Improving Medication Adherence in Alcohol Dependence

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Adherence to a medication regimen is difficult for many individuals with chronic disorders, but is especially problematic in patients being treated with medications for alcohol dependence. Poor treatment adherence adds a formidable barrier to the management of this challenging disorder, significantly reducing the chance of successfully treating alcohol dependence. Psychosocial interventions developed by experts in the field are currently available in published manuals and provide guidance for improving adherence in alcohol-dependent patients. Future directions in pharmacologic treatments that bypass the burden of daily pill taking include long-acting injectable formulations—a strategy that has already shown promise in the treatment of schizophrenia.

(J Clin Psychiatry 2006;67[suppl 14]:23–29)

Patient adherence to treatment is critical for the successful management of any disorder, but in practice, adherence is typically difficult to achieve. Studies of insulin adherence in diabetes treatment report poor adherence in nearly 40% of patients,[1] and up to 50% of patients with hypertension are medication nonadherent.[2] Adherence to treatment in alcohol-dependent patients is especially low. Nonadherence rates vary by alcoholism treatment (and by adherence definition), ranging from 20% to 60% for daily naltrexone,[3–8] and are as high as 80% for disulfiram.[9] A recent meta-analysis found an average adherence rate of 53% in acamprosate studies ranging from 3 to 24 months in duration.[8]

Despite the need to improve adherence, results of interventions to improve adherence have been disappointing. In one naltrexone study, investigators used a program to engage patients and encourage medication adherence, but they could achieve only 71% adherence in the short term, which dropped to 43% over a year's time.[6] Alcohol dependence is a complex disorder that can be difficult to manage even in treatment-adherent patients. Solving the problem of medication nonadherence is a necessary first step toward successful pharmacologic treatment and must be pursued diligently.

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Supported by an educational grant from Alkermes, Inc. and Cephalon, Inc.

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EFFICACY AS A FUNCTION OF ADHERENCE

The importance of adherence to achieving successful treatment outcome is well established in the pharmacologic treatment of alcohol dependence. At least 7 studies identified in the literature[3,5,6,9–12] evaluated efficacy as a function of adherence to a U.S. Food and Drug Administration (FDA)–approved therapy for alcohol dependence (Table 1). Six of the studies evaluated naltrexone,[3,5,6,10–12] and 1 evaluated disulfiram.[9] The effect of adherence on the efficacy of acamprosate is less well studied. However, in one of the few negative studies of acamprosate, in which there was no difference in complete abstinence between acamprosate and placebo after 6 months, adherence rates were poor: only 57% of patients were adherent to treatment (at least 90% of medication taken) after 2 weeks, and only 35% of patients completed the study.[13]

Most of the studies reported herein were double-blind and placebo-controlled and included counseling of some type. All studies reported improved efficacy in treatment-adherent patients. Four of the 7 studies found significant reductions in measures of alcohol consumption for naltrexone-treated compared with placebo-treated adherent patients, but found lesser effects or no effect in nonadherent patients.[5,10–12] Two studies found no differences in efficacy between active and placebo treatment groups but found reductions in drinking for adherent patients—regardless of treatment—compared with nonadherent patients.[6,9] Similarly, an open-label study with naltrexone reported significantly improved outcomes in naltrexone-adherent patients compared with nonadherent patients.[3]

The problem of nonadherence in the treatment of substance dependence is well known to clinicians, but finding the time to identify and eliminate the problem is still a challenge. Easy-to-implement strategies are needed to

