EFFECTS OF FLUVOXAMINE AND CITALOPRAM IN MAINTAINING ABSTINENCE IN A SAMPLE OF ITALIAN DETOXIFIED ALCOHOLICS

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Abstract — A 16-week, randomized study was performed to test the efficacy of two selective serotonin reuptake inhibitors (SSRIs) fluvoxamine and citalopram, in decreasing relapse and craving in alcoholics, and to investigate possible differences in their clinical profile. After detoxification, each of the 81 patients (55 males and 26 females) was randomly assigned to one of three groups: 23 subjects did not receive any pharmacological treatment, 25 were treated with fluvoxamine, 150 mg/day, and 33 with citalopram, 20 mg/day. All patients received standard cognitive-behavioural therapy. Craving was assessed twice a month using a 10-step scale. Every intake of alcohol was considered a relapse and the subject was taken out of the study. At the end of the study, both the fluvoxamine and citalopram groups showed a statistically higher rate of continuous abstinence (63.6 and 60.7%, respectively) compared to the group without pharmacological treatment (30.4%). Relapse severity did not differ among the three groups. Only citalopram showed a significant effect on craving throughout the study period. This study confirmed the efficacy of SSRIs as an adjunct to psychotherapy to prevent relapse in alcoholics. The relationship between the effects of these SSRIs on abstinence and craving, as well as the differences between their profiles, are discussed.

INTRODUCTION

Several neurotransmitters (e.g. dopamine, GABA, noradrenaline, etc.) have been implicated in the aetiology of alcoholism (Tabakoff and Hoffman, 1991). Recent studies have proposed a relationship between serotonin (5-HT) neurotransmission and alcohol consumption (Le Marquand et al., 1994a). Findings from animal studies have previously suggested the presence of a negative correlation between serotonergic functioning and alcohol intake (Le Marquand et al., 1994b).

Low levels of 5-hydroxyindoleacetic acid (5-HIAA) in cerebrospinal fluid (CSF) (Borg et al., 1985), low plasma tryptophan (TRP) availability (Buydens-Branchez et al., 1989), low platelet 5-HT content (Bailly et al., 1990), impaired functioning in some 5-HT receptors (Pandey et al., 1995) and reduced response to fenfluramine challenge tests (Baldin et al., 1994) have all been demonstrated in alcoholics. These data, despite some doubts concerning possible ethanol-induced alterations, support the hypothesis that serotonergic dysfunction may play a role in the aetiology of alcoholism. On the basis of this hypothesis, clinical trials investigated the efficacy of the selective serotonin reuptake inhibitors (SSRIs) in reducing alcohol intake in alcoholics. Fluoxetine (Gorelik and Paredes, 1992; Naranjo et al., 1994), fluvoxamine (Thomas, 1991; Alietti et al., 1993), and citalopram (Naranjo et al., 1987, 1992; Baldin et al., 1994) significantly reduced alcohol intake in alcoholics, thus increasing the length of abstinence or, at least, decreasing the number of drinks.

A possible explanation could be enhancement of 5-HT function which could result in a reduction of both the positive reinforcement of alcohol and craving. In fact, these effects did not seem to be due to the antidepressant or anxiolytic properties of these drugs, neither were they related to expectancy effects, nor to an alcohol-sensitizing reaction or adverse side-effects (Naranjo and Kadlec, 1991). On the contrary, all studies showed
Table 1. Demographic and clinical characteristics of the study sample

<table>
<thead>
<tr>
<th>Variable</th>
<th>No pharmacological treatment (n = 23)</th>
<th>Fluvoxamine (n = 25)</th>
<th>Citalopram (n = 33)</th>
<th>Significance (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48.4 ± 9.8</td>
<td>44.8 ± 10.4</td>
<td>52.2 ± 9.2</td>
<td>0.02</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>15</td>
<td>15</td>
<td>25</td>
<td>ns</td>
</tr>
<tr>
<td>Female</td>
<td>8</td>
<td>10</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Duration of alcohol-dependence (months)</td>
<td>159.3 ± 85.7</td>
<td>107.0 ± 88.5</td>
<td>124.8 ± 102.9</td>
<td>ns</td>
</tr>
<tr>
<td>MAST (scores)</td>
<td>32 ± 8.7</td>
<td>31.1 ± 7.6</td>
<td>35.1 ± 11.5</td>
<td>ns</td>
</tr>
<tr>
<td>Alcohol consumption (g/day)</td>
<td>381.1 ± 179.9</td>
<td>411.6 ± 101.4</td>
<td>428.6 ± 158.2</td>
<td>ns</td>
</tr>
</tbody>
</table>

Values are either numbers or means ± SD; ns denotes not significant.

a significant reduction in desirability, craving, and liking for alcohol in treated patients.

SSRIs are not a homogeneous class of drugs, as clinically relevant differences distinguish their molecules (Finley, 1994). While some differences of efficacy have already been suggested in some psychiatric disorders (Zanardi et al., 1996), to our knowledge these have not been reported in alcoholism.

