Forum

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).

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 desir-

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

able 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
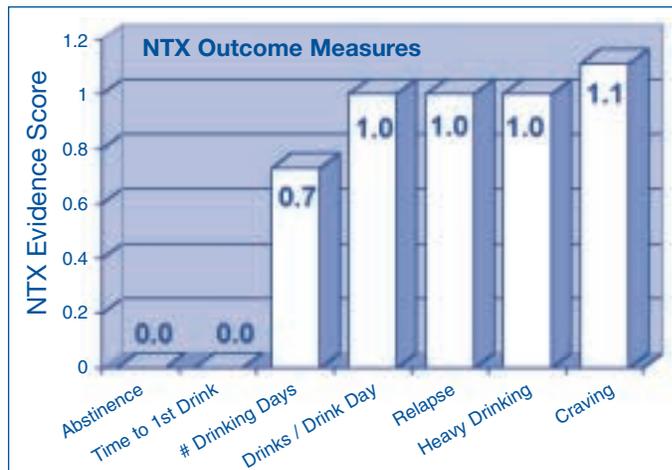

Figure 1: NTX score measures the strength of evidence favoring naltrexone, represented by averaging efficacy scores for all RCTs in Table 1 that measured the particular outcome. Points were assigned as: 0 (NS), 1 (+), and 2 (++). Score of 1 or above represents statistically significant advantage of NTX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

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.

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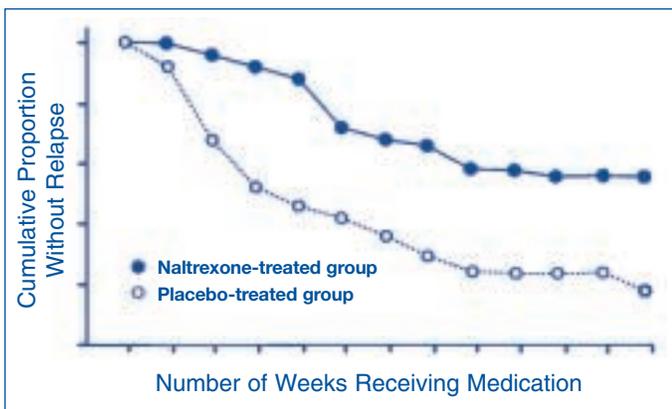
Figure 2: Progressive proportions of patients without relapse – "survival analysis" – for NTX vs PBO groups, significantly favoring NTX (data from Volpicelli et al. 1995a).

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 psy-

chosocial 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

194 persons recruited (94%). This is an unusually high acceptance rate and it is possible that the study population was biased in some way, resulting in a greater proportion of subjects with predispositions to adverse reactions when taking psychoactive medications. For example, a separate arm of this trial investigated possible benefits of nefazodone, an antidepressant, and also observed significant increases in side effects in that group.

On the basis of these two trials, any deficiencies of naltrexone's efficacy in particular patient populations cannot be concluded.

Interacting Factors

The efficacy of naltrexone in treating alcoholism has been demonstrated across a range of treatment programs, internationally, using differing psychosocial therapies, and in diverse patient populations. **Table 2** summarizes demographic data for all RCT participants.

It should be noted, that RCTs to date have focused on males between 39 and 58 years of age, on average. Other factors also may interact to influence efficacy outcomes.

Importance of Retention/Compliance

Naltrexone appears to be especially effective for patients who stay in treatment and comply with medication regimens (Chick et al. 2000; Monti et al. 2001; O'Brien et al. 1996; O'Malley et al. 1992; Volpicelli et al. 1997). As Table 2 shows, naltrexone was associated with slightly greater retention and compliance than placebo, although this trend was not statistically significant and there was a wide range across studies.

Most RCTs reported "intention-to-treat" (ITT) analyses that included data from *all* patients, whether or not they remained in the study or took their medication. This tends to understate medication efficacy and might have occurred, for example, in the Oslin et al. (1997) trial. There was very low treatment compliance (less than a third of patients in either group) and consequently few significant benefits of naltrexone were reported in the ITT analysis. (Oslin and colleagues also used an unusual dosing schedule: every other day – 100, 100, 150 mg – considered equivalent to 50 mg/day).

Four of the naltrexone RCTs – Chick et al. 2000; Morris et al. 2001; O'Malley et al. 1992; Volpicelli et al. 1997 – reported analyses focusing on patients who completed the trials and were compliant with medication regimens. These analyses, known as "per protocol," demonstrated significant effects of naltrexone and are reflected in Table 1.

