USE OF SEROTONIN (5-HYDROXYTRYPTAMINE) REUPTAKE INHIBITORS IN THE TREATMENT OF ALCOHOLISM

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Abstract — Animal studies have shown that alcohol consumption is reduced when serotonin (5-hydroxytryptamine, 5-HT) levels are increased in the central nervous system. Similarly, studies of alcohol-dependent human subjects have shown that treatment with 5-HT reuptake inhibitors (i.e., zimeldine, citalopram, fluoxetine, and fluvoxamine) decreases the desire to drink alcohol and improves symptoms of alcohol-related anxiety and depression in patients who have undergone detoxification. However, not all studies have shown them to be an effective treatment to help maintain recovery in alcohol dependence. The exact mechanisms of action of the 5-HT reuptake inhibitors are not yet fully understood and additional studies are needed. However, at this time, the 5-HT reuptake inhibitors may be effective pharmacotherapies for alcohol-related depression.

INTRODUCTION

Long-term pharmacological treatments can be prescribed for alcohol-dependent patients who have undergone detoxification. Psychotropic agents can be used to attenuate alcohol intake or treat psychiatric complications. It is hypothesized that some drugs, e.g., disulfiram, deter drinking because they cause adverse effects if alcohol is consumed after they are ingested. Other drugs, such as acamprosate (Lhuintre et al., 1990), lithium (Lejoyeux and Adès, 1993), zimeldine (Naranjo et al., 1984), buspirone (Bruno, 1989), bromocriptine (Borg, 1983), and naltrexone (Volpicelli et al., 1995), attenuate the desire to drink in a more direct manner.

Such substances may decrease the frequency of relapse, craving for alcohol, impulsivity, development of dependence and the need for alcohol (Adès and Lejoyeux, 1993). In addition, the serotonin (5-hydroxytryptamine, 5-HT) reuptake inhibitors can be administered to relieve symptoms of anxiety and depression in alcohol-dependent patients who have undergone detoxification.

THE EFFECTS OF 5-HT REUPTAKE INHIBITORS ON ALCOHOL INTAKE: ANIMAL STUDIES

Animal studies have shown that 5-HT plays a role in regulating alcohol consumption and that alcohol intake is reduced when 5-HT levels are increased in the central nervous system (McBride et al., 1989, 1993). In some studies, voluntary intake of alcohol was reduced and alcohol dependence was prevented when 5-HT reuptake inhibitors, such as zimeldine, citalopram, fluvoxamine, and fluoxetine were administered before the animals consumed alcohol. McBride et al. (1989) have shown that fluoxetine attenuates alcohol preference and decreases alcohol consumption, and Zabik (1989) reported that fluoxetine has a global effect on carbohydrate intake, liquid consumption, arousal and impulsivity.

A number of studies (McBride et al., 1989, 1993) have demonstrated that 5-HT and serotonergic agents mediate satiety: i.e. reduced concentrations of 5-HT in the brain stimulate overeating, and increased concentrations promote anorexia. In addition, the 5-HT reuptake inhibitors have been shown to have an effect on appetite. In some studies, rats that were treated with 5-HT reuptake inhibitors had a suppressed food intake, whether they were alcohol- or water-preferring (McBride et al., 1989, 1993). The 5-HT reuptake inhibitors do not suppress fluid intake and satiety through a sedative/hypnotic action. Rather, their effects are non-specific, since they also inhibit ingestion of dextrose and morphine-sucrose solutions (Zabik, 1989).

In summary, 5-HT reuptake inhibitors decrease the desire to consume reinforcing and/or palatable substances including alcohol. It is not known which 5-HT receptors are involved in the
regulation of alcohol consumption, and 5-HT reuptake inhibitors may not act by enhancing postsynaptic 5-HT receptor activity. Rather, they may act primarily at the level of the 5-HT cell body. Thus, 5-HT reuptake inhibitors block the synthesis, release and turnover of 5-HT, as well as the firing of 5-HT neurons.

