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The effects of combined acamprosate and integrative behaviour therapy in the outpatient treatment of alcohol dependence: A randomized controlled trial

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ABSTRACT

Aims: The aim of this randomized, controlled, multisite trial was to evaluate the efficacy of combined treatment with integrative behaviour therapy (IBT) and acamprosate on drinking behaviour in detoxified alcohol-dependent patients.
Methods: A total of 371 patients were randomized to one of the three treatment conditions: IBT plus acamprosate, IBT plus placebo, or supportive counselling ('treatment as usual', TAU) plus acamprosate. The main outcome was success rate, i.e., rate of abstinence plus improvement according to the criteria of Feuerlein and Küfner (1989), at the end of the six-month treatment phase and at the subsequent six-month follow-up. Drinking status was validated by blood parameters (CDT, GGT, and MCV). Data were analyzed by an intent-to-treat model and missing data were classified as relapse.
Results: The success rates at the end of treatment under both TAU plus acamprosate (37.7%) and IBT plus placebo (48%) almost reached the levels derived from the literature. However, adding acamprosate to IBT did not result in the expected increase in success rate (IBT plus acamprosate: 47.6%), and success rates did not differ significantly between groups. Similarly, there was no significant difference between treatment success rates at follow-up.
Conclusion: The results suggest that the combination of acamprosate and IBT is not more effective than treatment with either IBT or acamprosate alone. However, the two acamprosate conditions differed in success rate by about 10%, which might constitute a clinically relevant though statistically non-significant effect.

1. Introduction

Relapse prevention in alcohol dependence relies on psychosocial or pharmacological treatment or both, with the primary goal of long-term or lifelong abstinence (Soyka et al., 2008). Whereas psychosocial interventions may be offered as the sole treatment option, current treatment guidelines like the international WSBP guidelines (Soyka et al., 2008) and the national guidelines in Germany (Schmidt et al., 2006), the UK (NICE clinical guideline of alcohol-use disorders, NHS CG115) and the US (Kleber et al., 2006) recommend offering pharmacological treatment with anti-craving medication only in combination with some kind of professional psychosocial support or psychosocial therapy.

Several psychosocial interventions have shown efficacy in relapse prevention, including brief interventions, social skills training, the community reinforcement approach, behavioural contracting, behavioural marital therapy and case management, motivational interviewing and more intensive manualized psychotherapies (Mann and Hermann, 2010; Soyka et al., 2008). In particular, several clinical trials have proved the efficacy of cognitive behaviour therapy (CBT; Miller and Wilbourne, 2002), regardless of whether such CBT approaches focus more on behavioural or cognitive aspects of addiction (IBT; Burtscheidt et al., 2001).

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A recent Cochrane review of 24 randomized controlled trials (RCTs) found the anti-craving drug acamprosate to be an effective and safe treatment strategy for supporting continuous abstinence after detoxification in alcohol-dependent patients (Rösner et al., 2010). Because studies on pharmacological treatments usually include additional psychosocial treatments, but often do so in a manner that is not standardized, manualized or controlled by randomized psychosocial control treatments, it remains unclear to what proportion treatment results stem from pharmacological effects, psychosocial effects or a combination or interaction of both.

A comparison with historical controls found indications that the addition of acamprosate to an established CBT outpatient programme may improve abstinence rates significantly (38% vs. 14% with CBT alone) (Feeney et al., 2002). The large US multisite RCT COMBINE (Anton et al., 2006), which addressed similar issues, collected data from 1383 patients assigned to nine different treatment groups and evaluated the effects of combining two medications (acamprosate and naltrexone) and behavioural psychotherapy. All groups showed marked reductions in drinking from baseline to the end of the study. Naltrexone in particular proved to be effective both with and without CBT. Combining all interventions did not show greater effects. In contrast to formerly reported data, no evidence was found for the efficacy of acamprosate as a sole treatment.

The aim of the present multisite trial was to examine the effect of a combination of integrated behaviour therapy (IBT; Burtscheidt, 2001) and acamprosate in the outpatient treatment of alcohol-dependent patients. In accordance with modern CBT concepts, IBT integrates the elements of coping skills training and cognitive therapy, a previous study found both coping skills training and cognitive therapy to be superior to supportive counselling and found no significant differences between the two behavioural therapies (Burtscheidt et al., 2001, 2002). We hypothesized that the success rate of IBT combined with acamprosate would be higher than that of a combination of either IBT and placebo or "treatment as usual" (TAU) and acamprosate. The success rate of TAU plus acamprosate was expected to be about 40%, the average rate reported by several other studies (Kiefer and Wiedemann, 2002; Mann et al., 2004; Paille et al., 1995; Poldrugo, 1997; Sass et al., 1996; Tempesta et al., 2000; Whitworth et al., 1996). Based on our own previous results (Burtscheidt et al., 2002), which showed that the two major IBT constituents (coping skills training and cognitive therapy) were successful in 51% and 53% of patients, respectively, the success rate with IBT plus placebo at the end of six months' treatment was expected to be about 50% in the present study. Although this earlier study differed in two methodological aspects – it only investigated the two major IBT constituents and not the current integrated version of the IBT and used no additional placebo or anti-craving medication – these data were the best available with regard to comparability of other major methodological characteristics, in particular, all other aspects of the treatment, the kind of patients included and the definition of outcome parameters. A further increase of 10% in the success rate, to about 60%, was assumed to indicate a clinically significant advantage of adding acamprosate instead of placebo to IBT and was thus taken as the hypothesized outcome of the combination treatment.

