Adherence Monitoring in Naltrexone Pharmacotherapy Trials: A Systematic Review*

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ABSTRACT. Objective: The efficacy of naltrexone (Revia, Vivitrol) for the treatment of alcohol dependence exhibits a high degree of heterogeneity. The aim of the current study was to evaluate the extent to which variability in patient adherence to treatment contributed to the range of clinical responses observed during naltrexone treatment. **Method:** A systematic review was conducted of efficacy trials of naltrexone for the treatment of alcohol dependence to evaluate the level of adherence monitoring. **Results:** Of 49 identified trials, 22 (49%) met the inclusion criteria of being randomized, double-blind, placebo-controlled trials that reported adherence. The "adherence-assurance score" of these trials was calculated as a function of the frequency with which "low," "moderate," or "high" confidence levels of adherence monitoring were used. Of these 22 randomized, controlled trials, only 3 (14%) met criteria for high levels of adherence assurance, 5 (23%) met medium adherence-assurance criteria, and 14 (64%) met low adherence criteria. Of the three high-assurance studies, one used direct supervision of thrice-weekly oral dosing of naltrexone, and two used extended-release injectable formulations of naltrexone administered once per month. The Spearman correlation between risk ratios for return to heavy drinking (for naltrexone vs. placebo) and the level of adherence assurance (low vs. medium vs. high) was significant ($r = -.62$, $p = .025$). **Conclusions:** These findings suggest that the modest effect sizes for naltrexone reported in systematic reviews and meta-analyses may be attributable, at least in part, to variability in naltrexone adherence rates. High-assurance adherence strategies should be standard practice in clinical trials of medications being evaluated for the treatment of alcohol dependence. (*J. Stud. Alcohol Drugs, 72,* 1012–1018, 2011)

MEDICATION ADHERENCE (sometimes called "compliance") can be defined as taking a medication according to the recommended dose and schedule. Medication nonadherence is a common problem and is associated with medication variables (presence of side effects, need for frequent dosing, use of oral medication), illness variables (chronicity, current symptom severity, presence of comorbid illnesses requiring additional treatment), and patient variables (cognitive impairment, lack of insight, presence of comorbid depression and other psychological problems; Cramer and Rosenheck, 1998; DiMatteo, 2004; Osterberg and Blaschke, 2005; Pettinati et al., 2006; Substance Abuse and Mental Health Services Administration [SAMHSA], 2006). All of these factors are applicable to patients with alcohol dependence, and they contribute to the unusually high medication-nonadherence rates that have been reported in the medication treatment of alcohol-dependent patients (Cramer and Rosenheck, 1998; DiMatteo, 2004; Osterberg and Blaschke, 2005; Pettinati et al., 2006; SAMHSA, 2006).

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Naltrexone is an opioid antagonist medication with high affinity for the μ-opioid receptor. Oral naltrexone (Revia) was granted Food and Drug Administration (FDA) approval in the United States in 1994 for the treatment of alcohol dependence. An injectable extended-release form of naltrexone (Vivitrol) received FDA approval for alcohol dependence treatment in 2004. Systematic reviews and meta-analyses (Bouza et al., 2004; Kranzler and Van Kirk, 2001; Pettinati et al., 2006; Roozen et al., 2006; Rösner et al., 2010; Srisurapanont and Jarusuraisin, 2005; Streeton and Whelan, 2001) have found oral naltrexone treatment to be efficacious for the treatment of alcohol dependence but with relatively small effect sizes. In post hoc subgroup analyses, medication nonadherence has been shown to contribute to the reduced effect sizes observed for oral naltrexone (Chick et al., 2000; Krystal et al., 2001; Pettinati et al., 2000). Similarly, Baros et al. (2007) reported a notably larger effect size (.58) in patients who received stringent medication monitoring (medication event monitoring system [MEMS] + urine riboflavin adherence monitoring) compared with the modest effect size (.18) observed in the overall intent-to-treat population. Analyses of prescription databases confirm a low level of persistence on oral naltrexone treatment, with the majority of patients discontinuing medication by 1 month (Harris et al., 2004; McCarty et al., 2009) and more than 75% discontinuing by 6 months (Chalk et al., 2011; Hermos et al., 2004; Kranzler et al., 2008).

Because of the significant impact of nonadherence on clinical outcome in alcohol-dependent patients treated

with naltrexone, it is important to accurately measure adherence. In clinical trials, several methods are commonly used to monitor medication adherence, including patient self-report; counts of returned pills; use of blister packs; electronic monitoring of pill bottle opening (MEMS caps); the use of a biochemical marker, such as riboflavin, that is consumed along with the medication; supervised dosing to ensure consumption; monitoring of medication blood levels; and injection of once-monthly extended-release formulations.