Table 1. Effect of Adherence on Treatment Efficacy in Clinical Trials

Study	Treatment Duration	Adherence Definition	Treatment	Results in Total Group Regardless of Treatment (adherent vs not)	Results in Total or Nonadherent Group (active drug vs placebo)	Results in Adherent Group Only (active drug vs placebo)
Chick et al, 2000[10] (double-blind; N = 175)	12 wk	80% pill consumption and attendance at all follow-up visits	Naltrexone 50 mg qd or placebo + psychosocial therapy	NR	No difference in alcohol consumption (total group)	50% decrease in alcohol consumption ($p < .05$)
Cramer et al, 2003[6] (double-blind; N = 627)	12 mo	ND	Naltrexone 50 mg qd or placebo + individual counseling	Higher adherence predicted decreased drinks[a] ($p = .02$)	NR	NR
Fuller et al, 1986[9] (double-blind; N = 605)	12 mo	Positive urinary riboflavin ≥ 15 times/year[b]	Disulfiram 250 mg or 1 mg[c] or placebo qd + counseling	Abstinence in 43% of adherent group vs 8% of nonadherent[d] ($p < .001$)	Abstinence rates: 10%, 9%, and 6% for disulfiram 250 mg, disulfiram 1 mg, placebo, respectively (nonadherent patients)	Abstinence rates: 38%, 50%, and 43% for disulfiram 250 mg, disulfiram 1 mg, and placebo, respectively ($p = .46$)
Monti et al, 2001[11] (double-blind; N = 128)	12 wk	Pill consumption for ≥ 70% of treatment days	Naltrexone 25 mg bid or placebo	NR	No difference in alcohol consumption (total group)	Decreased heavy drinking ($p < .03$)
Namkoong et al, 1999[3] (open-label; N = 93)	10 wk	Pill consumption > median (87.2%) based on MEMS compliance[e]	Naltrexone 50 mg qd + counseling	Higher percentage abstinence and lower percentage relapse in adherent vs nonadherent group[f]	NA	NA
O'Brien et al, 1996[12] (double-blind; N = 99)	12 wk	Attended all research visits	Naltrexone 50 mg qd or placebo + counseling	Mean relapse 13.2% vs 43.5% in adherent vs nonadherent patients ($p = .0007$)	No difference in percentage of drinking days (nonadherent group)	Reduction in percentage of drinking days ($p = .05$)
Volpicelli et al, 1997[5] (double-blind; N = 97)	12 wk	Pill consumption ≥ 90% of treatment days	Naltrexone 50 mg qd or placebo + counseling	NR	No difference in percentage relapsed or drinking days (nonadherent group)	Reduction in percentage relapsed ($p = .002$) and drinking days ($p = .01$)

[a]Number of drinks per drinking day. There was no significant difference between treatment groups (naltrexone vs. placebo); adherence predicted efficacy regardless of treatment.
[b]A result of ≥ 1.5 µg/mL was considered positive. A maximum of 39 specimens/year were collected. Riboflavin was contained in all 3 treatments and was used as a marker for pill ingestion.
[c]One mg of disulfiram is an insufficient dose to cause a reaction with ethanol but was necessary for blinding purposes.
[d]There were no differences among treatment groups (disulfiram 250 mg, disulfiram 1 mg, or placebo). Abstinence was higher in adherent patients regardless of treatment.
[e]MEMS records date and time pill bottle is opened.
[f]All patients received naltrexone treatment.
Abbreviations: MEMS = Medication Event Monitoring System, NA = not applicable, ND = not defined, NR = not reported.

Table 2. Desirable Attributes of Various Methods of Monitoring Medication Adherence[a]

Desirable Attribute	Monitoring Method				
	Standard Bottle	Blister Card	MEMS Caps	Riboflavin Tracer	Blood Levels
Is direct indicator of ingestion of medication	No	No	No	No	Yes
Gives patient feedback on adherence at a glance	No	Yes	Yes[b]	No	No
Gives feedback on day and time pills were taken	No	Yes[c]	Yes[b]	No	No
Is easy to carry	No	Yes	No	Yes	Yes
Cost is relatively low	Yes	Yes	No	Yes[d]	No
Total "yes"	1	4	2	2	2

[a]Adapted with permission from Pettinati et al.[14]
[b]Some but not all MEMS caps provide a digital display on the cap that indicates to the patient the number of hours since the bottle was last opened and the total number of openings in that day. The display recycles each day. Information on the exact day and time the bottle was opened over a period of time is retained in a computer chip in the cap; to access those data, the chip must be downloaded on a computer with specialized software.
[c]Well-marked blister cards give feedback on day and dose (e.g., a.m. or p.m.) pill was taken, assuming an empty pocket means the pill was taken.
[d]Qualitative checks on urine riboflavin are relatively inexpensive when using an ultraviolet lamp to check urine for the presence of riboflavin (orange color). Quantitative riboflavin levels in urine are more exact but would be costly.
Abbreviation: MEMS = Medication Event Monitoring System.

identify nonadherent patients quickly and initiate patient-tailored steps toward improving adherence.

