

The Use of Selective Serotonin Reuptake Inhibitors in Treating Alcoholic Subtypes

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The usefulness of selective serotonin reuptake inhibitors (SSRIs) to treat alcohol dependence continues to be a subject of debate. Most recently, investigations have tried to predict whether a given patient will respond to SSRIs in terms of reducing excessive alcohol drinking. The subtyping of alcohol-dependent individuals has ranged from relatively simple classifications (e.g., presence of comorbid depression) to more complex classifications (e.g., potential to have abnormalities in serotonin [5-HT] neurotransmission). Although only a few studies have been completed, results thus far indicate that alcoholic subgroups are differentially responsive to 5-HT pharmacotherapy with respect to drinking-related outcomes. In addition, there are preliminary results encouraging the use of SSRIs in combination with other medications for treating alcohol dependence in patients with and without comorbid psychiatric disorders. Information from these studies is promising, suggesting the need for further investigation.

(*J Clin Psychiatry* 2001;62[suppl 20]:26-31)

The usefulness of selective serotonin reuptake inhibitors (SSRIs) to treat alcohol dependence remains controversial. This article reviews the extant literature on randomized clinical trials of SSRIs among alcohol-dependent patients. In-depth descriptions of these studies have been published elsewhere in 2 comprehensive reviews (trials prior to the mid-1990s by Pettinati¹ and trials from the mid-1990s to 2000 by Pettinati et al.²). In addition, this article presents information on 2 new lines of inquiry: SSRI response rates in alcoholic subtypes and recently initiated trials of medication combinations with SSRIs in the treatment of alcohol dependence.

RATIONALE FOR PRESCRIBING SSRIs IN THE TREATMENT OF ALCOHOL DEPENDENCE

The serotonin (5-HT) neurotransmitter system is extensive and serves multiple purposes in the brain. Thus, it is not surprising that 5-HT has been implicated in varied processes including appetite, mood, arousal, impulse control, and personality traits (e.g., antisocial or borderline personality disorder).³⁻⁶ The 5-HT system has also been implicated in alcohol consumption.⁷ Preclinical studies of acute alcohol administration in animals and humans,⁸⁻¹¹ neuropathologic examination of alcohol-preferring animals and humans,¹²⁻¹⁵ and application of pharmacologic probes that affect the 5-HT system¹⁶⁻²⁰ have all suggested that serotonergic neurotransmission and alcohol intake are linked. In addition, dysfunction of the 5-HT system has been implicated in alcohol disorders.^{1,21-26} Consequently, pharmacologic agents that are selective for 5-HT receptors have been utilized to treat alcohol dependence and its associated comorbid conditions. The SSRIs, in particular, have been tested in humans in a number of clinical treatment trials.

An advantage of the currently available SSRIs is their safety profile. These agents have a low potential for abuse, are associated with a low rate of seizures, do not potentiate alcohol effects on motor skills or cognition, and are relatively safe in overdose. In addition, the frequency of SSRI-related adverse events is relatively low, with most side effects reported as either mild or moderate in severity.

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Presented at the closed roundtable symposium "Pharmacological Treatment of Alcohol Abuse and Addiction," which was held on February 28, 2000, in Philadelphia, Pa., and supported by an unrestricted educational grant from Forest Laboratories, Inc.

Supported by grant R01-AA09544 from the National Institute on Alcohol Abuse and Alcoholism (NIAAA), Bethesda, Md.

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Typically, these adverse events subside with discontinuation of the medication. In the past, chronic drinkers were rarely prescribed medications due to safety concerns surrounding the coadministration of medications with alcohol or a depressed mood. Given the low-risk adverse event profile of SSRIs, there is a greater margin of comfort in providing pharmacotherapy to those with a history, or current episode, of chronic excessive drinking.

CURRENT STATUS OF CLINICAL TRIALS OF SSRIs TO TREAT ALCOHOLISM

Animal studies have consistently shown that treatment with 5-HT pharmacologic agents reduces alcohol intake.^{27,28} These studies, in combination with encouraging preclinical human data, stimulated various clinical investigations into the effectiveness of 5-HT agents in reducing alcohol consumption. However, despite the number of double-blind, placebo-controlled studies that have been conducted in the past 20 years, the efficacy of 5-HT medications for treating alcohol-dependent patients continues to be debated.