We report here the results of a systematic review of how rigorously adherence was monitored in published naltrexone clinical trials, and how the level of adherence monitoring correlated with treatment effect size.

Method

Clinical trials of naltrexone were identified through four meta-analyses (Bouza et al., 2004; Kranzler and Van Kirk, 2001; Srisurapanont and Jarusuraisin, 2005; Streeton and Whelan, 2001) and three systematic reviews (Pettinati et al., 2006; Roozen et al., 2006; Rösner et al., 2010) of pharmacological treatment for alcohol dependence. In addition, a search was performed in PubMed using the search terms *naltrexone* and *alcohol dependence.* The search was limited to double-blind, placebo-controlled efficacy studies with a duration of 12 weeks or longer in human subjects with alcohol dependence or abuse, published in the English language. Studies involving patients with comorbid substance dependencies or psychiatric conditions were included.

The study applied a metric "adherence-monitoring score" to the methods used to monitor naltrexone treatment adherence in each of the qualifying trials. First, the adherence-monitoring method was assigned a "low," "medium," or "high" confidence level, based on its susceptibility to circumvention by the patient. Study methods that lacked direct supervision (i.e., self-report, pill count, blister pack) were assigned a low confidence level. Measurement of a moderately reliable analyte (i.e., riboflavin tracer in urine [Del Boca et al., 1996]) and methods that would require considerable patient effort to circumvent (i.e., MEMS caps; Feinn et al., 2003) were assigned a medium confidence level. Supervised administration of medication by a treatment provider (i.e., supervised dosing and use of extended-release injectable formulations [Gastfriend, 2011]) or measurement of a highly reliable analyte in the blood or urine (i.e., 6β-naltrexol [Cone et al., 1974; Meyer et al., 1984]) were assigned a high confidence level.

Second, an adherence-assurance score for each qualifying study using a single adherence-monitoring method was calculated using the following formula:

adherence-assurance score = (monitoring confidence level) × (monitoring frequency),

where monitoring confidence levels have been assigned a numerical value of 1 (low), 2 (medium), or 3 (high), and monitoring frequency equals the percentage of dosing days on which the monitoring method was used.

For studies using multiple monitoring methods, the following formula was used:

adherence-assurance score = (monitoring confidence level for Method A) × (percentage of dosing days Method A used) + (monitoring confidence level for Method B) × (percentage dosing days Method B used).

Each positive test for 6β-naltrexol in plasma or urine or for riboflavin in urine was considered to provide confirmation for only a single dosing day because of the complex nature of inferring multiple administrations from an analyte concentration at a single time point. For trials that reported adherence rates and lacked a specific monitoring method frequency, adherence assurance was calculated as a lower limit, based on the available information. When multiple monitoring methods were used concurrently, scoring for that time interval was based on the highest confidence level. No additional assurance was allotted when methods having the same confidence level (e.g., pill counts and self-reports) were used concurrently. Calculated raw scores were normalized to 100%. Analyzed trials were ranked by adherence-assurance scores and assigned an adherence-assurance rating of high (3), medium (2), or low (1), based on their rank.

The relationship between the adherence-assurance score and treatment efficacy was evaluated with a Spearman correlation analysis. Efficacy was examined in terms of the risk ratio for return to heavy drinking (i.e., percentage of naltrexone-treated patients who returned to heavy drinking divided by the percentage of placebo-treated patients who returned to heavy drinking). Risk ratios were obtained from a Cochrane meta-analysis (Rösner et al., 2010) supplemented by additional values calculated from data from the original articles in the cases where the studies were not included in the Cochrane meta-analysis (Rösner et al., 2010). The results of two trials were not reported in a format that permitted calculation of heavy drinking risk ratios (Garbutt et al., 2005; Monterosso et al., 2001). The adherence-assurance ratings were converted into a 3-point scale (3 = high; 2 = medium; 1 = low), and a Spearman correlation was calculated relating the heavy drinking risk ratios to the adherence-assurance rating scale.

