoholism often show evidence of withdrawal when intake is interrupted, tolerance to the effects of alcohol, and evidence of alcohol-associated illnesses such and alcoholic liver disease and cerebellar degeneration[10].

The lifetime risk for alcohol dependence in Western countries is 10-15% for men and 5-8% for women[10]. Alcoholism may contribute to more than 80,000 preventable deaths per year and is responsible for 2.3 million years of potential life lost annually[1]. About 80% of people in Western countries have consumed ethanol, and two-thirds admit to being drunk in the past year, demonstrating how large of a demographic is at risk for alcoholism[10]. With this knowledge, it is imperative for the physician assistant to have a low threshold of suspicion for alcohol abuse or dependency in any person with a history of drug or alcohol consumption or clinical manifestations of acute or chronic intoxication.

In 2006, the overall cost to the United States for alcohol-related health problems was estimated to be $223.5 billion[1]. In 2006, there were more than 1.2 million emergency room visits and more than 2.7 million physician office visits for alcohol-related conditions[1]. Life span is decreased by 10 years in an alcoholic, with death most commonly resulting from heart disease, cancer, automobile accidents and suicide[10].

Alcohol dependence is a chronic disease that typically presents with a craving for alcohol and the inability to limit one's intake of alcoholonitnued use of alcohol despite negative social, physical and interpersonal problems or developmental of alcohol-related illnesses[4]. Potential health complications of alcoholism include cardiomyopathy, cerebellar degeneration, peripheral neuropathies, cirrhosis of the liver, esophageal varices, hormonal and nutritional deficiencies, coagulation defects, pancreatitis, depression, psychological disease, cancer and fetal alcohol syndrome in babies of alcoholic mothers[4,10]. Acute alcohol intoxication produces CNS depression, manifesting as drowsiness, psychomotor dysfunction, lack of inhibition, dysarthria, ataxia and nystagmus. Blood alcohol levels below 50 mg/dL rarely cause significant motor dysfunction, while alcohol ingestion coupled with nausea and vomiting suggest blood alcohol levels > 150 mg/dL[4].

Alcohol dependence is diagnosed clinically by the DSM-IV as repeated alcohol related difficulties in at least three of seven life areas over a 12 month period. Tolerance and withdrawal symptoms are associated with more severe dependence. Some lab values may aid in the diagnosis, including elevated liver enzymes, GTT> 35U, CDT > 20 U/L, high MCV (>91 $um^3$) and high serum uric acid (>416 mol/L)[10]. Questionnaires and interviewing methods such as the CAGE questions and the AUDIT (The Alcohol Use Disorders Test) are a valuable tool for identifying those patients with alcohol abuse or dependence[4].

Cognitive behavioral therapy with an emphasis on motivational interviewing is the primary intervention for alcoholism. Goals of CBT include emphasizing the positive actions that the patient can take to reduce their alcohol consumption, reducing any "enabling" behavior of a spouse or significant people, and facing denial. Rehabilitation, counseling and self-help groups

such as Alcoholics Anonymous are an integral component of successful treatment. After completing rehabilitation and CBT, over 60% of alcoholics remain sober for at least 1 year[10].

Medical therapies are available for the treatment of alcoholism and include Disulfiram, Acamprosate, and Naltrexone. Disulfiram, an ALDH inhibitor, produces symptoms of nausea and vomiting with rising levels of acetaldehyde (breakdown product of ethanol) in the blood[10]. This reaction may be dangerous for patients with heart disease, DM or stroke. Acamprosate has modest effects on alcohol intake and functions by inhibiting NMDA receptors, resulting in a decrease in the pleasurable side effects of ethanol ingestion. Naltrexone, an opioid receptor antagonist, appears to shorten relapses, especially in patients with a specific mu-receptor polymorphism[4,10]. Studies have suggested that use of Acamoprosate and Naltrexone in combination is more efficacious than use alone[10].

The CB1 cannabinoid receptor and mu-opioid receptors have been shown to have a similar distribution in the brain, specifically sharing the same pre-synaptic nerve terminals and signaling through a common receptor mediated G-protein coupled pathway[7]. Naltrexone, a mu receptor blocker, is currently the first-line medical therapy for alcohol dependence. Animal studies have shown that CB1 knockout mice had reduced voluntary alcohol consumption and increased alcohol sensitivity[2]. Based on the success of Naltrexone combined with the positive treatment response in animal studies, there is sufficient data to suggest that a CB1 cannabinoid receptor antagonist such as Rimonabant may have a similarly therapeutic response in treating alcoholism.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not Rimonabant (Acomplia) is a safe and effective treatment for patients with alcohol dependence.