5-HT AND THE ALCOHOL-DEPENDENT PATIENT

Van Praag et al. (1987) suggested that the impulse control disorders related to alcoholism may be caused by a deficiency in 5-HT. Boismare et al. (1987) found that, after 10 alcohol-dependent patients abstained from drinking alcohol for 3 weeks, platelet affinity for 5-HT increased. In addition, in a study by Bailly et al. (1993), alcohol-dependent patients had a significantly lower mean platelet 5-HT level than controls. This did not appear to be related to the patients' age, sex, weight, or prior history of alcohol consumption ($t = -4.7, P < 0.005$). This finding is consistent with data reported previously (Boismare et al., 1987; Buydens-Branchey et al., 1989).

According to Bailly et al. (1993), alcohol appears to have a biphasic effect on serotonergic mechanisms. Acute administration of alcohol results in a reserpine-like action of 5-HT release; chronic alcohol consumption results in an adaptive 'vicious circle' that leads to a depletion of 5-HT. This mechanism could explain the decrease in platelet 5-HT that is often seen in alcoholics.

In a recent study of alcohol-dependent criminal offenders, Virkkunen et al. (1994) found that impulsive, violent, and fire-setting behaviours were associated with low concentrations of 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid. Research has shown that 5-HIAA, the primary metabolite of 5-HT, can be measured in humans (Ortiz et al., 1988). Virkkunen et al. (1994) also reported that violent alcoholic offenders who premeditated their crimes had normal-to-high cerebrospinal fluid concentrations of 5-HIAA.

THE EFFECTS OF 5-HT REUPTAKE INHIBITORS ON ALCOHOL CRAVING

Data from animal studies and preclinical experiments have led researchers to test the use of 5-HT reuptake inhibitors as a putative treatment for alcohol craving. In controlled studies testing the efficacy of 5-HT reuptake inhibitors in the treatment of alcoholism, clinicians should evaluate patient compliance systematically (Naranjo et al., 1987a,b). At least one objective method, such as laboratory testing for the presence of drug metabolites, and one indirect method, such as patient self-report or pill count, should be used to evaluate patient compliance with therapy. Clinicians must also evaluate, with standardized methods, the evolution of alcohol consumption, psychiatric and somatic complications, and the presence or absence of the alcohol dependence syndrome (Naranjo et al., 1987a).

Zimeldine was the first 5-HT reuptake inhibitor to be evaluated for its effects on alcohol consumption. In a double-blind, randomized crossover study, Naranjo et al. (1984) found that the use of zimeldine (200 mg/day) slightly increased the number of days that 16 mildly to moderately dependent, non-depressed drinkers who were recruited by advertisements remained abstinent from alcohol during five 2-week periods. Zimeldine was poorly tolerated: three patients developed drug-induced hepatitis and three additional patients dropped out of the study because of side-effects. At the end of the study, only 10 subjects were still being treated with zimeldine. Zimeldine was significantly more effective than placebo during the short 2-week observation period, and 92.3% of the subjects were responders or partial responders. For the subjects who responded to zimeldine, the mean decrease in the total number of drinks consumed per day was 38.2% and the mean increase in the total number of days of abstinence from alcohol was 260% (Naranjo et al., 1984).

In another double-blind, randomized, crossover study of mildly to moderately dependent drinkers recruited by advertisements, Naranjo et al. (1987b) studied the effects of citalopram (20 and 40 mg/day) on alcohol consumption and reported that a 20 mg/day dosage of citalopram had no effect on alcohol consumption; however, a 40 mg/day dosage decreased both the total and the mean number of drinks consumed per day from baseline. The 40 mg/day dosage of citalopram also increased the number of days that subjects in the study remained abstinent from alcohol. In addition, patterns of response varied.
significantly among subjects enrolled in the study. Sixty-three per cent of the subjects who received citalopram (40 mg/day) were responders or partial responders. For those who responded to 40 mg/day of citalopram, the mean decrease in the total number of drinks consumed per day was 33.2%, and the mean increase in the total number of days abstinent from alcohol was 250% (Naranjo et al., 1987b).