ENHANCING MEDICATION ADHERENCE AND PROMOTING IDENTIFICATION OF TREATMENT NONADHERENCE

Patient adherence should be continually monitored by routinely asking patients about their pill taking at each treatment visit. Also, it is important to get patients to bring to the visit their pill bottles or blister cards, regardless of whether or not they took all of the pills. These materials should be part of the method the clinician uses to ask patients about their pill-taking behavior because using these materials in the inquiry will improve the validity of what patients tell the clinician. A number of tools have been developed to help validate patient pill-taking reports, although they vary in their reliability and clinical utility (Table 2).[14] Blister cards typically are easy to use and assist the patient who wants to take the pills as prescribed, because blister cards give pill-taking information at a glance (every single dose is labeled; typically if the dose is punched out of the card, it indicates to the patient that this dose was taken). While it would be most desirable for all medications to be dispensed in well-marked blister cards, to date, only acamprosate is commercially available in a blister card, most likely because its frequent dosing requirements (2 tablets, tid) can be a potential hindrance to adherence.[15] More data on whether blister cards reduce medication nonadherence might influence manufacturers to make medications available in well-marked blister cards.

MEMS (Medication Event Monitoring System; AARDEX Corp., Union City, Calif.) caps consist of an electronic switch built into a pill bottle cap that can let patients know via a digital display the hour and number of times the pill bottle was opened that day; the display is reset after 24 hours. With additional specialized software and equipment, clinicians can download more detailed information on the times and dates that the pill bottle was opened by the patient (and, presumably, when each dose was taken). Information for up to 3 years can be stored in memory and shared with patients.[6] (Note: Some MEMS caps do not have displays that indicate bottle opening at a glance; for these bottles, the only way to obtain that information is with the specialized software and equipment.) MEMS caps alone are about $100, but the additional computer equipment (presumably not purchased by the patient) is much more expensive. Current MEMS caps fit many standard-size pharmacy bottles (bottles may also be purchased with the cap). The bottles are generally bulkier than blister cards and, therefore, may be more difficult for patients to carry. This can result in patients forgetting to bring in their bottles at their treatment visits. When that happens, no data can be retrieved by the clinician, and there is the added expense of giving out another MEMS cap.

The B-vitamin riboflavin (either incorporated into the pill formulation, or taken as a separate pill at the same time that the active medications are ingested) is excreted in urine and can be measured either quantitatively in a lab assay or qualitatively by means of ultraviolet light detection (riboflavin in the urine imparts an orange color under the light).[16] Having a riboflavin marker inserted into the formulation would only be done in a research study, and it requires expensive testing (e.g., dissolution studies) to be acceptable as an agent for such a study. Consequently, only a few research studies have actually used a riboflavin tracer in the formulation of the pill, and this (nonclinical) option is excluded in Table 2. The option included in Table 2 indicates riboflavin as a separate pill, prescribed with each single dose of treatment medication. Thus, riboflavin becomes part of the daily medication dose regimen for the patient. An assumption is made with this method that patients unwilling to take medications as prescribed will also fail to take the riboflavin pill. Unfortunately, because it is possible to take the riboflavin pill without ingesting the actual medication, this method, like the other monitoring

methods described above, is an indirect marker of medication adherence. Of note, the qualitative method of checking the urine under an ultraviolet light is a less costly alternative to blood level monitoring.

Blood level monitoring provides the only direct evidence of pill ingestion but is costly and inconvenient. Moreover, individual differences in a patient's metabolism or excretion of the medication can complicate the interpretation of the blood levels that are determined.