Several double-blind, placebo-controlled trials with different SSRIs (zimelidine, citalopram, viquiline, and fluoxetine)^{29–32} demonstrated a reduction in alcohol consumption by heavy social drinkers, yet the daily doses were higher than those of suggested prescribing practices (reviewed by Pettinati¹). However, these studies were not directly relevant in the treatment of patients with alcohol-dependence disorders. Subsequently, there have been several double-blind, placebo-controlled studies of treatment-seeking alcohol-dependent patients who were treated with 60 to 80 mg/day of fluoxetine.^{33–35} In contrast to the results of preclinical research and the studies of heavy social drinkers, fluoxetine was not associated with greater reductions in drinking when compared with placebo (reviewed by Pettinati et al.²).

In an earlier review,¹ it was reasoned that although alcohol consumption has been linked to 5-HT systems, all individuals who drink excessively or meet diagnostic criteria for alcohol dependence may not have clinically significant 5-HT abnormalities. The 5-HT pharmacotherapy clinical trials conducted prior to the mid-1990s did not address whether all or just a portion of alcohol-dependent individuals had characteristics suggestive of 5-HT dysregulation. Therefore, it was recommended that SSRI response be re-evaluated in selected alcoholic subgroups distinguished by characteristics of potential 5-HT abnormalities in addition to excessive drinking. Alcohol-dependent patients with behaviors suggestive of 5-HT dysregulation, such as depression, anxiety, and compulsive and/or impulsive behaviors, might be better candidates for SSRI pharmacotherapy.

It was initially believed that the alcoholic subgroup with potential 5-HT abnormalities would benefit most from SSRI treatment.^{1,24} However, results from SSRI trials with alcoholic subtypes suggest that patients with multiple

signs of 5-HT abnormalities may be overly sensitive to SSRI treatment and respond poorly to an SSRI.^{2,36,37} The inconsistencies among the clinical trials of 5-HT pharmacotherapy for reducing alcohol consumption may be explained by the generic definition of alcohol dependence.

SSRI PHARMACOTHERAPY FOR SELECTED ALCOHOLIC SUBTYPES

Recently, various studies have tried to predict whose drinking will respond better to SSRI medications than placebo based on the characteristics of alcoholic subgroups. Subtyping has ranged from the simple (e.g., presence of comorbidity) to more complex classifications (e.g., potential to have multiple abnormalities in 5-HT neurotransmission). Alcoholic subtypes can be divided into those distinguished by other comorbid psychiatric disorders and those related to different forms of alcoholism. These 2 classifications will be discussed separately, since the rationale for 5-HT pharmacotherapy differs dramatically in each subtype, although the specific pharmacotherapy may be identical.

Utility of SSRIs for Comorbid Disorders in Alcohol Dependence

The presence of 2 or more disorders in the same patient is referred to as *comorbidity*. Two large epidemiologic studies conducted in the United States demonstrated that there is a high prevalence of alcohol dependence and comorbidity in the general population.^{38,39} The Epidemiologic Catchment Area study,³⁸ which obtained data on more than 20,000 people, reported that the lifetime prevalence of any psychiatric disorder was 44% in people with an alcohol disorder. Similarly, the National Comorbidity Study,³⁹ which conducted structured psychiatric interviews in more than 8000 people, reported that psychiatric disorders were more common in people with an alcohol disorder than in those without one.

A DSM diagnosis of depressive disorder is one of the most common comorbid problems associated with alcohol dependence.^{38–40} In fact, the majority of female alcoholics suffer from comorbid depression.⁴¹ It has been repeatedly demonstrated that depression can be treated successfully with pharmacotherapy, although the seminal studies excluded those with comorbid alcohol dependence. Nonetheless, it can be argued that individuals with a major depressive disorder, regardless of alcohol dependence, should be treated with pharmacotherapy. There are now a number of serotonergic medications that have received approval in the United States by the U.S. Food and Drug Administration (FDA) for the treatment of depression, with the most common being the SSRIs (citalopram, fluoxetine, paroxetine, and sertraline). However, there is not enough evidence to determine whether the SSRIs reduce the symptoms of depression among patients with alcohol dependence.