Results

A total of 49 trials assessing naltrexone efficacy for alcohol dependence were identified for this review. Twenty-eight (57%) of these were randomized, double-blind, placebo-controlled trials of at least 12 weeks' duration and published in English. Of these 28 "qualifying" trials, 22 (79%) met the

TABLE 1. Adherence-assurance rankings for qualifying studies (n = 22 studies)

	Monitoring method A				Monitoring method B						
Study	Method	Confidence[a]	Frequency (%)	Subscore	Method	Confidence	Frequency (%)	Subscore	Raw score (%)	Normal score (%)	Adherence-assurance rating
Garbutt et al., 2005[b]	Extended release	3	100	300	–	–	–	–	300	100	High
Kranzler et al., 2004[c]	Extended release	3	100	300	–	–	–	–	300	100	High
Oslin et al., 1997	Direct supervision	3	100	300	–	–	–	–	300	100	High
Krystal et al., 2001	6β-naltrexol (plasma)	3	1	3	MEMS caps	2	99	198	201	67	Medium
O'Malley et al., 2003 (Trial 2)	MEMS caps	2	100	200	–	–	–	–	200	67	Medium
O'Malley et al., 2003 (Trial 3)	MEMS caps	2	100	200	–	–	–	–	200	67	Medium
Petrakis et al., 2005	MEMS caps	2	100	200	–	–	–	–	200	67	Medium
Guardia et al., 2002	Intermittent direct supervision	3	43	129	Pill counts	1	57	57	186	62	Medium
Monti et al., 2001	Riboflavin	2	10	20	Pill counts	1	90	90	110	37	Low
Chick et al., 2000	6β-naltrexol (urine)	3	N.R.	Unknown	Pill counts	1	100 – N.R.	<100	>100	>33	Low
Gastpar et al., 2002	6β-naltrexol (urine)	3	N.R.	Unknown	Pill counts	1	100 – N.R.	<100	>100	>33	Low
Anton et al., 2006	Blister packs	1	100	100	–	–	–	–	100	33	Low
Balldin et al., 2003	Pill counts	1	100	100	–	–	–	–	100	33	Low
Kiefer et al., 2003	Pill counts	1	100	100	–	–	–	–	100	33	Low
Monterosso et al., 2001	Blister packs	1	100	100	–	–	–	–	100	33	Low
Morley et al., 2006	Pill counts	1	100	100	Self-report	1	N.R.	0	100	33	Low
Morris et al., 2001	Pill counts	1	100	100	–	–	–	–	100	33	Low
Petrakis et al., 2004	Pill counts	1	100	100	–	–	–	–	100	33	Low
Volpicelli et al., 1997	Pill counts	1	100	100	Self-report	1	100	0	100	33	Low
Schmitz et al., 2004	Direct supervision	3	24	72	Riboflavin	2	N.R.	Unknown	>72	>24	Low
Anton et al., 1999	Riboflavin	2	14	28	–	–	–	–	28	9	Low
O'Malley et al., 1992	Riboflavin	2	7	14	–	–	–	–	14	5	Low

Notes: N.R. = not reported. [a]Confidence: 1 = low (self-report, pill counts, blister packs); 2 = medium (MEMS [Medication Event Monitoring System], riboflavin testing); 3 = high (supervision, extended-release formulation); [b]Garbutt et al. (2005) used the extended-release formulation developed by Alkermes, Inc., Cambridge, MA; [c]Kranzler et al. (2004) used the extended-release formulation developed by DrugAbuse Sciences, Inc., Hayward, CA.

additional criterion of reporting adherence results and were included in the analysis. Six qualifying trials did not report adherence and thus were excluded from the analysis. The 22 analyzed studies spanned the period from 1992 to 2006, had sample sizes ranging from 31 to 618 patients treated with active naltrexone, had treatment durations of 12 to 52 weeks, and used doses ranging from 50 to 100 mg/day for oral naltrexone and from 150 to 380 mg/month for extended-release naltrexone. Twenty-one (43%) of the 49 identified efficacy studies did not meet the qualifying criteria. The reasons for exclusion included study design (seven open-label trials and six single-label trials), durations of less than 12 weeks (seven trials), and publication in a language other than English (one trial). A detailed summary of the qualifying trials and of the studies that were included and excluded is available on request from the first author.

High adherence-assurance scores were obtained for only a small fraction of the trials under consideration. Of the 22 qualifying trials reporting adherence, only 3 (14%) displayed high ratings for adherence assurance (Table 1 and Figure 1). These 3 represented only 6% of the 49 efficacy trials of naltrexone for alcohol dependence identified in the present study (Figure 1). An additional 5 trials (23% of 22) displayed medium ratings for adherence assurance, whereas the remaining 14 trials (64% of 22) displayed low ratings for adherence assurance (Table 1 and Figure 1).

Trials reviewed here used diverse adherence-monitoring strategies. As shown in Table 1, trials that received a high rating for adherence assurance used high-confidence monitoring methods on a daily basis throughout. Several trials received medium or low ratings for adherence assurance despite the use of high-confidence methods (typically 6β-naltrexol measurement) because such methods were used at low (or unreported) frequencies (Table 1). Of the 22 qualifying trials reporting adherence, 8 (36%) used multiple methods to monitor adherence; nevertheless, in 6 of these, the adherence-assurance rating was still low.

