ADJUVANT TRAZODONE IN THE TREATMENT OF ALCOHOLISM: AN OPEN STUDY

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(Received 25 September 1997; in revised form 21 January 1998; accepted 23 January 1998)

Abstract — Serotonergic drugs have been proven to be helpful to alcoholics in maintaining abstinence. In this open study, we report that the atypical antidepressant trazodone at low doses was able to significantly decrease craving for alcohol, depressive, and anxious symptoms in a number (25) of detoxified alcohol-dependent subjects after 3 months of treatment. Trazodone may, therefore, be an adjuvant in the therapy of alcoholism.

INTRODUCTION

Several studies show that serotonergic drugs consistently attenuate ethanol intake in both animals and humans (for review, see Amit and Smith, 1992). 5-Hydroxytryptamine (5-HT) uptake inhibitors and buspirone have been used in controlled clinical trials and found to be effective in reducing craving and alcohol consumption in dependent subjects (Naranjo and Bremner, 1993). Animal studies have demonstrated also that 5-HT2 receptor antagonism may attenuate the volitional intake of alcohol (McMillen et al., 1994).

Trazodone is an antidepressant drug displaying an atypical mechanism of action on serotonergic transmission: on the one hand, it inhibits selectively 5-HT reuptake, and on the other, it blocks 5-HT2 postsynaptic receptors. In addition, its main active metabolite m-chlorophenylpiperazine (m-CPP) has agonistic effects on various 5-HT receptor subtypes (Kahn and Wetzler, 1991). In the light of these considerations, we were particularly interested in the potential efficacy of trazodone as an adjunctive medication in reducing craving for alcohol and its intake in dependent patients during the post-detoxification period.

In the present study, 25 acutely detoxified alcohol-dependent subjects underwent an open 3-month trial of trazodone hydrochloride as an adjuvant in a rehabilitation programme, consisting of weekly counselling sessions and attendance at Alcoholics Anonymous (AA) meetings.

SUBJECTS AND METHODS

Patients were recruited from among those attending the Drug and Alcohol Addiction Clinic of a university hospital. Twenty-five nonconsecutive patients entered the study. Voluntary alcohol detoxification was performed on an outpatient basis according to a standard clinical protocol. This consisted in abrupt withdrawal from ethanol and administration of both chlordiazepoxide (50–100 mg/day orally) and tiapride (300–600 mg/day orally), with a decreasing regimen over a 10–14-day period. The patients were eligible to enter the trial only if for at least 1 week: (a) they had minimal or no signs of withdrawal and had been abstinent from alcohol; (b) tiapride had been discontinued; (c) the dose of chlordiazepoxide had been no more than 25 mg/day. All patients had a diagnosis of alcohol dependence according to DSM-III-R criteria (American Psychiatric Association, 1987). Additional inclusion criteria were age between 18 and 65 years and a duration of alcohol dependence of at least 3 years. Patients were excluded if they had major physical diseases or were pregnant, had been previously treated with

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anti-craving (5-HT reuptake inhibitors, γ-hydroxybutyrate) or aversive (disulfiram) medications, or had other psychiatric disorders interfering with assessment or requiring treatment with psychoactive drugs other than low doses of benzodiazepines (only chlordiazepoxide, 10–25 mg/day, was allowed). All patients at intake showed only minimal withdrawal signs (score <10/62) as assessed by the Alcohol Withdrawal Rating Scale (AWRS) (Janiri et al., 1991, 1996). They entered a post-detoxification programme according to previously described procedures (Janiri et al., 1996). The mean period of detoxification before entry in the study was 10 days.

Patients were treated for 90 days with slow-release trazodone. The mean dose required was 135 mg (range 75–300 mg). Besides a drinking questionnaire on alcohol-related behaviour, standard evaluation instruments consisted of three distinct Discan scales rating alcohol craving, subsyndromal anxiety, and depression (0, no symptoms; 1–2, mild; 3–4, moderate; 5–6, severe) (Singh and Bilsbury, 1984). These evaluations, along with drinking behaviour, were conducted at baseline pretreatment and on days 30, 60, and 90 thereafter.

Discan scales are rating analogue scales for self- and observer-reported evaluations of discrete symptomatological dimensions. Singh and Bilsbury (1984) consider the Likert scale and the visual analogue scale as variants of Discan scales. They are useful to assess psychopathological traits and symptoms, such as those explored in our study. Rating may range from 0 to 6 (as in the case of BPRS) or up to 14 (e.g. scales for pain). For subsyndromal symptoms, we used the range 0–6 of a full-extended 0–12 scale (>6 = syndromal symptoms).

Compliance to the therapy protocol requirements and drinking behaviour were verified by means of clinical interviews with the aid of a knowledgeable informant. Statistical analysis was performed by the Student’s paired t-test.

RESULTS

Demographic data and clinical characteristics of the sample are summarized in Table 1. All 25 patients consumed wine and seven of them also consumed beer.