2. Methods

2.1. Study design

After inpatient detoxification – the usual setting for detoxification in Germany – and baseline assessment, 371 alcohol-dependent patients were randomly assigned to one of the three groups for six months' outpatient treatment: the first group received IBT plus acamprosate; the second group, IBT plus placebo; and the third group, unspecific support and counselling visits ('treatment as usual', TAU) plus acamprosate. A combination of placebo and TAU was not included for ethical reasons as both verum treatments (IBT and acamprosate) have been shown to be effective in monotherapy; thus, a double-placebo approach would have deprived patients of active treatment conditions.

Individuals were assessed at inclusion in the study, i.e., before treatment (T0), once during the six-month treatment period (T1, after 3 months), at the end of treatment (T2), and three (T3) and six (T4) months after the end of treatment.

Inclusion criteria included age between 25 and 60, alcohol dependence according to DSM-IV, addictive behaviour for the past 6 months and adequate German language skills. Patients were excluded in case of additional substance use disorders (except nicotine), psychotic disorders, concurrent antidepressant medication, mental retardation or brain damage, unstable medical condition, known hypersensitivity to acamprosate, pregnancy or nursing. Each participant gave written informed consent. The study (clinical trials registration number NCT00159107) was performed in accordance with the Declaration of Helsinki and approved by the ethics committees of all participating centres.

Blinding of acamprosate and placebo and randomization of participants to treatment conditions was realized by an independent external centre, the pharmacy of the Johannes Gutenberg University, Mainz, Germany.

The Coordination Centre for Clinical Studies (KKS) of the University of Düsseldorf was responsible for independent audits of the study, in particular regarding adherence to Good Clinical Practice guidelines (Directive 2001/20/EG). The KKS also provided a professional Remote Data Entry (RDE) system, 'eResearch Network', for capturing, storing and validating data.

2.2. Treatment conditions

2.2.1. Medication. Blinded study medication and placebo were dispensed in doses of two tablets, three times a day, corresponding to a daily dose of 1998 mg acamprosate in the verum group. Compliance was ensured by pill counting.

2.2.2. Psychotherapeutic intervention. IBT (Burtscheidt, 2001) is a manual-guided treatment that was developed on the basis of results from an earlier study that compared two different outpatient behaviour interventions in the treatment of alcohol relapse prevention (Burtscheidt et al., 2001, 2002).

IBT comprises elements of relapse prevention programmes, social skill trainings and motivational and cognitive methods and consists of four modules of six sessions each. Thus, a total of 24 IBT sessions are applied. The topic of the first module is 'alcohol-related problems'. It includes psychoeducation and covers focussing alcohol-related thoughts, dealing with relapse, refusing offers to drink and dealing with the accusation of a relapse. The second module, 'techniques of communication', consists of training assertiveness, criticizing, receiving criticism and rejecting claims. The third module targets 'complex issues' and comprises issues such as partnerships, building social networks, convenient activities and special personal problems of individual patients. The last module, 'emotion and problem solving' deals with perception of emotions, handling negative emotions and using strategies for problem solving. Hence, IBT combines cognitive techniques for modifying persisting thoughts and perception biases concerning alcohol with elements from social skills training programmes. The aim is to strengthen abilities to cope with general and addiction-specific situations. Treatment sessions were held once a week for six months in groups of 2–9 people and lasted about 100 min each.

In the TAU condition, patients were also seen once a week but in an individual setting. As each session lasted about 15 min, the average time spent with each patient was roughly the same as in the IBT sessions. The aim of this supportive conversation was to encourage both motivation to maintain abstinence and the development of motivation for life changes; techniques from motivational interviewing were allowed (Miller, 1996). In contrast to motivational interviewing, the topics addressed in the TAU sessions were completely driven by the patient and patients were not directed toward the discrepancy between their problem behaviour and broader personal values. Also, cognitive behavioural techniques like cognitive restructuring or skills training were not permitted. However, basic principles used in motivational interviewing like expressing empathy, developing discrepancy, rolling with resistance and supporting self-efficacy, as well as basic techniques like open questions, affirmations, reflections and summaries, were allowed in TAU, in accordance with the manual.

Relapsing patients were excluded from the study treatment, but were encouraged to stay in contact with the hospital as an outpatient or inpatient. Since IBT was realized within a group setting, leaving relapsing patients in the group may have put the abstinence of the other participants at risk. Relapse was defined as drinking alcohol for more than seven consecutive days (Feuerlein and Küfner, 1989). In addition, absence for more than three consecutive therapy sessions without notice was a reason for terminating treatment.

To ensure treatment quality, all therapists in both intervention conditions were fully qualified psychologists or physicians with psychotherapeutic qualifications and were trained and supervised by authorized supervisors. Therapy sessions were recorded on videotape to check for adherence to the treatment manuals.

2.3. Assessment

2.3.1. Outcome measures. Since all patients were detoxified and abstinent at randomization and since maintaining abstinence is the principal goal within the German health care system, success rate was chosen as the primary outcome