These data prompted us to test whether the association of an SSRI with standard cognitive-behavioural therapy could decrease the frequency and the severity of relapse, as well as craving, in a group of alcoholics. We also decided to compare the efficacy of two SSRIs (fluvoxamine and citalopram) on treatment outcome.

MATERIALS AND METHODS

Sample

Eighty-one in-patients, 55 male and 26 female, admitted consecutively to our Alcohol Related Disorders Unit, were included in the study. Patients were aged from 18 to 70 years (mean 48.8 ± 10.1 SD) and all met the DSM-IV (American Psychiatric Association, 1994) criteria for alcohol physiological dependence. In particular, 44 subjects had a positive history for tolerance and 37 for withdrawal. All patients gave their informed consent. Table 1 shows demographic and clinical features of the sample.

Exclusion criteria were: (1) psychiatric co-diagnosis on Axis I; (2) pregnancy or nursing mothers; (3) severe somatic diseases not being treated.

Treatment

All patients were hospitalized for 3 weeks. After physical examination (including an electrocardiogram) and laboratory tests on blood and urine, they were treated for a mean time of 10 days (detoxification phase) with glutathione, S-adenosylmethionine, thiamine, and electrolytes. Chlorodesmethyldiazepam i.v. (mean dose 0.143 mg/kg/24 h) was used to control the occurrence of withdrawal symptoms. Trial medication, as well as psychological treatment, were started after the detoxification phase, when the patient was abstinent and had stopped any psychotropic treatment. All subjects were randomly included in groups 0 (no pharmacological treatment), 1 (fluvoxamine, 150 mg/day), or 2 (citalopram, 20 mg/day). The citalopram group was deliberately made larger a priori to achieve more experience with this drug, which is relatively new in Italy.

Any therapy for somatic diseases which had been started prior to the study, vitamin supplements and any other medication that was considered necessary (other than psychotropics), were not stopped during the study. After discharge, patients continued the treatment as out-patients and received the same cognitive-behavioural group therapy, daily for 8 weeks after detoxification, then weekly.
Table 2. Outcome results: patients abstinent and relapsed at the end of the study and abstinence duration in relapsed patients

<table>
<thead>
<tr>
<th>Patients abstinent at the end of the study</th>
<th>Fluvoxamine (n = 22*)</th>
<th>Citalopram (n = 28*)</th>
<th>Significance (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>7</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>Severe</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Mean duration of abstinence in relapsed patients (weeks)</td>
<td>7.3 ± 1.9</td>
<td>8.1 ± 2.8</td>
<td>8.1 ± 3.1</td>
</tr>
</tbody>
</table>

Expressions are as in Table 1.
*Patients who moved to other facilities or who dropped out because of side-effects were excluded from the analysis.

Assessment

Prior to detoxification, all patients were clinically assessed according to DSM-IV criteria. Alcohol-related problems were assessed by means of a specific questionnaire (MAST) (Selzer, 1971). Drinking history, as well as medical reports and family history, were also recorded. Daily alcohol consumption was calculated according to the following formula:

\[ g \text{ pure alcohol} = (\text{ml alcoholic drink} \times \% \text{ alcohol content by volume} \times 0.8) / 100. \]

Psychiatric assessment was made by a trained psychiatrist (blind to the medication) every 2 weeks starting from the fourth week. The presence of relatives, or other key individuals for the patient, was required at each assessment, to confirm the patient's report and to obtain additional information about their alcohol intake. Craving was assessed by means of a self-administered scale scored from 0 (no craving) to 9 (uncontrollable craving). A very conservative definition of relapse was chosen. Consequently, any alcohol intake was considered a relapse, and the patient was removed from the study. However, for the purposes of the study, the degree of the relapse was recorded clinically as moderate (simple abstinence violation or low and occasional intake, in any case lower than previous consumption) or as severe (four or more drinks on an occasion for both men and women, or any sign suggesting acute intoxication). All adverse events were classified in accordance with the WHO classification.

Statistical analysis

The \( \chi^2 \)-test and one-way ANOVA were used for inter-group comparisons of the same variable (SPSS Inc., 1988). The survival distribution of the three therapy groups was compared using a Survival Analysis (Statistica for Windows, 1993).

RESULTS

The three groups did not differ for sex distribution and length of alcohol dependence. Age was significantly different among the groups; however, this variable did not significantly affect the outcome measures. Thirty-eight patients completed the study, 35 were considered as having relapsed, seven (three in the fluvoxamine group and four in the citalopram group) moved to other facilities, and one (citalopram group) dropped out due to side-effects (severe nausea and anorexia) at week 12.

Table 2 shows the outcome results. At the end of the study, the percentage of patients continuously abstinent was statistically highest in the fluvoxamine (63.6%) and in the citalopram (60.7%) groups. The percentage dropped to 30.4% in the group treated only with psychologi-
Fig. 1. Survival analysis: cumulative percentage of non-relapsed patients.