To date, there is only 1 double-blind trial that evaluated drinking reductions in patients prescribed 5-HT pharmacotherapy (20–40 mg/day of fluoxetine) for current depression who also met diagnostic criteria for alcohol dependence.^{42,43} The 51 patients in the study were seeking treatment for depression, had a current diagnosis of major depression, were suicidal at the time of admission, and were also found to be alcohol-dependent. After 10 weeks, the investigators found significantly greater reductions in both depressive symptoms and alcohol consumption in the fluoxetine-treated group as compared with placebo-treated patients. Also of note is one double-blind study⁴⁴ (N = 36) in which sertraline reduced depressive symptoms in recently abstinent alcoholics. However, sertraline's effects on drinking were not assessed. Thus, double-blind studies on the treatment of depressed alcoholics with 5-HT pharmacotherapy are scarce. Although the results thus far support the prediction that SSRIs could have a significant impact in alcohol-dependent patients with comorbid depression, replication and further investigation are required.

In an attempt to determine whether SSRI therapy could reduce alcohol intake in the absence of comorbid depressive illness, Pettinati and colleagues⁴⁵ studied the effects of sertraline, 200 mg/day, among 47 alcohol-dependent patients with no personal or family history of depression. During the 14-week, double-blind, placebo-controlled trial, all patients received weekly sessions of Twelve-Step Facilitation Treatment.⁴⁶ A significant reduction in the number of drinking days was found in the sertraline-treated alcohol dependent patients compared with those taking placebo. The fact that treatment with an SSRI was useful in a strictly defined nondepressed subgroup of alcoholics is counterintuitive and warrants replication.

There are several published studies in which buspirone, a 5-HT_{1A} partial agonist, was given to highly anxious alcohol-dependent patients.^{24,47–49} Several, but not all, of the studies found that buspirone reduced both anxiety and drinking, yet research work is needed to clarify the conflicting results obtained in these studies. It is also of importance to examine the effect of SSRIs on comorbid anxiety and alcohol dependence given that several have recently been studied for their anxiolytic properties.⁵⁰

The studies mentioned above, while few in number, raise questions about the usefulness of SSRI treatment in alcoholics with comorbid psychiatric disorders other than depression and anxiety, including posttraumatic stress disorder (PTSD) and borderline personality disorder. Open clinical trials on alcohol dependence and PTSD have been encouraging⁵¹; larger double-blind studies are needed.

Utility of SSRIs for Different Types of Alcohol Dependence

Alcohol dependence has been described as a complex, multidimensional disorder.⁵² There have been several attempts to discriminate alcohol subtypes, e.g., using the age

at onset of problem drinking, presence or absence of a family history of alcoholism, patterns of drinking, extent or kind of psychopathology, or personality characteristics. The primary aim of developing alcohol subtypes is to determine whether genetic and environmental factors contribute to the development of alcoholism. For this purpose, many of the univariate and multivariate models for segregating alcoholics are useful.

Discussions that have centered on the possibility that subtyping may provide a method for matching alcohol-dependent patients with specific pharmacotherapies are most relevant to this article.^{1,2,24,53,54} In particular, the potential for an alcohol typology to discriminate patients on the basis of potential differential 5-HT reactivity may be important in evaluating the usefulness of SSRI treatment in alcohol dependence. Individuals at high risk for severe alcoholism have all of the characteristics associated with 5-HT abnormalities, i.e., earlier-onset alcoholism, more childhood risk factors, sociopathy, psychopathology (e.g., depression), alcohol-related problems, severe alcohol dependence, and use of multiple drugs.^{21,22,25,55–58} For example, Buydens-Branchey et al.^{21,22} found that patients with early-onset alcohol dependence (before the age of 20 years) exhibited an inverse relationship between plasma tryptophan levels—a precursor of 5-HT—and the extent of depression and aggression. Individuals with early-onset alcohol dependence also became anxious,^{58,59} displayed an increased craving for alcohol,⁵⁵ and showed a blunted cortical response when given *m*-chlorophenylpiperazine (*m*-CPP), a 5-HT agonist.⁵⁸

High-risk/severe alcoholics have been classified in a number of ways.^{60–62} For example, Babor and colleagues^{61,62} have empirically constructed a dichotomous alcohol typology in which high-risk/severe alcoholics, referred to as “type B,” are characterized by early onset of alcohol problems, greater severity of dependence, use of multiple drugs, a more chronic treatment history (despite their younger age), greater psychopathology, and a poorer prognosis following alcoholism treatment. By comparison, “type A” alcoholics are characterized by later onset of problem drinking, fewer childhood risk factors, less severe alcohol dependence, less drug use, fewer alcohol-related problems, less psychopathology, and a better response to traditional alcoholism treatment.

