ADDICTION TREATMENT

Forum

NALTREXONE CLINICAL UPDATE

Evidence for the Efficacy of Naltrexone in the Treatment of Alcohol Dependence (Alcoholism)

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ABSTRACT

Each year, more than 1.5 million Americans seek treatment for alcohol-related problems. In 1994, naltrexone became only the second drug approved to date for treating alcoholism by the U.S. FDA. Naltrexone blocks opioid receptors in the brain, stemming the endorphin-mediated reinforcing effects of drinking alcohol.

Recognizing that healthcare providers need credible scientific information for decision-making purposes when considering pharmacotherapies for alcoholism, such as naltrexone, this report focuses on the highest level of clinical evidence – randomized controlled trials (RCTs). Through year 2001 there were 14 RCTs assessing the effectiveness of naltrexone compared with placebo for treating alcoholism, enrolling 2127 subjects, in five countries.

An analysis of these trials, consistent with prior systematic reviews and meta-analyses, concludes: A) RCTs of naltrexone in the treatment of alcoholism are recent, extensive, and of good quality, B) There is strong evidence that naltrexone significantly reduces alcohol relapses to heavy drinking, the frequency and quantity of alcohol consumption in those who do drink, and alcohol craving.

In brief, naltrexone is significantly beneficial in helping those patients who cannot remain abstinent to reduce their drinking behaviors, breaking the vicious, self-destructive cycle in alcoholics whereby one drink leads to another, and allowing more quality time for psychosocial therapy to be productive. Naltrexone has demonstrated effectiveness in a variety of alcohol-treatment settings using adjunctive psychosocial therapies that provide motivation to stay in treatment, avoid relapses, and take medications.

Individualized, flexible naltrexone dosing can be of benefit. Longer-term naltrexone therapy extending beyond three months may be most effective, and naltrexone might be used on an as-needed, "targeted," basis indefinitely. It is expected that the information in this report will help healthcare providers to better use this effective medication.

From Snake Pits to Science

About 14 million American adults meet diagnostic criteria for alcohol abuse or alcohol dependence (alcoholism). And, every year, more than 1.5 million seek treatment for their alcohol-related problems (Highlights… 2000; Kurtzweil 1996).

Throughout history, attempts to treat alcoholics have been ill-conceived and gave disappointing results. A first treatment for chronic drunkenness may have been devised by ancient Romans, who lowered habitual drunkards into snake-filled pits, thinking the terror would shock them into abandoning their wayward practices (Sournia 1990).

By the close of the 19th Century, *Merck's Manual of the Materia Medica* (1899) was recommending such nostrums for alcoholism as arsenic, bromides, cocaine, chloral hydrate, opium, and strychnine. Roughly 50 years later, in 1948, disulfiram became the first U.S. Food and Drug Administration (FDA) approved drug for alcoholism treatment (Kurtzweil 1996). It induces nausea, vomiting, and other aversive reactions in those who drink alcohol while taking the medication.

After nearly another half-century passed, in late 1994, naltrexone became only the second drug approved to date for alcoholism by the FDA (Kurtzweil 1996).This new indication was authorized in part because of naltrexone's accumulated record of safety during extensive prior use for opioid detoxification and in the treatment of heroin addiction (Naltrexone… 1997; Miller 1997, p75).

A deciding factor, however, was results from two pivotal studies demonstrating naltrexone's usefulness as part of a clinical program for treating alcoholism (O'Malley et al. 1992; Volpicelli et al. 1992). In its approval, the FDA recommended that naltrexone also be used with adjunctive psychosocial therapies for alcoholism.

Naltrexone's pharmacologic actions are fairly straightforward. Alcohol is a complex substance, affecting a number of chemical systems in the brain. Among other effects, it is suspected that, when an alcoholic imbibes, the brain's opioid system releases endorphins triggering reinforcement that entices the person to drink more (Goldstein 1997; Naltrexone…1997; O'Brien 1997; O'Malley 1998, Swift 1995).

Naltrexone is not addictive and does not react aversively with alcohol.

Unlike earlier drugs used to treat alcoholism, naltrexone is not addictive and does not react aversively with alcohol. It blocks opioid receptors in the brain (it is an antagonist), and this has been proposed as stemming the endorphin-mediated reinforcing effects of drinking alcohol. The validity of this concept has been supported by observations that alcoholics experience increased opioid system activity in response to alcohol (Herz 1997; Miller 1997).