This apparently did not slant the summarization of outcomes in this report, since a recent meta-analysis by Streeton and Whelan (2001) using only ITT data reached the same conclusions as presented above in figure 1. That is, *naltrexone significantly improves outcomes in terms of alcohol consumption, relapse to heavy drinking,*

Measure	No.*	Mean**	Range
Males	14	84%	71% - 100%
Age (years)	13	44.5	39 - 58
Married	12	42%	16% - 73%
Employed	9	62%	27% - 84%
Years Drinking	7	21	15 - 30
Drinks Per Day Prior	7	12	10 - 13.5
Study Retention	12		
Naltrexone		72%	41% - 91%
Placebo		70%	42% - 91%
Medication Compliance***	10		
Naltrexone		66%	32% - 98%
Placebo		64%	31% - 98%

and alcohol craving.

It should be noted that advantages of naltrexone are also based on its specific nature, rather than simply study retention and/or medication compliance. As Litten and Allen (1998) have observed, in most RCTs, patients do better with naltrexone than placebo-treated subjects who are equally retained and compliant.

Long-Term Efficacy

Six of 14 RCTs examined long-term effects of naltrexone during followup periods ranging from 14 to 40 weeks after the end of drug treatment (ie, off-treatment). Results suggest that naltrexone is effective as long as it is taken, but benefits begin fading once the medication is terminated (see Table 1 "Notes" – Anton et al. 1999; Heinala 2001; Krystal et al. 2001; Monti et al. 2001; O'Malley et al. 1996a; Mansson et al. 1999).

Some researchers have recommended a minimum of six months treatment with naltrexone (Naltrexone…1997; Volpicelli 2001). It also has been proposed that, following a course of daily treatment, naltrexone can be useful on an as-needed or short-term basis; using the drug during high-risk periods or after a resumption of drinking following successful abstinence (O'Malley 1998; Volpicelli 2001).

In their RCT, Heinala et al. (2001) included a 20-week "targeted" naltrexone period following daily dosing. Subjects were instructed to take naltrexone only when craving alcohol and/or drinking was likely. This intervention was of significant benefit in warding off relapse. Others have reported using this targeted-naltrexone approach effectively in reducing all measures of alcohol consumption (Kranzler et al. 1997).

Naltrexone Dose

Most research on naltrexone for alcoholism has used a 50 mg/day dosing schedule. This is comparable to daily naltrexone doses used for opioid-abstinence therapy, and is believed to be optimal for opiate-receptor blockade (Saitz and O'Malley 1997).

Individualized dosing regimens have been investigated and recommended for selected patients, ranging from 12.5 mg/day to 150 mg/day (Croop et al. 1997, O'Malley 1998; Saitz and O'Malley 1997). Lower doses are sometimes initiated to minimize potential side effects and then gradually increased.

In the RCT by Monti et al. (2001), patients were started at 25 mg/day for the first two days and then given 25 mg twice daily. Although the authors did not report on adverse events, minimization of side effects with this dosing schedule might have contributed to an unusually high naltrexone-group retention rate (91%) in this trial.

Current thinking is that doses of 100 mg/day up to 150 mg/day can be safely and effectively used in many patients (Volpicelli 2001). Monterosso et al. (2001) administered 100 mg/day (50 mg BID) in their RCT, and retention/compliance rates were well above average.

Naltrexone in Dual-Diagnosed Patients

RCTs reviewed in this report primarily included subjects without substantial psychiatric comorbidity, yet such disorders are common in alcoholics (Bowden 1997; Khantzian 1997). An exception was the trial by Morris et al. (2001), in which more than half of subjects had psychiatric diagnoses concurrent with alcoholism. These researchers observed that significant benefits of naltrexone were independent of such coexisting disorders.

In an observational study (non-RCT), Salloum (1998) evaluated naltrexone in depressed alcoholics who had failed to abstain from alcohol despite treatment with antidepressants. There were significant decreases in alcohol use and in cravings with naltrexone, plus improvements in depressive symptoms and overall functioning. Similarly, in a study of mentally ill alcoholic patients taking multiple psychiatric medications, Maxwell and Shinderman (2000) found that naltrexone produced a 75% reduction in alcohol consumption in more than 80% of patients.