In contrast to Babor's broadly defined alcoholic subtypes A and B, Cloninger's subtypes 1 and 2 are based primarily on personality structure and early onset of alcohol dependence.⁶⁰ Nonetheless, there is significant overlap between type B and type 2 alcoholics, as well as type A and type 1 alcoholics (see comparison of traits between Babor's and Cloninger's typologies described in the review by Pettinati¹). However, Babor's typology repeatedly has had good predictive validity.⁶²

There have been 3 randomized trials of different SSRIs investigating type A or type 1 and type B or type 2 alcohol-

ics. Two placebo-controlled studies evaluated an SSRI in type A and B alcoholics,^{36,37} and the third examined type 1 (late-onset) and type 2 (early-onset) alcoholics.⁶³ The latter study found no differential response rates to drinking when patients were classified as type 1 and 2 alcoholics. However, this was not the case in the 2 studies that used Babor's typology.

Kranzler et al.³⁶ evaluated drinking outcomes in type A (N = 60) and B (N = 35) alcoholics who had received 60 mg/day of fluoxetine treatment or placebo, as well as weekly cognitive-behavioral therapy, for 12 weeks. This study (a reanalysis of an earlier negative clinical trial of fluoxetine³⁵) used a k-means clustering procedure to determine type A and B subjects. All patients reduced their drinking to a certain extent, mostly credited to the psychosocial treatment provided to all patients. However, since type B alcoholics had the most characteristics suggestive of 5-HT abnormalities, it was anticipated that they would do even better than type A alcoholics with fluoxetine treatment. Unexpectedly, type B alcoholics drank more frequently during the trial when treated with fluoxetine as compared with placebo. Although there was a trend for medication to provide an advantage over placebo in type A alcoholics on some of the outcome variables, the differences were not statistically significant.

A more recent double-blind, placebo-controlled study by Pettinati and colleagues³⁷ attempted to replicate or refute Kranzler and colleagues' findings in a comparably large treatment population (N = 100) using another SSRI, sertraline (200 mg/day), for 14 weeks. Again, a k-means clustering procedure was applied to the sample of alcohol-dependent subjects to classify them into lower risk/severity (type A, N = 55) and higher risk/severity (type B, N = 45) subgroups. The results supported those reported earlier by Kranzler and colleagues³⁶; all patient groups significantly reduced their drinking during the trial, and individuals with type B alcohol dependence drank more frequently during the trial if they had taken sertraline rather than placebo. Pettinati and colleagues³⁷ also found that patients with type A alcohol dependence had an exceedingly high rate of total abstinence during the 14-week trial when treated with sertraline (64% abstinent) compared with placebo (< 10% abstinent).

Taken together, the results of these 2 studies initiated a reevaluation of the hypothesis that 5-HT abnormalities related to certain subtypes of alcohol dependence would be successfully treated by 5-HT stimulation, resulting in reductions in drinking and total abstinence. In fact, the opposite effect seems to occur: type B alcoholics were not responsive to 2 SSRIs, fluoxetine and sertraline. In addition, the findings suggest that type B alcoholism, which potentially includes multiple indicators of 5-HT abnormalities, may be more sensitive than type A alcoholism to SSRI pharmacotherapy. For example, type B alcoholics may have an abnormally low capacity to synthesize 5-HT,

which may result in an adaptive up-regulation of 5-HT receptors, making the system more sensitive to 5-HT agonist agents.⁵⁹

In sum, although the results were opposite of what was predicted, these 2 studies support the hypothesis that distinct forms of alcohol dependence differentially respond to 5-HT pharmacotherapy. These results may, in some cases, appear to contradict the prior review by my colleagues and me of successful drinking outcomes in depressed and anxious persons with alcohol dependence. The explanation may be as parsimonious as the definition of a singular versus a complex alcohol subtype—that is, if a singular 5-HT pathway is disrupted, perhaps SSRI pharmacotherapy can restore some balance, whereas disruption of multiple overlapping 5-HT systems may aggravate rather than ameliorate 5-HT dysfunction³⁶ (see also Sahakian et al.⁶⁴ and Virkkunen and Narvanen⁶⁵). Nonetheless, it is premature to speculate further until more studies evaluating SSRIs in alcoholic subtypes are conducted, i.e., studies evaluating subgroups related by common comorbidity, and, independently, subgroups related by characteristics of higher risk/severity versus lower risk/severity. Also, in the latter case, future studies should focus on the reliability and validity of univariate versus multivariate approaches to distinguish alcoholics on the dimension of the degree of risk/severity. See, for example, 5-HT studies using univariate approaches of early versus late onset of problem drinking^{54,66} and presence versus absence of family history of alcoholism.⁶⁷