Some controversy has surrounded the use of naltrexone for alcoholism (Freed and York, 1997). First, healthcare providers, and patients themselves, sometimes question the value of using any drug to treat drug or alcohol addiction. Second, research on the effectiveness of naltrexone and how best to use it in treating alcoholism has evolved rapidly during just the past decade and cumulative findings are not widely known or appreciated.

In this era of managed care and increasing pressures of accountability, healthcare providers need credible scientific information for decision-making purposes in recommending medications such as naltrexone. They need to respond authoritatively to questions such as:

- Where did you learn that naltrexone is effective in treating alcoholism?
- How do you know the information is reliable and valid?
- What results do you expect from using naltrexone?

These questions serve as the foundation of this clinical update report. The goal is to provide healthcare providers with useful, evidence-based answers.

Treatment Expectations

It has been stressed that *both* alcoholics and alcohol abusers need treatment, although the goals may differ. According to the FDA, "In most cases of alcohol abuse, the goal is to limit drinking, while for alcoholism, it is to stop drinking altogether" (Kurtzweil 1996).

The immediate goal of most recovery programs is alcohol abstinence, yet that is often too strict a standard. According to some studies, about half of patients experience a relapse to heavy drinking within 12 weeks of beginning treatment, and up to 90% will relapse at least once during four years following treatment. (Kurtzweil 1996; Nathan 1986; Volpicelli et al. 1992).

When sustained abstinence cannot be achieved, other goals, such as reducing the number, frequency, or severity of relapses could be of significant clinical value. A great potential benefit of naltrexone, in combination with appropriate psychosocial therapy, would be providing the patient relief from the self-destructive cycle of intoxication to enhance engagement in treatment and achieve long-term recovery objectives (Miller 1997, p59).

Volpicelli et al. (1992) have suggested that the ideal pharmacological agent for use in alcoholism treatment would, first, decrease alcohol craving and reduce the initial motivation to drink. Second, if drinking does occur, the agent should block the reinforcing or desirable qualities of alcohol to decrease further drinking behavior, so a "lapse" does not progress to a relapse. Naltrexone's ability to fulfill those requirements is examined in the research evidence.

Evidence Selection

The various types of research study designs may be ranked according to a "hierarchy of evidence," based on their relative strengths for providing results that are likely to be valid and free of bias. Randomized controlled clinical trials (RCTs) are considered by many as the "gold standard" when addressing questions of a drug's therapeutic efficacy (Guyatt and Drummond 1993; Sackett et al. 1997), and are the focus of this report.

Naltrexone Clinical RCTs

Through year 2001 there were 14 clinical RCTs to assess the effectiveness of naltrexone for treating alcoholism, enrolling 2127 subjects, and conducted in five countries.

Table 1 presents summaries of those trials. For some of the earlier studies, multiple published articles have discussed data from the same treatment population and are grouped together. Unless noted otherwise, all of the RCTs reported in Table 1 had the following characteristics in common:

- Subjects met criteria for alcohol dependence according to the *Diagnostic and Statistical Manual of Mental Disorders* 3rd or 4th editions (DSM 1987, 1994), had a recent history of alcohol intoxication, and were between 18 and 65 years of age.
- Subjects were excluded if they had significant liver disease, a psychiatric diagnosis beyond alcohol dependence that was being treated with psychotropic medication, or substance abuse (other than alcohol and excluding nicotine or occasional marijuana use). Pregnant women or those likely to become pregnant while on naltrexone also were excluded.
- Subjects were withdrawn (detoxified) from alcohol and abstinent for a period of time prior to administration of study medication. An exception was the RCT by Heinala et al. (2001), in which prior alcohol abstinence was not required.
- Subjects were randomly assigned to treatment groups and there were no significant demographic differences between groups at the start.
- Naltrexone (NTX) was compared to an identical-appearing inert substance (placebo, PBO). The naltrexone dose was equivalent to 50 mg/day, except in the study by Monterosso et al. (2001; 100 mg/day).
- Neither subjects nor investigators knew if NTX or PBO was being taken (double-blind).

Outcome Measures

Table 1 shows seven outcome measures used to compare the efficacy of naltrexone with placebo. The first two – abstinence and time to first drink – portray alcohol avoidance during the respective trial.