Balldin et al. (1994) recently studied the effect of citalopram on alcohol intake in a randomized, double-blind, placebo-controlled crossover study. Thirty men with a history of heavy alcohol consumption (mean daily alcohol intake [±SD], 111 ± 51 g) completed the study. After a 2-week baseline period, subjects received either citalopram (40 mg/day) or placebo for 5 weeks. No difference was found between citalopram and placebo treatment in mean daily alcohol intake or the number of days of abstinence; however, the response to citalopram was negatively correlated ($r = 0.67, P < 0.01$) with baseline levels of mean daily alcohol intake. Therefore, the sample was divided into two subgroups on the basis of whether mean daily alcohol intake was above or below 107 g — the median baseline level of daily alcohol intake. In the group with higher baseline intake (138 ± 25 g), citalopram treatment did not reduce daily alcohol intake compared with placebo treatment. In contrast, subjects with lower baseline alcohol intake (85 ± 15 g) who received citalopram experienced a significantly greater reduction in mean daily alcohol intake compared with subjects who received placebo ($P < 0.01$). Citalopram appears to be effective in a subgroup of heavy drinkers who consume between 60 and 100 g of ethanol daily.

In another double-blind, placebo-controlled study of citalopram (40 mg/day), Naranjo et al. (1992) confirmed the effect of this 5-HT reuptake inhibitor on alcohol craving. During the week of treatment, citalopram significantly decreased desire, craving and liking for alcohol compared with placebo (all $P < 0.05$).

Naranjo et al. (1988) have also shown that fluoxetine (40 and 80 mg/day) decreases craving for alcohol. In a 4-week study of 10 subjects who met the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R) criteria for alcohol dependence, they measured alcohol consumption by direct observation. Craving for alcohol was rated each morning and evening by using a visual analogue scale. Results showed that subjects who were treated with fluoxetine had a 14% decrease in alcohol consumption and a significant decrease in evening craving for alcohol (Naranjo et al., 1988).

In a 12-week, randomized, placebo-controlled trial, Kranzler et al. (1995) administered fluoxetine and concomitant weekly psychotherapy to 101 alcohol-dependent subjects. Study subjects were not selected on the basis of the presence of comorbid major depression. Fluoxetine-treated subjects received an initial dosage of 20 mg/day that was increased to a maximum of 60 mg/day as tolerated. In contrast to other researchers' findings, Kranzler et al. observed that placebo-treated subjects were more compliant with the medication regimen and remained in the study longer than fluoxetine-treated subjects. In addition, both groups consumed less alcohol during treatment as compared with before treatment. The number of drinking days ($F = 566.44; df = 1, 77; P < 0.0001$), drinks per day ($F = 211.19; df = 1, 77; P < 0.0001$) and drinks per drinking day ($F = 118.82; df = 1, 77; P < 0.0001$) were decreased in both groups. Both male and more compliant subjects showed a greater reduction in alcohol consumption. These effects continued during the 6-month follow-up period. Fluoxetine treatment did not reduce relapse frequency or severity when compared with placebo treatment. However, alcohol consumption was significantly reduced during the period of active treatment and relapse prevention training, which was provided to all subjects and which also reduced their alcohol consumption.

The absence of an untreated control group that received neither fluoxetine nor relapse prevention training makes it impossible to determine what impact psychotherapy had on alcohol consumption. The potent non-pharmacological effects observed in this study may have obscured a modest effect of treatment with fluoxetine. The pharmacological effect of fluoxetine on alcohol intake also may have been transient and not observed by the researchers who assessed drinking outcome after a mean of 8.7 (SD = 4.3) weeks of treatment.