In practice, none of these methods has proven superior to all others. For a patient who seeks treatment, it makes sense to monitor medication adherence by discussing with the patient at each visit his or her medication adherence, supplemented by pill counts of returned blister cards, bottles, or any available methods. A situation in which treatment appears to be failing but pill counts indicate adherence may necessitate using MEMS caps, a riboflavin tracer, or blood level monitoring—in addition to pill counts—to expose nonadherence in a seemingly adherent patient.

Once nonadherence is identified as a problem, the clinician should question the patient to uncover the rationale behind it. The manner of questioning should be empathetic and nonjudgmental. Nonadherence to medications or poor attendance at clinic visits is predicted by a variety of potentially modifiable factors in the treatment of alcohol dependence. Patients who have better social support[6] or believe that the medication will be effective[17] tend to show better adherence. Worse adherence is predicted in patients who report side effects from treatment (particularly nausea or fatigue) or who abuse other drugs.[17] In addition, adherence may be adversely affected by the treatment setting (e.g., long wait time for appointments) or by medical staff who are seen as unhelpful or make the patient feel uncomfortable.[18]

Clinicians should probe patients for these risk factors early in the course of treatment. Problems predicted to interfere with treatment may be correctable. For instance, social support can be encouraged among family members and friends, and problems with medical staff or wait time at the clinic can be improved. Medication side effects such as nausea and fatigue may be minimized by taking medications with food or dosing at bedtime.[17] In some cases, use of an antinausea agent such as bismuth subsalicylate can be helpful. Moreover, the clinician's attitude about the medication's effectiveness is critical because it may be transferred to the patient. To improve adherence, clinicians must convey complete confidence in the efficacy of the treatment.[17]

INTERVENTIONS FOR MANAGEMENT OF NONADHERENCE

Investigators have recently developed formalized psychosocial interventions that focus on improvement of adherence to pharmacologic treatments for alcohol dependence. BRENDA is one such intervention that is tailored for use by health care professionals (medically and nonmedically trained in addiction treatment) within a primary care setting or an office-based private practice.[14] A manual is available describing the intervention in a step-by-step approach.[19] BRENDA is an acronym for the 6 stages of the intervention: Biopsychosocial evaluation (baseline assessment of medical and psychosocial problems), Report (report back to patient after the initial evaluation), Empathy (conveyed by clinician), Needs assessment/goals (needs are identified and related to goals), Direct advice (to support goals, i.e., decrease drinking), and Assessment (of response to clinician's advice).

Although components of BRENDA are intended to enhance motivation to stop drinking, a special focus of BRENDA is the improvement of medication adherence. BRENDA instructs the clinician in the provision of feedback on adherence and strategies to improve it. In the initial session, patients who have had problems with pill taking in the past and inexperienced pill takers are identified and provided with additional information on adherence. The technique is tailored to each patient's biopsychosocial status and needs and requires about 30 minutes to deliver at each visit.[14]

Preliminary comparisons across studies of placebo-controlled naltrexone studies indicate that BRENDA is associated with better medication adherence than prior studies that had not specifically focused on improving medication adherence in their psychosocial intervention.[14] Seventy-seven percent of patients who received the BRENDA intervention (regardless of treatment) took at least 80% of their pills, whereas only 61% of patients who did not receive BRENDA met this adherence criterion ($p < .01$).

Another structured intervention with a focus on improving medication adherence was designed for inclusion in a large, multicenter clinical trial sponsored by the National Institute on Alcohol Abuse and Alcoholism (Combining Medications and Behavioral Interventions for Alcoholism [COMBINE] study).[20] This intervention, termed *medical management* (MM), is available in a manual that details its implemention.[21] MM treatment is a minimally intensive intervention that can be implemented by medical practitioners within a primary care setting or an office-based private practice.[20]

The goal of MM is to support the use of pharmacotherapy and provide individualized advice to patients to help them stop drinking.[20] Through the use of MM, the clinician provides information on the patient's disease (i.e., alcoholism) and the treatments, including pharmacotherapies, available. The MM clinician creates a dialogue with the patient meant to specifically increase medication adherence across treatment. All of this is done in a supportive atmosphere that conveys optimism for recovery. The initial visit requires 40 to 60 minutes to complete and involves re-