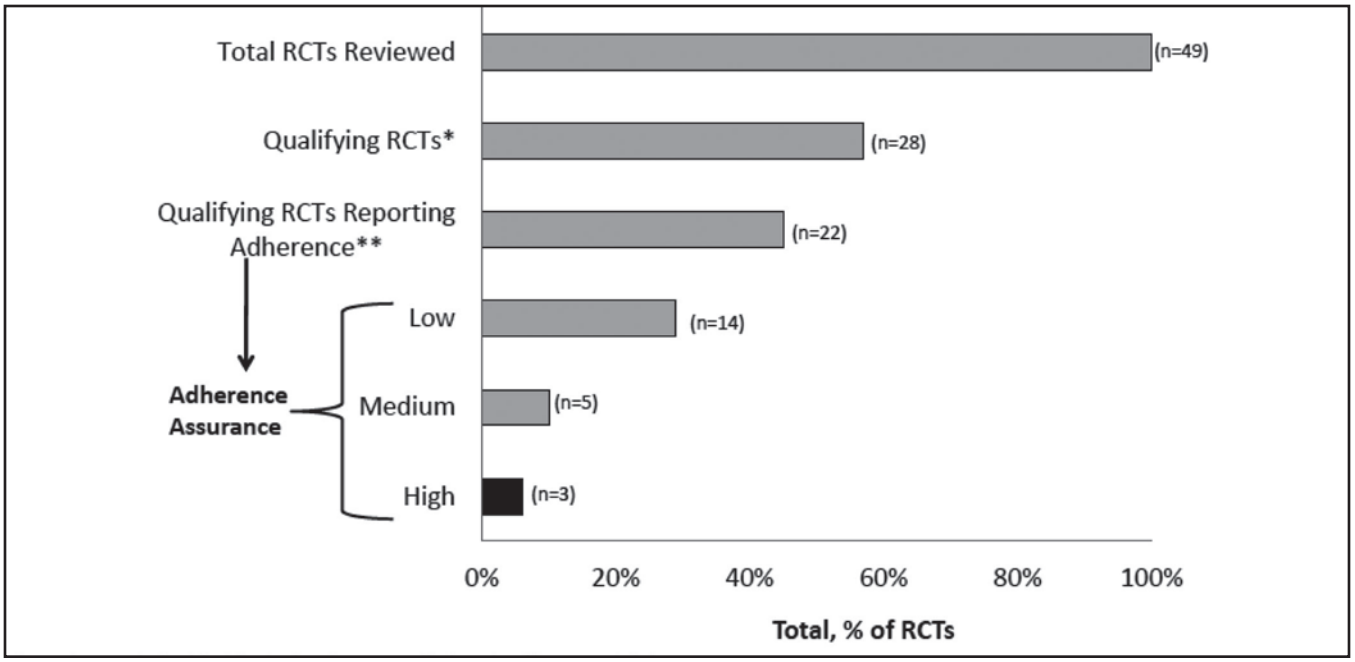

FIGURE 1. Adherence assurance of efficacy trials with naltrexone. RCTs = randomized controlled trials. *Randomized, double-blind, placebo-controlled trials of ≥12 weeks' duration; **adherence rate reported with results.

The Spearman correlation between risk ratios for return to heavy drinking (for naltrexone vs. placebo) and level of adherence assurance (low vs. medium vs. high) was statistically significant (r = -.62, p = .025).

Discussion

A fundamental precondition for determining the efficacy of any treatment is confirmation that the treatment was, in fact, administered as prescribed. This systematic review of naltrexone randomized controlled trials indicates that the vast majority of clinical trials (71%) either did not report adherence rates (21%) or used low assurance-monitoring strategies (50%). Given the consensus regarding the negative impact of nonadherence on naltrexone response (Bouza et al., 2004; Kranzler and Van Kirk, 2001; Pettinati et al., 2006; Roozen et al., 2006; Rösner et al., 2010; Srisurapanont and Jarusuraisin, 2005; Streeton and Whelan, 2001), this review raises questions about the reliability of current estimates of the efficacy of naltrexone. These estimates are largely based on meta-analyses and systematic reviews in which the majority of included studies leave open the question as to how much of the prescribed medication was ingested.