The next four are alcohol consumption outcomes in those subjects who were not abstinent: number of drinking days, drinks per drinking day, relapse rate, and days of heavy drinking. In most stud-

Table 1: RCTs (Randomized, Controlled Clinical Trials) – Naltrexone (NTX) vs Placebo (PBO)

Study* (Authors/Year Country, Sites)	*N*	Study Duration	Type of Psychosocial Therapy	NTX Efficacy Outcomes							Notes
				Abstinence	Time to 1st Drink	Drinking Days	Drinks per Drinking Day	Relapse	Days Heavy Drinking	Craving Score	
O'Malley et al. 1992, 1996a, 1996b; Jaffe et al. 1996. USA-single site.	97	12 wk	CST vs ST	*NS*		++	+	++		+	CST had the significant effects on all outcomes, and results were better in trial completers. During a 24 wk off-tx followup, NTX group had fewer heavy drinking days and fewer redeveloped the full syndrome of alcoholism.
Volpicelli et al. 1992, 1995b. USA-single site.	70	12 wk	TAU	*NS*		+		++		++	NTX had greatest effect in decreasing subsequent drinking once drinking occurred. Besides reducing relapse rate, NTX significantly increased the time to relapse.
Volpicelli et al.1995a, O'Brien et al. 1996. USA-single site.	99	12 wk	TAU	*NS*		+		+		++	NTX reduced the risk of excessive drinking in the event of a slip. (Some subjects in this study overlap with those in the earlier report by Volpicelli et al. 1992.)
Balldin et al. 1997; Bergland 1997, Mansson et al. 1999. Sweden-multisite.	120	24 wk	CST vs ST	*NS*	*NS*	+			+	+	Effects seen only in the NTX/CST group, and persisted during 24 wk off-treatment follow-up period. ST was described as Treatment As Usual by the authors and was abstinence-oriented.
Oslin et al. 1997. USA-single site.	44	12 wk	ST	*NS*	*NS*	+			*NS*	*NS*	Studied older men (mean age 58 years). Relapse was 20% less in NTX group, but was *NS*. NTX significantly reduced relapse progression in subjects sampling any alcohol.
Volpicelli et al. 1997. USA-single site.	97	12 wk	CST	*NS*		+		+		*NS*	Outcomes are expressed for study completers; ITT analyses demonstrated weaker effects of NTX. Subjective "high" associated with drinking was reduced by NTX.
Anton et al. 1999, 2001. USA-single site.	131	12 wk	CST	*NS*	*NS*	+	++	+		*NS*	For those who drank, NTX significantly increased number of days between episodes. By the end of a 14-wk off-tx followup period, significant benefits of NTX had faded.
Chick et al. 2000. UK-multisite.	175	12 wk	TAU	*NS*	*NS*	*NS*	+			++	Outcomes are expressed for completing & compliant subjects. Only craving remained significant in ITT analysis.
Kranzler et al. 2000. USA-single site.	124	12 wk	CST	*NS*	*NS*	*NS*	*NS*	*NS*			NTX-compliant patients had better outcomes, but these were *NS* compared with PBO. Only study in which retention and compliance were significantly lower in NTX group.
Heinala et al. 2001. Finland-single site.	121	12 wk	CST vs ST	*NS*	*NS*			++			NTX/CST had the primary effect. There was a 20 wk followup using NTX on a "targeted" basis, during which reduced relapse rates persisted in NTX/CST group.
Monterosso et al. 2001. USA-single site.	183	12 wk	TAU						+	+	NTX dose was 100 mg/day (50 mg BID). NTX was associated with significantly less clinical deterioration. Positive NTX effects were associated with higher initial craving and a greater family history of alcoholism.
Monti et al. 2001. USA-single site.	128	12 wk	CST vs ST		*NS*		+	*NS*	+	+	More significant effects seen in patients compliant with medication and in the CST group. Compliant patients also had fewer relapses, but was *NS*. Beneficial NTX effects faded during off-tx followup at 6 and 12 months.
Morris et al. 2001. Australia-single site.	111	12 wk	CST	*NS*		*NS*	++	++			Outcomes are for study completers. ITT analysis for relapse was *NS*, but time to relapse was highly significant.
Krystal et al. 2001. USA-multisite.	627	13 wk & 52 wk	ST			*NS*	*NS*	*NS*			NTX tx was either 13 wk or 52 wk vs PBO 52 wks. ITT analyses shown; however, in all groups, more compliant subjects and those attending more therapy or AA sessions had better outcomes.