Table 3. Algorithm for Determining Appropriate Patient Dialogue in Medical Management Treatment[a,b]

		Medication Adherent?	
		Yes ↓	No ↓
Drinking?	Yes →	Dialogue 1	Dialogue 2
	No →	Dialogue 3	Dialogue 4

[a]Reprinted with permission from Pettinati et al.[20]
[b]Brief description of dialogues:
Dialogue 1: Remind the patient that the medication may take some time to work, and review benefits of abstinence.
Dialogue 2: Review consequences of drinking and the benefits of abstinence, provide suggestions for minimizing cues that may be eliciting drinking, probe reasons for medication nonadherence, and reconstruct an adherence plan that aims to remove the identified barriers to adherence.
Dialogue 3: Ask the patient how success was achieved, and encourage continuation with the plan.
Dialogue 4: Congratulate the patient for not drinking, probe the reason for nonadherence, and explore strategies for improving it.

viewing results of the intake evaluation, with emphasis on drinking-related problems and need for treatment. It includes patient education on alcohol dependence and the rationale for treating it with medication, instructions on dosing, side effect management, construction of a medication adherence plan for the patient to follow, and referral to local support groups. The plan for follow-up visits is also reviewed at the initial visit. Lasting only 15 to 30 minutes, follow-up visits involve a brief check of medical status and patient status regarding drinking and pill taking. Advice given at follow-ups is tailored to the current status of the patient and follows the algorithm depicted in Table 3.[20] Mean medication adherence in the COMBINE study was 85.8% (median, 96.4%), and the mean number of MM sessions attended was 7 out of 9 (median, 9).[22]

The results of the COMBINE study, which studied MM with naltrexone, acamprosate, and specialized alcohol counseling (a combined behavioral intervention [CBI]), were recently reported.[22] All patients in this study who received pills also received the MM intervention. While, overall, participants reduced their prestudy drinking, regardless of the group to which they were assigned, patients who received MM with naltrexone, or received MM with CBI plus either naltrexone or placebo, demonstrated the best drinking outcomes after 16 weeks of outpatient treatment. A group that received CBI without any pills demonstrated the worst outcomes, even poorer than those receiving MM plus placebo pills. This latter finding emphasizes the potency of providing pills to patients. One implication of these COMBINE results is that naltrexone with MM could be delivered in health care settings where traditional specialty treatment is unavailable.

LONG-ACTING MEDICATIONS TO IMPROVE ADHERENCE: NEUROLEPTICS AS A MODEL

Simple treatment regimens with a low frequency of dosing are well known to improve treatment adherence across a variety of disorders.[15] Therefore, part of the strategy toward achieving high adherence has been to use long-acting medications that are dosed less frequently. While longer-acting formulations of naltrexone have not been evaluated for improving retention rates in community samples, the example of depot antipsychotics may prove an interesting anecdotal comparison. This strategy has been pursued within the treatment of schizophrenia—a disorder with nonadherence rates reported at about 50% on average and ranging from 4% to 72% across studies.[23]

Table 4. Barriers to Treatment Adherence Shared by Schizophrenic and Alcohol-Dependent Patients[a]

Belief about efficacy of medication[17,23,25]
Cognitive problems[25,26]
Comorbid substance use disorder[17,23,27]
Denial of or poor insight into illness[25,27–29]
Motivational and/or mood problems[23,29]
Poor social support[16,18,27]
Side effects of medications[17,23,25,28]

[a]Barriers in table are listed alphabetically.

In an effort to improve adherence in schizophrenic patients, researchers developed long-acting depot neuroleptics in the early 1960s. Fluphenazine was the first neuroleptic formulated as a depot injection,[24] but over the years, additional typical antipsychotics, as well as the atypical antipsychotic risperidone, became available as depot intramuscular injections. Outcomes from trials comparing long-acting depot antipsychotics with shorter-acting oral forms have been the subject of meta-analyses and reviews. We will examine these reports briefly, as they may be predictive of expected outcomes from long-acting medications used for alcohol dependence. Although the patient populations being treated are different, and, thus, may comply differently with medications, they do share a number of characteristics that impact negatively on adherence (Table 4). Given these shared characteristics and the similarly low adherence rates across the alcohol-dependent and schizophrenic populations, results from these neuroleptic studies are most likely the best predictors of adherence-related outcomes in the treatment of alcohol dependence with long-acting medications.