In addition, in an open study, fluvoxamine has also been reported to decrease depression and alcohol craving in the alcohol-dependent patient (Archambault and Douge, 1988). Sixty alcohol-
dependent subjects received either fluvoxamine (200–300 mg/day) or arginine (3 g/day) for 28 days. All subjects who fulfilled DSM-III criteria for alcohol dependence underwent inpatient detoxification. After 28 days, four subjects who received fluvoxamine and eight subjects who received arginine interrupted treatment. Fluvoxamine-treated subjects were significantly less depressed than arginine-treated subjects. Mean Montgomery–Asberg Depression rating scale scores were 0.7 and 5.6, respectively ($P < 0.0001$, Kruskal–Wallis test). Craving for alcohol, as assessed with a visual analogue scale, was lower among the fluvoxamine- than among the arginine-treated subjects (0.3 and 1.4, respectively); however, the difference was not statistically significant.

In summary, zimeldine, citalopram, and fluoxetine exert significant inhibitory effects on alcohol intake. The inhibitory effects were transient and, in most cases, were noted only in early-stage, non-dependent problem drinkers. Patients with a lower level of alcohol intake also responded better to treatment with 5-HT reuptake inhibitors. In these cases, the use of 5-HT reuptake inhibitors effectively reduced alcohol consumption by 20–30% (Naranjo and Sellers, 1989). However, the effects on alcohol intake and craving were not always associated (i.e. some patients experienced a significant reduction in desire for alcohol, but a slight reduction in alcohol intake).

In all studies, there was variation in individual patterns of response. Unfortunately, no subject trait, other than the baseline level of daily alcohol consumption (Balldin et al., 1994) or medication-related factor predicts therapeutic response. Therefore, therapeutic effects cannot be maximized by grouping patients according to possible predictors of treatment outcome.

The clinical effects of the 5-HT reuptake inhibitors were different from those produced by other agents that deter alcohol intake: patients treated with 5-HT reuptake inhibitors did not experience alcohol-sensitizing reactions. Since most of the patients who were treated with 5-HT reuptake inhibitors were not depressed and their depression scores remained unchanged from baseline, it is likely that the very modest therapeutic effect of the 5-HT reuptake inhibitors did not result from an antidepressant effect or from the treatment of 'secondary alcoholism'.

In addition, the effects of 5-HT reuptake inhibitors, particularly fluoxetine, were transient. Studies that evaluated the effects of 5-HT reuptake inhibitors after 1 or 2 weeks of treatment were positive more often than long-term studies, which evaluated the patients after 1 month of treatment. Even when the effect on alcohol intake was statistically significant, its intensity was mild to moderate. Kranzler et al. (1995) found that relapse prevention training alone reduced alcohol intake better than concomitant treatment with fluoxetine. Studies of potential treatments for alcoholism involving both humans and animals demonstrate that 5-HT reuptake inhibitors may reduce alcohol consumption by decreasing desire, craving and liking for alcohol (Naranjo et al., 1992).

Published studies on the treatment of alcoholism still cause controversy about the interpretation of results; therefore, there is clearly a need for long-term studies that include simultaneous evaluation of anxiety, depression and alcohol intake. Long-term treatment with 5-HT reuptake inhibitors is often limited because of the development of drug tolerance. Tolerance, which might develop as early as 1 week into treatment, might lower the effectiveness of the 5-HT reuptake inhibitors at decreasing alcohol intake.

According to Gorelick (1993), lower doses of 5-HT reuptake inhibitors may produce 5-HT receptor changes that are different from changes produced by higher doses; therefore, drug tolerance may develop less rapidly when lower doses of 5-HT reuptake inhibitors are used. Gorelick (1993) also suggested that specific 5-HT receptor agonists and combinations of lithium and 5-HT reuptake inhibitors should be studied in the future. In the meantime, combinations of serotonergic agents should be prescribed cautiously, because they may put depressed or alcohol-dependent patients at risk for the 5-HT syndrome (Lejoyeux et al., 1994). This syndrome is associated with myoclonus, tremor, digestive symptoms, anxiety and occasionally delirium.