Fifteen patients (60%) were still abstinent at the end of the trial. Out of these, 12 were always abinent during the trial, two resumed drinking a limited amount (<20 g of alcohol/day) during week 2 of the study and one presented an episodic drinking pattern (around 40 g of alcohol in 1 day on two separate occasions) between T30 and T90.

Seven patients resumed drinking in a limited fashion (<40 g alcohol/day) within T30. Out of these, three went on consuming alcohol daily in a regular and controlled pattern (around 20 g alcohol/day), two went on consuming alcohol daily in a regular but higher pattern (around 60 g alcohol/daily) and two patients relapsed into a continuous heavy alcohol abuse (>70 g of alcohol daily) so that trazodone had to be discontinued at T60 after an abstinence of 30 days and 40 days, respectively.

Of the remaining three patients who were not abstinent between T30 and T90, two resumed drinking a limited amount (<20 g alcohol/day) and one went on consuming alcohol daily in regular and high amounts (around 60 g/day) until the end of the study. No dropouts were recorded and the compliance was good for all subjects.

Mean Discan scale scores at baseline (T0) and after 90 days (T90) of trazodone treatment are shown in Table 2. On all scales, the T0–T90 comparison showed a significantly greater mean score decrease at the end of the trial (P < 0.0001) for anxiety, craving and depression.

DISCUSSION

The main finding of this open-label trial is that trazodone may reduce relapse rates in alcohol-dependent subjects after acute detoxification.
Table 2. Discan scales for craving and subsyndromal anxiety and depression before and after treatment with trazodone

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$T_0$</td>
<td>$T_{90}$</td>
</tr>
<tr>
<td>Craving</td>
<td>4.52 ± 1.56</td>
<td>2.20 ± 1.96*</td>
</tr>
<tr>
<td>Sub-syndromal anxiety</td>
<td>3.72 ± 1.4</td>
<td>1.72 ± 1.34*</td>
</tr>
<tr>
<td>Sub-syndromal depression</td>
<td>4.52 ± 1.36</td>
<td>2.16 ± 1.34*</td>
</tr>
</tbody>
</table>

Sub-syndromal symptoms in detoxified alcoholics are usually in the range 3-5. $P < 0.0001$.

Abstinence was recorded in 60% of patients. This percentage of abstinence, added to the rate of controlled drinking pattern, is similar (73.3%) to that reported for other 3-month studies with anti-craving drugs, such as γ-hydroxybutyric acid (72%) (Gallimberti et al., 1992) and naltrexone (82.5%) (Volpicelli et al., 1992). The relapse rate (13.3%) is also similar, but smaller, with respect to those reported for naltrexone (18.5%) (Volpicelli et al., 1992) and acamprosate (20%) (Pelc et al., 1995).

Our previous results with fluoxetine (20 mg/day) in detoxified alcoholics with moderate to severe dependence showed an outcome of ~62% abstinence (vs 34.5% with placebo) after 60 days (Janiri et al., 1996). However, the same drug at a dosage of 60 mg/day is probably not of use for relapse prevention in alcoholics with mild to moderate dependence (Kranzler et al., 1995).

Trazodone in our detoxified alcoholics has shown anxiolytic, antidepressant, and anti-craving efficacy. As to whether the drug could play a role in alcohol-oriented compulsive behaviours, this should be demonstrated by further controlled investigations. Trazodone has proven to be significantly more effective on anxiety than on craving and depression. We therefore cannot exclude the possibility that the drug may exert its anti-craving effects by controlling negative aspects of craving, i.e. subclinical symptoms of a protracted withdrawal such as anxiety, and that it could be used in the treatment of alcoholism after detoxification. In fact, it is well known that trazodone is an antidepressant drug endowed with a sedating spectrum of action (Feighner and Boyer, 1988; Beasley et al., 1991), so that with its use in alcoholism, withdrawal-related anxious symptoms are expected to improve.

As to the possible mechanism of action, trazodone as a serotonergic drug could be generally involved in the regulation of compulsive behaviour and in impulse control, as suggested by some recent clinical studies (Zubieta and Alessi, 1992; Khouzam et al., 1995). However, preclinical evidence suggests that trazodone, contrary to other 5-HT$_2$ antagonists, does not alter alcohol preference in rats (McMillen et al., 1994). Thus, the efficacy of the drug on craving could be indirectly due to its antidepressant and anxiolytic activity.

The previously cited trials with fluoxetine (Kranzler et al., 1995; Janiri et al., 1996) have been conducted under double-blind placebo-controlled conditions, so that any comparison between them and the present study should be made with caution. In fact, our data would indicate efficacy of a serotonergic drug on craving for alcohol, but, differently from fluoxetine (Janiri et al., 1996), the activity of trazodone does not appear to be independent of its activity on mood and anxiety. However, the outcome obtained in our sample of alcoholics could be subject to the bias of open studies. The encouraging results of the absence of dropouts may be also related to the type of post-detoxification programme adopted.

Acknowledgements — We gratefully acknowledge Dr Paolo Decina (Catholic University, School of Psychiatry, Rome, Italy) for his stimulating comments on the manuscript.

REFERENCES