*Multiple analyses of the same patient population are grouped together as one study. NTX dose = 50 mg/day, except Monterosso et al. 2001.
Psychosocial Therapy: CST = Coping Skills (relapse prevention) Therapy; ST = Supportive (abstinence-oriented) Therapy; TAU = Treatment As Usual or "standard therapy."
Outcomes: Favoring NTX: + - p< 0.05; ++ - p< 0.01. *NS* = No Significant Difference (equivalent). Blank means the outcome was not reported in the study.
Abbreviations: NTX = naltrexone; PBO = placebo; wk = week; ITT = intention to treat (includes dropouts & noncompliers); tx = treatment

ies, relapse was defined as having 5 or more drinks on any single occasion for men and 4 or more drinks for women, or drinking 5 or more days within one week, or attending a treatment session intoxicated. "Heavy" drinking was commonly defined as more than five drinks, which would make this measure equivalent to a relapse day.

Finally, nine studies evaluated craving, although this was variously defined by investigators using different assessment instruments to arrive at a patient-determined score. Often, craving at the beginning of treatment was compared with craving at end of treatment to note differences.

Unfortunately, there is no standard set of efficacy outcome measures used in all studies. Blank boxes in Table 1 indicate those measures not mentioned in the respective published RCT reports.

Adjunctive Psychosocial Therapy

Researchers have paired naltrexone and placebo with different psychosocial therapies to compare the combined efficacy. Table 1 indicates three general types that have been variously described and used:

Supportive Therapy (ST) – focuses on abstinence from alcohol, without teaching specific coping skills to avoid relapse. ST may be 12-step oriented and include encouragement to attend Alcoholics Anonymous meetings.

Coping Skills Therapy (CST) – also called relapse prevention therapy or cognitive behavioral therapy (CBT) – teaches patients ways of dealing with situations and feelings that provoke a return to drinking, and how to keep a drink ("slip") from leading to a relapse.

Therapy As Usual (TAU) – is the "Standard Therapy" at the particular study center and may mix components of CST and/or ST modalities. If it could be determined that TAU seemed slanted toward either supportive or coping skills therapy, the psychosocial therapy was respectively coded ST or CST in Table 1.

Research teams appeared to modify psychosocial approaches based on their clinical experience, so there may have been some differences in how the same type of therapy was structured in various RCTs. For the two multisite RCTs, there also is the question of whether the same therapy was delivered consistently at various locations by different therapists.

Summary of RCT Results

Drinking Outcomes

Outcome values in Table 1 are denoted in terms of the statistical significance of data comparing naltrexone with placebo (see sidebox on "Significance"). Thus, on each particular measure, the effects of naltrexone were either comparable to placebo (*NS* or nonsignificant), of significant advantage (+), or very significantly beneficial (++). In no case was naltrexone of less benefit than placebo.

Figure 1 graphically summarizes the advantages of naltrexone relative to placebo. It represents for each outcome an averaging of results across all RCTs that reported the measure.

Naltrexone does not appear to exert an influence compared with placebo on maintaining abstinence or in postponing the first drink in those patients who cannot avoid alcohol. However, *there is clear and consistent evidence that naltrexone is significantly beneficial in helping those patients who cannot remain abstinent to reduce their drinking behaviors. They drink less often and in lower quantities, avoiding full-blown relapse*.

Volpicelli et al. (1992) reported that naltrexone appeared to be most effective in decreasing drinking in subjects who had at least one alcohol-sampling episode or "slip." Whereas, almost all (95%) placebo-treated subjects who slipped proceeded to relapse, those taking naltrexone typically drank less during a slip and only half of them actually relapsed to heavy drinking.

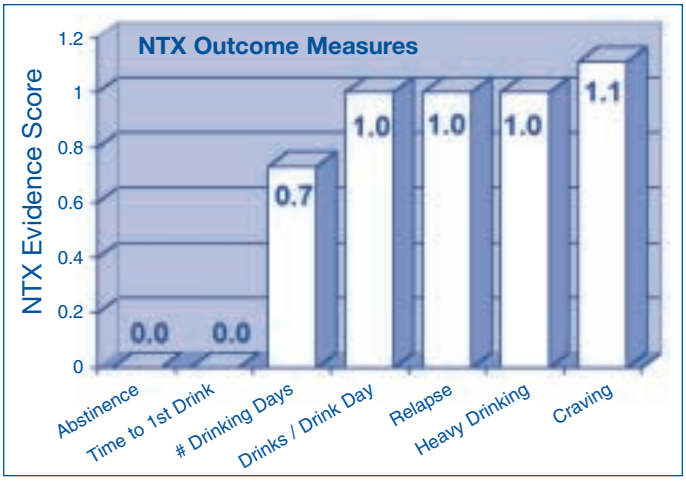

Figure 1: NTX score measures the strength of evidence favoring naltrexone, represented by averaging efficacy scores for all RCTs in Table 1 that measured the particular outcome. Points were assigned as: 0 (NS), 1 (+), and 2 (++). Score of 1 or above represents statistically significant advantage of NTX over PBO.