A number of Cochrane reviews have compared outcomes between depot and oral formulations of various antipsychotics, including haloperidol, pipotiazine, and fluphenazine, among others. In 2001, a meta-analysis of these high-quality, systematic reviews was published in order to provide a summary of the data across all antipsychotics.[30] The reviews analyzed include randomized, controlled clinical studies ranging from 2 weeks to 3 years in duration. Although medication adherence was not an analyzed outcome, adherence-related efficacy outcomes, that is, relapse and global functioning, were compared between formulations, as were study attrition rates. Significant differences were detected for global functioning. Patients

allocated to depot medication experienced more global improvement compared with patients taking oral medications ($p < .001$). Although no significant difference in relapse rates emerged, the authors noted that the patients who would be best suited for treatment with a depot formulation, that is, patients who least adhere to treatment, are also the least likely to volunteer for a clinical trial.[30] The fact that global functioning was significantly improved in depot-treated patients from these trials is meaningful.[30] Study attrition rates were not different for oral versus depot medications.

In an earlier review from 1994, Davis et al.[31] reported on 6 double-blind studies of depot versus oral antipsychotic treatments for outpatients. Study lengths ranged from 9 months to 2 years. While only a couple of these studies showed significant differences in the relapse rates between the treatments, the 6 studies analyzed as a whole found the depot medication to be significantly superior in reducing the incidence of relapse ($p = .0002$). Additionally, Davis and colleagues also reanalyzed data from 6 "mirror image" trials, in which patients who were switched from oral to depot medication were compared for the number of days spent in hospital, on each formulation, over the same length of time. For each study, there was a significant reduction in number of hospital days from oral to depot treatment.[31] Although these studies could be criticized for their open-label, nonrandomized design, Davis et al. note that they are "especially pertinent" for the study of an adherence-related measure because they occur in a naturalistic setting that is more likely to include nonadherent patients.[31]

It is difficult to extrapolate adherence rates of oral versus depot medications in schizophrenic patients who participate in a trial, as these patients are not necessarily representative of patients in clinical practice.[30–32] Thus, there are no definitive answers about whether depot medications vastly improve adherence in the general clinical population. Nevertheless, it is not unreasonable to think that long-acting formulations have the potential to improve adherence. The reports reviewed here suggest these formulations may improve treatment outcomes.

FUTURE DIRECTIONS FOR IMPROVING ADHERENCE IN ALCOHOL DEPENDENCE

The problem of nonadherence and its downstream consequences is well documented in the treatment of alcohol dependence. New strategies are needed not only in psychosocial interventions to improve adherence, but also in the formulation of medications. Three of the 4 medications approved for the treatment of alcohol dependence are oral, requiring daily dosing. Acamprosate requires dosing 3 times a day, and oral formulations of naltrexone and disulfiram must be dosed once per day. Oral naltrexone has been used on a 3-times-weekly dosing schedule for opioid dependence and has been tested as an on-demand treatment in alcoholism.[33] Several long-acting, injectable formulations of naltrexone are currently under development. One of these long-acting injectables has been approved by the FDA for the treatment of alcohol dependence. The article in this supplement entitled "New Therapeutic Options for Alcohol Dependence: Long-Acting Intramuscular Formulations of Naltrexone," by James C. Garbutt, M.D.,[34] details results from recently completed clinical trials of these long-acting injectable formulations for once-monthly dosing.

Drug names: acamprosate (Campral), disulfiram (Antabuse), fluphenazine (Prolixin and others), haloperidol (Haldol and others), naltrexone (ReVia, Vivitrol, and others), risperidone (Risperdal).

Disclosure of off-label usage: The author has determined that, to the best of her knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

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