## METHODS

Specific selection of three double-blind, placebo controlled randomized control trials (RCT) were used for this review. The chosen population included adults > 18 years old with a diagnosis of alcohol dependence or abuse. Interventions studied included Rimonabant 20 mg PO QD and Naltrexone 380 mg IM and 190 mg IM. Comparisons were made between treatment groups receiving Rimonabant or Naltrexone versus a placebo. Outcomes measures include event rate of heavy drinking (>5 standard drinks/day for men, >4 standard drinks/day for women), number of drinks per day, time to drinking and time to heavy drinking relapse (in days). All outcomes were measured using patient self-reporting via call-ins or the timeline follow-back method (based on calendars and personal recall). Safety associated and tolerability of Rimonabant and Naltrexone were measured on the basis of adverse events (AE) and serious adverse events (SAE).

Over the time period of November 2011-January 2012 the author accessed PubMed, Medline, OVID and Cochrane Systemic Reviews using the key words “Rimonabant”, “Alcohol dependence”, “alcohol” and “Naltrexone” to search for relevant RCTs. While searching for articles inclusion criteria included: English language, human adult participants, articles published within the past 10 years, peer-reviewed journals, randomized control trials and relevance to my clinical question. All outcomes investigated are based on outcomes that are important to patients (POEMs). Exclusion criteria can be found in Table 1. The statistics included in the data analysis include NNT, NNH, p-values, hazard ratios and F-score.

**Table 1**- Demographics and Characteristics of Included Studies

| Study | Type | # pts | Age | Inclusion Criteria | Exclusion Criteria | W/D | Interventions |
|---|---|---|---|---|---|---|---|
| **Garbutt (2005)**[5] | Double Blind RCT | 624 | 45 ± 10 years | >18 y/o with current DSM-IVdiagnosis of alcohol dependence with a minimum of 2 episodes of heavy drinking in 30 days prior to study | Evidence of liver failure, current diagnosis major psychiatric illness, dependence on drugs, previous inpatient treatment for substance abuse | 3* | Naltrexone 380 mg or 190 mg IM gluteal injection q 4 weeks x 24 weeks |
| **George (2010)**[6] | Double Blind RCT | 39 | 32 ± 2 years | Age 21-45 who consumed 20-50 drinks/week with a BMI of 18-30, taking no other medications and tested negative for HIV and hepatitis with normal 12-lead EKG | Major psychiatric illness, history of withdrawal symptoms, not currently seeking treatment for alcohol consumption | 0 | 20 mg of Rimonabant PO QD x 14 days |
| **Soyka (2008)**[11] | Double Blind RCT | 253 | 44.8 ± 8.8 years | Age 18-65 with DSM –IV diagnosis of alcohol dependence who are detoxified from alcohol for 7-28 days prior to randomization without withdrawal symptoms | Symptoms of alcohol withdrawal or drinking alcohol in 3 days prior to study. History of WK syndrome, withdrawal seizures, delirium, cirrhosis, or alcohol-induced psychosis. Pending legal charges, IQ < 80, major psychiatric illness | 80 | 20 mg of Rimonabant PO QD x 12 weeks |

*Although 246 participants dropped out of this trial, all patients who received at least 1 injection of the long acting naltrexone were included in the final data analysis (624 people).

OUTCOMES MEASURED

The outcomes measured were based on actual patient self-reports. Event rate of heavy drinking was measured by taking the number of heavy drinking days divided by the number of days at risk for heavy drinking. Heavy drinking is considered to be intake of > 5 standardized drinks/day for men or > 4 standardized drinks/day for women[5]. Another outcome measured the

amount of daily alcoholic beverages consumed by daily patient call in, in an effort to capture the patient's consumption in their natural home setting[6]. The last outcomes were measured by quantifying the number of days before a patient relapsed (based on reported drinking status, Timeline Followback report of alcohol consumption, ethanol breath testing, plasma GGT level and CDT value). The time until relapse to first period of heavy drinking was also investigated[11]. Drinking status was assessed using the Timeline Followback method and the OCDS (Obsessive Compulsive Drinking Scale) at every visit.

## RESULTS

Two of the randomized control trials in this systematic review compared treatment with oral Rimonabant to placebo, while another RCT compared treatment with intramuscular long-acting Naltrexone to intramuscular placebo of the same volume.

The article by Soyka et.al was a 12 week study assessing the efficacy of Rimonabant 20 mg/day given in two 10 mg oral doses in the prevention of relapse to alcohol consumption in recently detoxified alcoholics. Of the 260 patients who began the study, only 71.8% of the participants in the Rimonabant group completed therapy while only 62% of participants in the placebo group completed therapy[11]. All dropout patients were considered to have relapsed using the Fischer exact test in one of the sensitivity analyses. The primary outcomes of this study included time to relapse and time to heavy drinking relapse. The time to relapse of drinking and heavy drinking (in days) was increased in the group receiving Rimonabant when compared to placebo, however no statistically significant difference was found between the treatment groups.