Volpicelli and colleagues (1995a, 1995b) also observed that naltrexone-treated subjects reported that the subjective "high" or eupho-

The Significance of "Significance"

The RCTs evaluated for this report compared naltrexone with placebo on each particular outcome measure studied to determine superiority of one over the other. Statistical analyses were used by the researchers to evaluate and quantify the significance of any differences, with a standard cut-off point for significance of $p < 0.05$ (designated '+' in Table 1).

Probability- or p-values are considered in this report as a relative indicator of effect size and strength. In a broad sense, a $p < 0.05$ means that the observed benefit for naltrexone on the particular outcome measure is large enough to be considered a true and "significant" advantage; that there is less than a 5% *probability* that the effect occurred merely due to chance. Put another way, with a p-value of 0.05 or less there is at least a 95% certainty that the observed effect is "real" and valid, rather than being merely a coincidence.

Probability-values less than 0.01 (designated '++' in Table 1) suggest the effect favoring naltrexone is even stronger. There is 99% certainty the effect is not due to chance.

Conversely, any p-value greater than the 5% cut-off point (e.g., $p = 0.06$), suggests that differences between groups may be due merely to chance and are not statistically significant (designated *NS* in Table 1). In essence, the effect of naltrexone, although possibly appearing to be favorable in terms of absolute value, must be considered as no better than placebo on the particular measure.

Hypothetically, it is possible to have negative effects; that is, naltrexone producing worse results than those observed in the placebo group. However, this was not observed in any of the clinical RCTs to date.

Also, it is important to note that an outcome may not be statistically significant but still have *clinical significance*. For example, due to study limitations or variability in results, an overall 20% reduction in relapse rate associated with naltrexone may not reach statistical significance (as in the study by Oslin et al. 1997). However, this still can be clinically valuable by preventing full-blown relapse in one additional patient for every five treated with naltrexone.

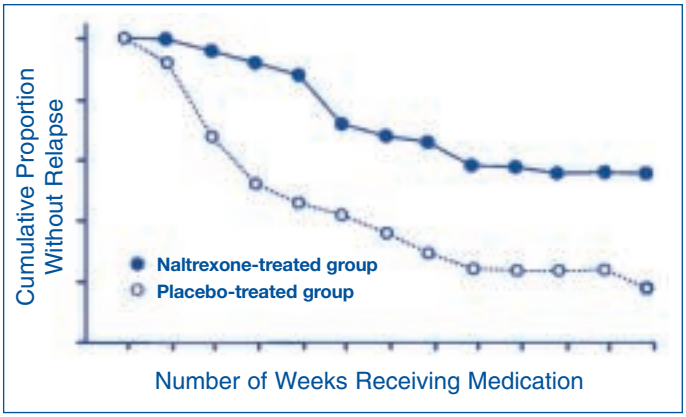

Figure 2: Progressive proportions of patients without relapse – "survival analysis" – for NTX vs PBO groups, significantly favoring NTX (data from Volpicelli et al. 1995a).

ria produced by alcohol was significantly less than usual. This is consistent with naltrexone's action in blocking opioid receptors and diminishing pleasurable effects associated with alcohol drinking.

Besides reducing overall relapse rates, naltrexone also appears to significantly prolong the relapse-free time in those who eventually do relapse. **Figure 2** depicts the typical relationship plotted over time, called a "survival curve," comparing naltrexone with placebo (Morris et al. 2001, Volpielli et al. 1995a).

Furthermore, Anton et al. (1999) found that naltrexone effectively doubled the time between a first relapse (or heavy drinking day) and a second such episode. Taken together, *naltrexone's effects in stemming relapse to heavy drinking allow more quality time for psychosocial therapy to be productive*.