COMBINATION PHARMACOTHERAPY WITH SSRIs IN TREATING ALCOHOL DEPENDENCE

In comparison to other psychiatric disorders, the use of combination pharmacotherapy to treat alcohol dependence is in its infancy; no large randomized controlled trials are yet available. This is quite likely due to the fact that, until recently, pharmacotherapy for alcohol dependence was limited to treating alcohol withdrawal. In addition, there are persistent concerns that the possibility of mixing medications with drinking may increase mortality and morbidity (described above). However, such fears have been greatly reduced with the advent of SSRIs and other medications with a favorable safety profile. Finally, treatment compliance has typically been poor among those addicted to alcohol, resulting in poor outcomes that are misattributed to the medication's level of effectiveness.⁶⁸ Increased awareness, knowledge, and strategies for maximizing medication compliance are now available.^{69,70}

The development of rationales for combination pharmacotherapies has paralleled the subtyping of alcoholics in terms of evaluating specific types of therapies. That is, alcoholic subtypes can be divided into those distinguished by other comorbid psychiatric disorders and those related to different forms of alcoholism. As a result, one additional line of inquiry into combination medications is to pursue

dual medications for dual disorders. For example, depressed alcoholics may be treated with an antidepressant (sertraline or fluoxetine) and with an opiate antagonist (naltrexone, which has received FDA approval for treating alcohol dependence). Another line of inquiry is to pursue dual medications for dual neurochemical pathways thought to be involved with excessive drinking, including serotonergic, opioidergic, and dopaminergic systems. Thus, while different investigations across the United States evaluate the same combination of 2 medications, there may be major differences among studies in the rationale and patient populations that are being evaluated.

While no major studies have been completed, case reports and pilot data have been very encouraging with respect to treating comorbid⁷¹ and noncomorbid alcohol-dependent patients⁷² with combination pharmacotherapy including an SSRI. For example, Salloum and colleagues⁷³ reported on 14 severely depressed, alcohol-dependent patients who were being openly treated with an SSRI (type varied). No reduction in depressive symptoms was observed, and all of the patients continued to drink heavily. When naltrexone (50 mg/day) was added to the SSRI, reductions in drinking occurred with a concomitant reduction in depression.

There are also a few reports on the treatment of non-comorbid alcohol dependence using a combination pharmacotherapy that included an SSRI. In one report, 9 alcoholics were treated with sertraline (50–100 mg/day) in combination with naltrexone (50 mg/day) for 10 weeks.⁷⁴ Drinking among sertraline-treated patients during the trial was compared with that of patients treated with open-label naltrexone (50 mg/day). Of the alcoholic subjects treated with a combination of sertraline and naltrexone, 66% were continuously abstinent during 10 weeks of treatment, while only 33% of the subjects treated with naltrexone monotherapy were continuously abstinent ($p < .09$). Furthermore, patients taking the combination of sertraline and naltrexone were more likely to stay in treatment longer than those on naltrexone. Another small pilot study demonstrated that the combination of sertraline and nalmefene, an investigative opioid antagonist, significantly reduced drinking in alcohol-dependent patients who did not respond to an adequate trial of nalmefene alone.⁷⁵

The National Institute of Alcoholism and Alcohol Abuse (NIAAA) is currently funding several ongoing, large, well-controlled studies on medication combinations, the results of which are expected within the next 5 years.

COMMENTARY

There is still much to be done, including finding the most useful way to differentiate alcohol subtypes, studying a variety of 5-HT medications, and prescribing combination pharmacotherapy in which one or more agents are 5-HT selective. All of these areas show promise in the

evaluation of SSRI pharmacotherapy for the treatment of patients with alcohol dependence.

Drug names: citalopram (Celexa), fluoxetine (Prozac), nalmefene (Revex), naltrexone (ReVia), paroxetine (Paxil), sertraline (Zoloft).

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