The number needed to treat (NNT) value for relapse to heavy drinking in this study is 10, meaning that ten patients would need to be treated with Rimonabant to prevent one patient from

relapsing to heavy drinking. The p-values are not significant (see Table 3), and the odds ratio is very close to 1 in both drinking relapse and heavy drinking relapse, showing that the treatment effect was small. Patients taking placebo relapsed to heavy drinking 22 days before patients taking Rimonabant.

**Table 2.** Primary Outcomes: Time to Relapse and Relapse Rates[11]

| | | Placebo (n=124) | Rimonabant 20 mg (n=129) |
|---|---|---|---|
| **Drinking** | Non-relapse Patients | 50 (40.3%) | 60 (46.5%) |
| | Relapse Patients | 57 (46.0%) | 53 (41.1%) |
| | Time to Relapse | 24 days | 33 days |
| **Heavy Drinking** | Non-relapse Patients | 58 (47.2%) | 71 (57.7%) |
| | Relapse Patients | 40 (32.5%) | 32 (26.0%) |
| | Time to Relapse | 52 days | 74 days |

**Table 3**. Calculations for efficacy of relapse prevention[11]

| | Relative Risk Reduction (RRR) | Absolute Risk Reduction (ARR) | Number Needed to Treat (NNT) | Odds Ratio | P-value (< 0.05 is significant) |
|---|---|---|---|---|---|
| **Relapse to Drinking** | 15% | 6% | 16 | 0.77 | 0.375 |
| **Relapse to Heavy Drinking** | 22% | 11% | 10 | 0.65 | 0.125 |

The study by George, et. al. was a 2 week double-blind study with 49 non-treatment seeking adult heavy alcohol drinkers who were randomly given either oral Rimonabant 20 mg/day or placebo. The data showed that there was no significant treatment effect between the Rimonabant and placebo groups. The data uncovered in this study is represented in a continuous manner and could not be converted to dichotomous data; there for RRR, ARR and NNT cannot be calculated. The treatment effect (number of drinks/day) is described by an F-score of $F_{(1,36)}$= 0.05 and a p-value of p=0.83[6]. Based on these values, the author determined that the treatment effect was small and of no statistical significance.

The study by Garbutt, et al. was a 6-month, randomized, double-blind placebo controlled trial investigating the event rate of heavy drinking days after treatment with long-acting intramuscular Naltrexone versus placebo in 627 actively alcohol-dependent adults. Although only 378 participants actually finished the 6-month trial, all patients who received at least 1 injection of Naltrexone were included in the final data analysis (624 participants)[5]. The data showed that participants taking 380 mg IM naltrexone had a 25% reduction in the event rate of heavy drinking when compared to placebo (p=0.03)[5]. This p-value is <0.05, showing that there was a statistically significant decrease in the rate of heavy drinking days between the treatment groups. Male patients and patients without lead in drinking taking Rimonabant had an even more significant reduction in the rate of heavy drinking, 44% and 80% respectively. Since the data is represented in hazard ratios and no specific data points are given, data is continuous and ABI, RBI and NNT cannot be calculated.

**Table 4.** Analysis of Outcomes for article by Garbutt et.al.

| | | **Naltrexone 380 mg v. Placebo** | | **Naltrexone 190 mg v Placebo** | |
|---|---|---|---|---|---|
| | Population | Hazard Ratio* | P-value | Hazard Ratio | P-value |
| **Heavy Drinking** | 624 | **0.75 (0.60-0.94)** | **0.03** | 0.83 (0.68-1.02) | 0.07 |
| **Female** | 201 | 1.23 (0.85-1.78) | 0.28 | 1.07 (0.73-1.58) | 0.72 |
| **Male** | 423 | **0.56 (0.41-0.77)** | **<0.001** | 0.83 (0.64-1.07) | 0.16 |
| **Lead in drinking** | 571 | 0.79 (0.62-1.00) | 0.05 | 0.93 (0.75-1.12) | 0.48 |
| **No lead in drinking** | 53 | **0.20 (0.07-0.62)** | **0.005** | **0.05 (0.02-0.15)** | **<0.001** |

*Hazard ratio is an estimate of treatment effect size for each individual treatment relative to placebo and should be interpreted as follow: HR = 1 indicates no treatment effect, HR = 0.75 is a 25% reduction in heavy drinking relative to placebo, HR = 1.25 is a 25% increase in heavy drinking relative to placebo, etc.

SAFETY

Based on data compiled by Soyka et al, Rimonabant 20 mg/day resulted in a NNH of 23, meaning that 23 patients must be treated for one patient to experience a treatment emergent

adverse event. NNH for serious adverse events was -38, meaning that thirty eight people would have to be treated with Rimonabant for one less serious adverse event to occur versus placebo. Of note, three suicide attempts occurred in the placebo group compared to 1 attempted suicide in the Rimonabant group. No deaths occurred during the study period.