Alcohol Craving

Alcohol craving was measured and reported in 9 of 14 RCTs. As Figure 1 indicates, naltrexone therapy quite significantly reduced craving.

Various researchers have noted that patients with higher initial craving appear to derive greatest benefit from naltrexone (Jaffe et al. 1996; O'Malley et al. 1992; Monterosso et al. 2001). Volipicelli (2001) recently observed that naltrexone seems to have an immediate effect of reducing the urge to drink and this can be very useful in helping patients focus on other issues besides alcohol craving, especially during early stages of recovery.

There is the question of why this reduced craving effect did not enhance abstinence in the RCTs. First, craving may be but one drive motivating drinking. Second, heavy drinking may itself induce craving and, since naltrexone-group patients drank less often and in lower quantities, this helps explain their lower craving scores but only equivalent abstinence compared with placebo-treated subjects (Chick et al. 2000).

Impact of Psychosocial Therapy

RCT results suggest that the efficacy of naltrexone can be dependent on the type of psychosocial therapy with which it is paired. As Table 1 demonstrates, supportive, abstinence-oriented, therapy (ST) was largely ineffective in conjunction with naltrexone on any outcome measures, with the single exception of the trial by Oslin et al. (1997) in older patients.

Oslin and colleagues found naltrexone significantly effective in reducing the extent of drinking and progression to relapse in subjects sampling alcohol. This was unlikely related to the supportive psychosocial therapy, since its goal was to avoid any drinking at all.

In general, coping skills therapy (CST), emphasizing relapse-prevention strategies, proved much more effective than supportive therapy in achieving positive outcomes associated with naltrexone. "Treatment as usual" (TAU) therapies also were effective, and observed primarily in three investigations at University of Pennsylvania treatment centers (Volpicelli et al. 1992, 1995a; Monterosso et al. 2001). The approach here emphasized support of abstinence, including participation in group therapy stressing motivational enhancement, relapse prevention skills, and compliance with the medication regimen. Therapy was customized to patient needs and seemed to benefit from a synergism of the best that supportive and coping skills therapy might offer individually.

Contrary Evidence

Only 2 of 14 RCTs to date have failed to demonstrate significantly favorable effects of naltrexone: Kranzler et al. 2000 and, most recently, Krystal et al. 2001.

Krystal and colleagues raised doubts about the utility of naltrexone in older patients with chronic, severe alcohol dependence. They studied a population of men averaging 49 years of age and 20 years of heavy drinking. However, their findings conflict with other RCTs, involving almost identical populations of older males with long drinking histories, which reported significantly favorable results for naltrexone in terms of relapse, frequency of drinking, and quantity of alcohol consumed (Morris et al. 2001; Oslin et al. 1997).

A critical factor in the RCT by Krystal et al. was the adjunctive use of strictly abstinence-based therapy focusing on 12-step facilitation counseling. In prior research, this was not found to be effective in combination with naltrexone. Still, these researchers did observe that naltrexone treatment extended the time to relapse by nearly 70% and this might have been a significant benefit clinically. A survival analysis of the sort shown in Figure 2 was not reported.

Finally, the Krystal et al. trial was conducted at 15 Veterans Affairs medical centers, so the quantity, quality, and consistency of psychosocial therapy across treatment centers is questionable. This intersite variability combined with relatively small numbers of patients at each center might have led to reduced effect sizes.

This phenomenon also was evident in a multisite RCT by Chick et al. (2000) in which psychosocial therapy reportedly varied widely by center and naltrexone benefits were most significant for those patients staying in treatment and taking medication. In their trial, Krystal et al. did not report on the subgroup of completing and compliant patients.

The earlier Kranzler et al. (2001) trial, was the only RCT to date in which naltrexone-treated patients exhibited significantly less medication compliance and more study withdrawals than the placebo group. In all other trials reporting the measures, naltrexone treatment was associated with greater or equivalent compliance and retention compared with placebo.

Also in contrast to other RCTs, Kranzler and colleagues reported significantly more side effects with naltrexone, primarily gastrointestinal-related (eg, nausea, vomiting, diarrhea). They observed that subjects with more GI complaints pretreatment were more susceptible to subsequent GI symptoms when treated with naltrexone, resulting in less medication compliance and, eventually, early withdrawal from the study. Patients who were able to tolerate naltrexone had better outcomes, but the trends were not statistically significant.

Although standard inclusion/exclusion criteria were used for subject selection by Kranzler et al., they reported enrolling 183 of

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