...cal therapy. Drop-out patients (i.e. moved or excluded for side-effects) were not entered in this analysis. Both the severity of relapse and the mean duration of abstinence in relapsed patients did not approach statistical significance.

Age and sex did not differ between relapsed and non-relapsed patients. Only duration of dependence (mean 158.2 ± 111.4 SD months vs 113.4 ± 75.5 SD months, respectively) were significantly different \((P = 0.04)\) in all groups.

Figure 1 shows the cumulative percentage of non-relapsed patients in the three groups according to the Survival Analysis. This analysis confirmed the different survival distribution among the groups \((\chi^2 = 7.28, \text{df} = 2, P = 0.02)\), with the lowest cumulative percentage of survived patients in the group without pharmacological treatment.

Table 3 shows a comparison of the craving values. Craving differences were statistically significant at each assessment, except at week 16. The citalopram-treated group always had the lowest craving score of the three groups.

We used a contrast matrix to test the significance of the different craving values comparing groups two by two. No drug vs fluvoxamine was statistically different only at week 6 \((P = 0.05)\), while no drug vs citalopram was not statistically different except at week 12. Fluvoxamine vs citalopram showed significant differences at each assessment \((P = 0.00\) from the weeks 4 to 12, \(P = 0.01\) at week 14 and \(P = 0.03\) at week 16). We did not perform a within-group analysis, because of the large size reduction of the sample throughout the study period. The last records reflect only the craving of non-relapsed patients.

Table 4 shows the craving values in relapsed and non-relapsed patients at weeks 4, 6, and 8. We analysed only these three intervals, because the majority of relapsed patients ended the study after week 8. In the global sample, relapsed vs non-relapsed patients had significantly higher craving scores at each assessment. When the sample was divided into three groups according to treatment, a significant difference was found only at week 8 in the no drug, and at week 4 in the citalopram group.

Adverse events were not significantly different among the three groups, although the number of gastric symptoms was greater in the fluvoxamine and citalopram groups (data not shown).

**DISCUSSION**

In our sample of alcoholics, cognitive-behavioural therapy alone gave unsatisfactory results with regard to the short-term outcome.
findings suggest the usefulness of a combination of behavioural and pharmacological treatment with SSRIs. In fact, patients treated with fluvoxamine and citalopram showed a significantly higher percentage of continuous abstinence.

With regard to the effect of citalopram on alcohol intake, which was previously reported by Naranjo et al. (1992, 1995), we observed no significant reduction in intake in patients who relapsed. However, in our study, consumption was considered only for the clinical assessment of relapses. Thus, our findings are not necessarily comparable with the above mentioned reports. No relationship between pre-detoxification daily alcohol consumption and outcome was found in the present study.

In our study, fluvoxamine and citalopram showed a similar efficacy in preventing relapse in alcoholics, but not in reducing craving. In fact, only patients treated with citalopram reported a significant reduction in craving. This finding may be partly explained on the basis of the different pharmacological and pharmacokinetic profiles of the SSRIs (Lane et al., 1995; Zanardi et al., 1996). On the other hand, craving does not seem to be the only risk factor, as several other internal factors i.e. personality traits (Stark, 1992; Movalli et al., 1996), cognitive variables (Tiffany, 1990), and external cues (i.e. life events) could play a significant role in precipitating relapse.

We chose a medium-low dose for both drugs, despite previous reports suggesting higher doses, at least for citalopram (Naranjo et al., 1992, 1995; Baldin et al., 1994). Our choice was clearly conservative, in particular for fluvoxamine, given previous findings of adverse effects in alcoholics (Kranzler et al., 1993). However, it should be noted that previous studies focused mainly on reduction of alcohol intake and not on maintaining abstinence in previously detoxified subjects, making a strict comparison unlikely. Furthermore, either ethnic, sociocultural, or sample-linked differences could have played a role in conditioning pharmacological response. In conclusion, the adjunct of both fluvoxamine and citalopram to cognitive-behavioural therapy seems to be an effective tool to prevent relapse in detoxified alcoholics, at least in our sample. Although citalopram was effective in reducing craving, fluvoxamine did not show a similar effect. Furthermore, citalopram has been shown to display low inhibition of cytochrome P-450 enzymes (Brosen, 1993), lower protein binding than other SSRIs (Jusko and Gretch, 1976; Fredricson Overo, 1987) and, consequently, minor interactions with other drugs. Thus, citalopram may represent a first-choice drug in alcoholics, who frequently require treatment for alcohol-related somatic diseases.

Our findings should be considered very preliminary, given the reduced size of our sample and the short period of observation. However, at least for citalopram, they are in agreement with a previous study, suggesting the efficacy of this SSRI in short-term follow-up of abstinent alcoholics (Batel, 1995). Finally, the efficacy of SSRIs in the management of alcoholics supports the hypothesis of a serotonergic dysfunction in these patients, even though further research is required to better understand the specific factors which underly relapse and craving.

REFERENCES