Garbutt and colleagues found that 7.2% of patients in the placebo group discontinued therapy secondary to a serious adverse event compared to 5.4% of patients in the Naltrexone 380 mg group. The participants treated with Naltrexone were two times as likely to have an adverse event compared to those taking placebo. For every 14 people treated with Naltrexone 380 mg IM one more patient experienced an adverse treatment reaction. As for serious adverse events such as hospitalization or pneumonia, 55 patients would need to be treated with Naltrexone 380 mg IM to experience one less serious adverse event when compared to placebo.

The study by George et al cited no specific adverse drug reactions, however the author states that no significant differences for drug side effects were found using a Visual Analog Scale to monitor patients at every clinical visit. No participants reported feelings of depression of suicidal ideation.

**Table 5.** Safety and tolerability of Rimonabant and Naltrexone

| | **Medication regimen of interest** | **Most common adverse side affects** | **Placebo (%)** | **Treatment (%)** | **Number needed to harm (NNH)** |
|---|---|---|---|---|---|
| **Soyka, et.al.**[11] | Rimonabant 20 mg/day | Serious adverse events: hospitalization due to alcoholism and suicide attempts. | 11.8% | 9.2% | -38 |
| | | Treatment Emergent Adverse Events: Headache, Alcoholism, Diarrhea, Fatigue, Nausea, Insomnia, Anxiety, Hypertension, Asthenia, | 48.8% | 53.3% | 23 |

| | | | | | |
|---|---|---|---|---|---|
| | | Depression | | | |
| **George, et.al.**[6] | Rimonabant 20 mg/day | No adverse reactions reported | N/A | N/A | N/A |
| **Garbutt, et.al.**[5] | Naltrexone 380 mg IM injection/month | SAE: Hospitalization for alcohol detoxification, pneumonia | 7.2% | 5.4% | -55 |
| | | AE: Nausea, headache, fatigue, insomnia, vomiting, decreased appetite, diarrhea | 6.7% | 14.1% | 14 |

DISCUSSION

The endocannabinoid and opioid neural signaling pathways have both been implicated in the development and maintenance of alcohol dependence and abuse disorders. The opioid signaling pathways have already been utilized clinically with the introduction of Naltrexone, an opioid mu-receptor antagonist which has been FDA approved for the treatment of alcohol dependence. Rimonabant, a CB1 endocannabinoid receptor antagonist, acts on a pathway with a very similar mechanism of action in the brain as the opioid signaling pathways[7], leading clinical scientists to investigate the efficacy of Rimonabant as a treatment for alcohol dependence, based on the relative success of Naltrexone. Although animal studies were encouraging and showed a significant positive treatment effect with Rimonabant[2], the human RCTs discussed in this systematic review show no significant treatment effect between Rimonabant and placebo. Although Soyka et al found a 11% absolute risk reduction of heavy drinking in participants taking Rimonabant, these results were not found to be significant.

Limitations to this systematic review were numerous. The study by George et al investigated a very small population size (n=49) and treated the participants for a duration of only two weeks[6]. Of the two studies investigating Rimonabant vs. placebo, the treatment groups varied significantly: one population included recently detoxified alcohol dependent patients

while the other included non-treatment seeking alcoholics. The obvious contrast in the population's willingness and initiative to obtain treatment for alcoholism may substantially confound the medication treatment effects.

Only two placebo-controlled randomized control trials are currently in circulation investigating the use of Rimonabant for the treatment of alcohol abuse disorders in humans. Reasons for the lack of RCTs may include the numerous treatment options that are already available for alcohol dependence, the serious side effects discovered from administration of Rimonabant in 2007 by the FDA, including increased risk of suicidal ideation (OR=1.9)[3] and severe depression (OR=2.5)[3], and the lack of FDA approval for the drug Rimonabant. For these reasons, coupled with the lack of significant treatment effect found in two randomized control trials by Soyka and George, the author believes that future research into this therapeutic option should be limited until a more thorough investigation into the drug safety has been concluded and FDA approval has been obtained.

## CONCLUSIONS

Rimonabant (Acomplia) is a safe treatment for alcohol dependence based on the information reported in this systematic review. However, based on previous reports of suicidal ideation and severe depression in patients taking Rimonabant, the safety profile for this drug requires serious consideration and further study. Effectiveness as evidenced by increased days to first relapse and reduced risk of relapse to drinking and heavy drinking were seen, however no statistically significant differences were found when comparing treatment with Rimonabant to placebo. Future research is warranted to evaluate treatment with a peripherally acting neutral

CB1 antagonist[8] in a sufficiently large population of alcohol dependent adults who are seeking treatment and have already begun cognitive behavioral therapy.

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