**USE OF 5-HT REUPTAKE INHIBITORS IN THE TREATMENT OF ALCOHOL-RELATED DEPRESSION**

Data from clinical practice and epidemiological studies confirm that depression is common among
alcoholics (Roy et al., 1991; Brown et al., 1995). Brown and Schuckit (1988) found that 25–60% of alcohol-dependent patients have symptoms of clinical depression that are severe enough to interfere with daily functioning. Depression modifies the evolution of alcoholism and increases its severity; depressed alcoholics have an increased risk of suicidal behaviour (Roy et al., 1990) and poorer treatment outcomes (Rounsaville et al., 1987).

The association between alcoholism and depression is especially frequent in women (Turnbull and Gomberg, 1988, 1990) and elderly people (Miller et al., 1991). In such populations, depression is often induced by the ingestion of alcohol or by the negative consequences that alcohol dependence has on personal or professional relationships. In 90% of the cases, depressive symptoms disappear if the patient abstains from drinking alcohol (Brown and Schuckit, 1988). In rare cases, when depressive symptoms last more than 1 month, the administration of antidepressants can improve the clinical state of the patient (Brown and Schuckit, 1988).

5-HT reuptake inhibitors are an effective treatment for alcohol-related depression. They alleviate symptoms of anxiety and are well-tolerated. In an open-label study, Cornelius et al. (1993) found that depressive symptoms and alcohol consumption were significantly reduced in alcohol-dependent patients with major depression who were treated with fluoxetine (20 to 40 mg/day). Beck Depression Inventory (BDI) scores were reduced 10.6 points (t = 3.39, df = 1, P < 0.05), and Hamilton depression scale scores were reduced 6.4 points (t = 2.75, df = 1, P < 0.01). Kranzler et al. (1995) demonstrated that, compared with placebo, fluoxetine reduced BDI scores among alcohol-dependent subjects. Depressed subjects showed a greater reduction in BDI scores (mean decrease of 6.7) than non-depressed subjects (mean decrease of 2.7). BDI scores also declined significantly after detoxification in placebo- and fluoxetine-treated patients. For subjects with current major depression, Hamilton depression scale scores declined significantly more among fluoxetine- than among placebo-treated subjects [reduction of 7.3 and 1.8, respectively (F = 22.32; df = 1, 68; P < 0.001)].

Linnola et al. (1993) administered fluvoxamine (50 or 100 mg) to healthy patients as a single agent and in combination with alcohol, and found that neither treatment regimen produced psychomotor or cognitive impairments. Fluvoxamine did not alter autonomic nervous system functioning, nor did it exacerbate or improve alcohol-induced memory impairments; however, patients who took fluvoxamine appeared to have an enhanced recognition of words (Linnola et al., 1993).

Other antidepressants, such as tricyclic antidepressants (TCAs), have been shown to be effective in treating alcohol-related depression (Weiss and Mirin, 1989). However, in the event of over-dosage, the effects of 5-HT reuptake inhibitors are not as lethal as the effects of TCAs (Ciraulo and Renner, 1991). In addition, combination therapy may benefit alcohol-dependent patients who are depressed; pharmacotherapy should be administered in conjunction with psychotherapeutic interventions, social treatment and group therapy. Combining several modes of treatment will maximize therapeutic effect. Finally, clinicians should advise patients that abstinence from alcohol is the best treatment for alcohol-related depression.

In conclusion, patients with a lower level of alcohol intake respond better to treatment with 5-HT reuptake inhibitors. In addition, the effects of these treatments on alcohol intake and craving are not always associated. Patients who report a significant decline in craving for alcohol may slightly decrease their alcohol intake. No subject trait, other than the amount of alcohol consumed (Ballin et al., 1994), or medication-related factor predicted therapeutic response. Therefore, therapeutic effects cannot be maximized by grouping patients according to these possible predictors of outcome. Studies of potential treatments for alcoholism involving both humans and animals demonstrate that 5-HT reuptake inhibitors may reduce alcohol consumption by decreasing desire, craving and liking for alcohol (Naranjo et al., 1992). However, interpreting published study results on the treatment of alcoholism is still controversial. There is clearly a need for long-term studies that include simultaneous evaluation of anxiety, depression and alcohol intake.

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relationship to clinical and cerebrospinal fluid variables. 
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