Baros et al. (2007) reported effect sizes that were progressively larger, not just for reduction in heavy drinking days but also for abstinence, in patient subgroups subjected to more rigorous adherence-monitoring strategies. This finding is noteworthy because it contrasts starkly with the results of the two most recent reviews of naltrexone efficacy, both of which concluded that naltrexone is not efficacious in promoting abstinence (Pettinati et al., 2006; Roozen et al., 2006). Interestingly, in an analysis of patients treated with an extended-release formulation of naltrexone, O'Malley et al. (2007) also found a strong abstinence effect in patients abstinent at treatment initiation.

The current systematic review confirmed the finding of Baros et al. (2007). There was a moderate and significant correlation (r = -.62, p = .025) between the adherence-assurance score and the risk ratios for return to heavy drinking for naltrexone, compared with placebo.

In community-based alcoholism-treatment programs, even in the most sophisticated programs, almost all of the strategies used to ensure adherence in the trials reviewed here are impractical. Direct supervision of oral-medication administration is generally unrealistic because of patient burden and staff cost. In the Oslin study, participants were required to come to treatment three times a week for observed dosing by a staff member (Oslin et al., 1997). Technological adherence-monitoring methods—such as MEMS caps, blister packs, riboflavin tracer, and blood and urine assays—also may not be realistic or cost-effective outside the clinical trial arena. We were able to identify only one community-based naltrexone trial that used MEMS caps, and the researchers found that only 51% of the medication was taken as prescribed (Killeen et al., 2004). However, at this time, we are unaware of any reports on the incorporation of these monitoring technologies into real-world practice.

Psychosocial methods have been used to foster adherence in clinical trials. These methods include medication management (Pettinati et al., 2005); BRENDA (Anton et al., 2006; Garbutt et al., 2005); behavioral family counseling (O'Farrell and Fals-Stewart, 2002); and contingency management (Carroll and Onken, 2005). In practice, these interventions have not been widely adopted in community settings—and other than family counseling, these methods do not provide inherent adherence assurance. The challenges associated with the transfer of research-based psychosocial therapies have been well-documented (Backer et al., 1995; Carroll et al., 2002; Miller et al., 2004; Morgenstern et al., 2001).

Another approach to improving medication adherence is to reduce the administration frequency through the use of long-acting formulations (Center for Substance Abuse Treatment, SAMHSA, 2007; Kleber et al., 2007; Weiss, 2004). The issue of noncompliance with oral naltrexone has been recognized in the substance use disorders field for more than 30 years (Willette, 1975), and indeed the National Institutes of Health called for the development of a long-acting form of naltrexone to increase adherence (Willette, 1975).

The two extended-release naltrexone studies included in this review both qualified as high adherence-assurance studies, because the pharmacokinetics of these formulations ensure medication exposure for at least 30 days and administration of injection by a health care professional provides verification that each dose was received (Garbutt et al., 2005; Kranzler et al., 2004). One of these formulations was approved by the Food and Drug Administration in April 2006 and may pharmacokinetically fully address the challenge of adherence and adherence monitoring (Center for Substance Abuse Treatment, SAMHSA, 2007). In real-world use, three retrospective insurance-claims data analyses have confirmed significantly longer mean refill persistency with extended-release naltrexone in comparison with approved oral agents (Chalk et al., 2011; Mark et al., 2010; McCarty et al., 2009).

One limitation of this review is the retrospective nature of the analysis. In addition, the analysis was limited to medication adherence and did not evaluate other study-design variables that might be relevant. Other limitations include the use of only one bibliographic database to identify studies and the use of a nonvalidated scoring algorithm to compare adherence methods. Notwithstanding such limitations, the results show the high degree of heterogeneity of adherence-reporting and adherence-monitoring methods and illustrate the challenges in formulating conclusions on the efficacy of pharmacologic agents, such as oral naltrexone, in the treatment of alcohol dependence.

Conclusions

Differing standards in adherence-assurance monitoring and reporting contribute to the variance in outcome in published clinical trials of naltrexone for the treatment of alcohol dependence. This structured review demonstrates that, to date, a preponderance of studies published on alcohol-dependence pharmacotherapy have used methods that do not provide high levels of adherence assurance. As a result, valid inferences cannot confidently be made concerning the efficacy of naltrexone in treating alcohol dependence. However, it is important to note that the use of rigorous adherence-monitoring methods, such as observed daily dosing, may increase the internal validity of a clinical trial but only at the expense of external validity, and thus the results may not generalize to "real-world" clinical practice settings. The availability of an extended-release injectable formulation of naltrexone may ensure treatment adherence in a manner that is relevant to actual clinical practice.

In conclusion, accurate quantitative determination of treatment adherence, and assurance of treatment adherence, would appear to be an essential requirement for valid research in the alcohol-dependent patient population. The current findings have implications for research design, grant review; editorial review; and, most important, clinical practice.

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