Pretreatment Abstinence

Almost all RCTs required alcohol abstinence prior to beginning naltrexone therapy – ranging from a few days to several weeks. This may have affected some results, especially time to first drink, retention, and medication compliance (Streeton and Whelan 2001).

However, Heinala et al. (2001), in Finland, enrolled nonabstinent subjects. Naltrexone was well-tolerated and significantly reduced relapse rates, while also achieving above average study-retention (84%). Further RCTs investigating this approach seem warranted.

Safety Profile

At usual doses, there have not been any reported serious adverse events directly attributed to naltrexone in the treatment of alcoholism (Highlights… 2000). Overall, RCTs to date have demonstrated that the incidence of subjects reporting side effects or discontinuing from naltrexone treatment due to such effects was roughly equivalent to placebo (Streeton and Whelan 2001).

Naltrexone has been associated with increased nausea and vomiting. Less common side effects include headache, dizziness, fatigue, or insomnia. These effects are usually mild, often single occurrences, and resolve soon after dose stabilization (Lynch et al. 1998; Naltrexone… 1997; O'Malley et al. 1992; Salloum et al. 1998; Volpicelli et al. 1992).

Naltrexone undergoes first-pass metabolism in the liver, although it does not interact with the P450 enzyme system (Naltrexone… 1997). Product literature specifies that naltrexone is contraindicated in patients with acute hepatitis or liver failure (DEPADE® 2000; ReVia® 1997), and liver function monitoring is recommended in some cases (O'Malley 1998).

However, in the absence of preexisting hepatic dysfunction, naltrexone at doses up to 200 mg/day has not been associated with liver damage (Croop et al. 1997; Marrazzi et al. 1997). In some studies, naltrexone-treated patients experienced an improvement in liver enzyme values (Volpicelli et al. 1992; Volpicelli 2001), most likely associated with abstinence or reduced alcohol consumption.

> **Naltrexone appears to break the vicious, self-destructive cycle in alcoholics whereby one drink leads to another.**

Practice Implications

Consistent with a prior systematic review of naltrexone trials by the Agency for Health Care Policy and Research (Garbutt et al. 1999), this present report concludes:

• Randomized controlled trials of naltrexone in the treatment of alcoholism are recent, extensive, and of good quality.

• There is good evidence that naltrexone *significantly reduces* alcohol relapses, the frequency and quantity of alcohol consumption in those who do drink, and alcohol craving.

In brief, naltrexone appears to break the vicious, self-destructive cycle in alcoholics whereby one drink leads to another.

Harm Reduction Strategy

Just as with the medication management of other serious chronic illness, a more pragmatic strategy, using naltrexone, seeks to induce remissions when possible, limit relapses, slow deterioration, and support patients in improving their quality of life (Olson and Willenbring 1999).

This approach is known as "clinical harm reduction," to distinguish it from the "abstinence-or-fail" outlooks of other alcoholism treatments (Freed and York 1997). According to the evidence reviewed in this report, naltrexone can be an important adjunct in fostering harm-reduction as a component of alcoholism-recovery goals, including eventual sustained abstinence.

Clinical Action Steps

Treatment plans using naltrexone ideally respond to individual patient needs. In that regard, practitioners may want to consider the following evidence-based conclusions:

1. Naltrexone is effective in a variety of alcoholism-treatment settings where motivation to stay in treatment, avoid relapses to heavy drinking, and take medications is supported by appropriate psychosocial therapy.
2. Naltrexone may be especially useful in repeat alcohol relapsers, by reducing the frequency and scope of drinking episodes to allow continued progress toward recovery goals.
3. Individualized naltrexone dosing regimens can be of benefit, possibly starting at lower doses and titrating upward.
4. Alcohol abstinence prior to initiating naltrexone therapy may not be necessary in all cases.
5. Extended daily use of naltrexone may be helpful: longer-term therapy (6 to 9 months) can be more effective than short-term (3 months).
6. Following daily therapy, naltrexone might be used on an as-needed, "targeted," basis indefinitely.

Research results require careful consideration. Statistical significance of outcomes is important but can be misleading, for even small improvements can be *clinically and socially significant* when each percentage point may represent thousands of lives benefitted. As Enoch Gordis, MD, former Director of the National Institute on Alcohol Abuse and Alcoholism (NIAAA), once observed, "While not a 'magic bullet,' naltrexone promises to help many patients in their struggle against chronic relapsing disease" (Naltrexone…1995).

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