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Effect of early and late compliance on the effectiveness of acamprosate in the treatment of alcohol dependence

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Abstract

Background: The aim of this study is to assess the influence of early and late compliance of acamprosate on attendance and abstinence duration in the treatment of alcohol dependence. **Methods:** Individual patient data of 2,305 patients from 11 randomized controlled trials comparing acamprosate (n = 1,128) with placebo (n = 1,177) were used to predict early and late compliance and to study the effect of early and late compliance on attendance and abstinence duration using regression analysis and structural equation modeling. **Results:** Early compliance was predicted by baseline motivation to become fully abstinent and baseline abstinence (R^2 = .26); late compliance was predicted by early compliance (R^2 = .13); treatment discontinuation was predicted by young age, marital status, compliance, and treatment condition (R^2 = .26); and abstinence duration was predicted by motivation to become fully abstinent early compliance and the interaction of early compliance and treatment condition (R^2 = .27). Structural equation modeling showed that abstinence duration was significantly associated with motivation at baseline, late compliance, and treatment condition (Goodness of Fit Index [GFI] χ^2/df = 1.56; Parsimonious Goodness of Fit Index [PGFI] = 0.69). **Conclusions:** Motivation to become fully abstinent and abstinence at the start of treatment are important for early compliance. Early compliance in turn predicts late compliance. Late compliance, in combination with motivation to become fully abstinent, and treatment condition (acamprosate vs. placebo) predict duration of abstinence. This suggests that motivational interventions directed toward full abstinence motivation and abstinence at the start of treatment are crucial for both compliance with acamprosate and successful treatment outcome.

Keywords: Compliance; Acamprosate; Alcohol dependence; IPD meta-analysis

1. Introduction

In 2002, Miller rank-ordered, in a large review, 46 different treatment modalities on the basis of their proven efficacy for the treatment of alcohol dependence. Two pharmacotherapies appeared in the top 10: glutamate antagonist acamprosate at Rank 3 and opiate antagonists like naltrexone at Rank 4 (Miller & Wilbourne, 2002). After Miller's review, additional studies showed significant but moderate effects of pharmacological treatments for alcohol dependence (Bouza et al., 2004; Kranzler, 2008). Prescribed medication has to be taken by the patient to be effective. Medication compliance, however, is a problem, not only in the addiction field but also in somatic medicine and psychiatry. In the field of somatic disorders, most patients take approximately 50%–90% of the doses (Weiss, 2004). Rates of compliance to medication for psychiatric disorders are even lower, with nonadherence rates ranging from 10% to 76% for antipsychotic medication and from 10% to 50% for antidepressants (Weiss, 2004). Pharmacological treatment of substance abuse disorders has also been shown to have high rates of nonadherence, and these rates are

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comparable to levels of nonadherence to medical regimens characteristic for patients with a chronic medical illness such as hypertension or asthma (McLellan et al., 2000). In the treatment of alcohol abuse, adherence is further dependent on the fragile balance between the treatment goal of reducing alcohol consumption and the patient's desire to drink (McDonough, 2007).

The best reported medication adherence rates are probably obtained in clinical trials. However, even in these situations, where people are often paid for their participation, many people fail to continue their medication (Bouza et al., 2004). In general clinical practice, the level of adherence is probably much lower (Weiss, 2004).

Adherence to treatment regimens is generally believed to be related to treatment efficacy. This seems even more logical for pharmacological treatments. The effect of a pharmacological substance can only be achieved if this substance actually enters the body. Consequently, there is widespread agreement that poor adherence to prescribed medications may undermine treatment benefits and lead to suboptimal outcomes. Underdosing, overdosing, and erratic dosing intervals can all diminish drug efficacy (Baros et al., 2007; Bouza et al., 2004; Feinn et al., 2003; Weiss, 2004). For example, the effect of naltrexone relies heavily on patient's compliance. In a study among alcohol-dependent patients, relapse occurred in 14% of those who took their medication regularly and in 50% of those who took less than 90% of the prescribed pills (Volpicelli et al., 1997). In addition, Baros et al. (2007) reported a doubling of the effect size when comparing the results of the intention-to-treat (ITT) with the completers' analysis. Some studies even reported an effect of compliance but no effect of treatment condition on treatment outcome suggesting selection bias, that is, compliant patients differed from noncompliant patients on characteristics related to outcome but not related to the active medication (Baros et al., 2007; Cramer, 2002). This introduces the possibility that the effect of compliance (in studies comparing compliant with noncompliant patients) cannot automatically be attributed to the effect of the active ingredient (medication) and hence does not necessarily support the conclusion that the medication is effective.

The general view, however, is that medication compliance is a prerequisite for efficacy and effectiveness of medical treatment of alcohol use disorders. However, compliance is a complex concept. It is too simple to restrict compliance to a dichotomy between compliant and noncompliant. People may comply with the treatment regimen to a different degree in different situations. Compliance may also change over the course of long-term treatment. The latter refers to a distinction between early compliance (EC) and late compliance (LC; sometimes called persistence). People may also comply with one part of the treatment but not with the other (Evangelista, 1999; Kyngas, Duffy, & Kroll, 2000).

This article aims at a better understanding of compliance and attendance in patients treated with acamprosate for alcoholism. Because acamprosate is a drug taken three times a day, compliance is harder to establish than with drugs taken once a day, such as disulfiram or naltrexone. In addition side effects like diarrhea may cause (temporal) noncompliance. Our main objectives are (a) to provide a reliable estimate of treatment compliance throughout the treatment and an estimate of treatment completion based on a sufficient number of patients; (b) to assess the characteristics of compliant and noncompliant patients; (c) to predict compliance and treatment completion from baseline patient characteristics; and (d) to assess the extent to which compliance effects the efficacy of the treatment. With regard to the last objective, we assessed the main effects of compliance and treatment and whether the effect of treatment was modified by compliance.

To achieve these objectives, we performed an individual patient data (IPD) meta-analysis using patient data from 11 randomized clinical trial comparing acamprosate with placebo (Simmonds et al., 2005; Smith, Williamson, & Marson, 2005). These trials are subsamples of the international research program of acamprosate, which involves more than 4,400 patients in randomized controlled trials (RCTs) and comprises an extensive list of baseline and follow-up data for each patient.

2. Materials and methods

2.1. Trial selection

A language-unrestricted search of 10 databases (CINHAL, PsychINFO, MEDLINE, EMBASE, and EMBASE databases), covering the period from January 1, 1985, to April 30, 2006, was undertaken based on a number of keywords, including *alcohol drinking*, *clinical trials*, and *acamprosate*. The combined lists were manually deduplicated; MEDLINE-retrieved references were given preference because they included keywords. The printouts from the electronic searches were reviewed, and all treatment trials were selected. An additional manual search was conducted of relevant journals, symposia, and conference proceedings, and relevant trials were retrieved; all identified publications were cross-referenced. Personal contact was made with the authors of the selected studies, if necessary, to request additional unpublished or published results. Finally, access was provided by the manufacturer of acamprosate (Merck) to the internal trial reports of all European studies, irrespective of publication status. All identified publications and internal trial reports were retrieved and reviewed.

The quality of each study report was assessed using a validated scale (Chalmers et al., 1981) that scores multiple aspects of the experimental design of the trial, including sample size, randomization methods, methods to preserve blinding, selection and withdrawal criteria, outcome criteria, and statistical analysis; scores range from 0 to 100. The arithmetic mean of the three independent scores was