The Role of Selective Serotonin Reuptake Inhibitors in Reducing Alcohol Consumption

Claudio A. Naranjo, M.D., and Della M. Knoke, M.A.

Preclinical and clinical studies demonstrated an inverse relationship between serotonergic activity and alcohol consumption. The selective serotonin reuptake inhibitors (SSRIs) fluoxetine, citalopram, and fluvoxamine have subsequently been examined for their ability to reduce alcohol consumption in alcoholic subjects. Interindividual variability in response to SSRIs is large, with reductions in alcohol consumption ranging from 10% to more than 70%. Several factors, including gender, alcoholic subtype, and extent of drinking, appear to affect the treatment efficacy of the SSRIs. A significant challenge for researchers is to identify the subject variables that predict treatment response, providing a basis for guiding alcohol-dependent individuals to the treatment that is most likely to be effective for them. This article reviews the available clinical studies, discusses possible mechanisms of action for the SSRIs, and describes a model for predicting treatment responses in alcoholic subjects.

(J Clin Psychiatry 2001;62[suppl 20]:18–25)

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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.

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The development of substance use disorders results from the interaction of drugs of abuse with multiple neurochemical substrates within a social and cultural context. Although the present article focuses on the role of serotonin, various neurotransmitter and receptor systems have been associated with drug reward and the pathophysiology of substance use disorders. Substantial evidence supports the role of direct or indirect stimulation of dopaminergic neurotransmission as a fundamental property of drugs of abuse, including cocaine, opioids, nicotine, and ethanol in both animals and humans. In addition, drug reward is also mediated by the opioid system (including the amygdala, locus ceruleus, and periaqueductal gray area) and the γ-aminobutyric acid system incorporating the cortex, cerebellum, hippocampus, and nucleus accumbens. Other neural systems such as acetylcholine and various other neuropeptides may also have roles in the pathophysiology of substance use disorders.

Serotonin plays an important role in several aspects of addiction, including reward, craving, and relapse.

STUDIES IN ANIMALS

Several inbred strains of alcohol-preferring animals have been selected from heterogeneous populations and examined as animal models of genetic predisposition for alcohol preference. Reduced levels of serotonin (5-HT) and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) have been found in alcohol-preferring mice and rats (e.g., AA rats and C57BL6J mice) before ethanol exposure and after washout, suggesting reduced serotonin synthesis (for reviews, see LeMarquand et al. and Li and McBride). These results suggest an inverse relationship between serotonin concentrations and alcohol preference.

In the 1980s, several selective serotonin reuptake inhibitors (SSRIs) became available, mostly as novel antidepressants in various stages of development. SSRIs block the serotonin uptake pump, enhancing serotonin neurotransmission. Therefore, these agents provided an opportunity to examine the impact on alcohol consumption of increasing serotonergic neurotransmission (for a review, see Naranjo and Bremner). Preference paradigms were employed to provide rats the choice of a nonalcoholic solution or an alcoholic solution. Precision in recording improved with the development of a “drinkometer” (an electronic device for measuring alcohol intake) with a pressure transducer, developed with our biomedical engineering colleagues. This drinkometer was connected to a Hewlett-Packard computer, and the data were transcribed as they were acquired. Research using preference and other paradigms consistently reported that a variety of
Table 1. Fluoxetine and Alcoholism: Placebo-Controlled Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Drinker (N)</th>
<th>Dose</th>
<th>Treatment Duration</th>
<th>Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naranjo et al, 1990</td>
<td>Mild to moderate (29)</td>
<td>40 mg/d</td>
<td>4 weeks</td>
<td>Δ drinks/d, Δ abstinence</td>
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<td></td>
<td></td>
<td>Δ drinks/d, Δ abstinence</td>
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<td></td>
<td></td>
<td>60 mg/d</td>
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<td></td>
</tr>
<tr>
<td>Gorelick and Paredes, 1992</td>
<td>Dependent (20)</td>
<td>Up to 80 mg/d</td>
<td>4 weeks</td>
<td>Δ drinks/d, Δ abstinence</td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Δ drinks/d, Δ abstinence</td>
</tr>
<tr>
<td>Naranjo et al, 1994</td>
<td>Mild to moderate (16)</td>
<td>60 mg/d</td>
<td>2 weeks</td>
<td>Δ drinks/d, Δ abstinence</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Kranzler et al, 1995</td>
<td>Dependent (101)</td>
<td>Up to 60 mg/d</td>
<td>12 weeks</td>
<td>Δ drinks/d, Δ abstinence</td>
</tr>
</tbody>
</table>

SSRIs reduced alcohol consumption by 50% to 70%, depending on the SSRI dose administered (for a review, see LeMarquand et al.).

Results of animal studies provided a basis for early clinical pharmacologic tests. Some difficulties were apparent in extrapolating from rat to human studies. For example, it was difficult to extrapolate from rat studies the SSRI dose required to reduce alcohol consumption in humans. In clinical practice, the desired doses are within the therapeutic range for antidepressant effect. In addition, the standards for assessing efficacy often differ in clinical and human studies. Efficacy in animal studies is dependent on the drug’s ability to reduce alcohol consumption. However, in the United States, human studies often seek to evaluate the drug’s ability to maintain a state of abstinence. Thus, although animal models of alcoholism provide a mechanism for screening new drugs, the clinical value of a new medication is ultimately dependent on the results of human studies.

**STUDIES IN HUMANS**

Protocols assessing the effect of medication on alcohol consumption tend to be similar. At intake, psychosocial tests are administered to assess degree of alcohol dependence (e.g., the Alcohol Dependence Scale), psychological/psychiatric status, and level of function (DSM-IV). In addition, a brief medical assessment, laboratory tests, and a urine screen for drugs of abuse are included to assess medical eligibility for participation. Once included in the study, subjects monitor on a daily basis alcohol intake, tobacco use, and use of the study medication. Compliance can be assessed by adding riboflavin to the study medication and then measuring the concentration of riboflavin in the urine. During the baseline phase, riboflavin concentration in urine is relatively low, followed by a 7- to 12-fold increase when subjects take the medication. Studies that include a washout period show reductions in riboflavin during this period, with increases once treatment resumes. Reasonable self-reported compliance has been supported by measuring riboflavin concentrations in urine daily. Compliance also can be assessed by measuring the concentration of medication and its metabolites in platelets. Inhibition of 5-HT uptake by platelets also provides a direct measurement of drug effect.

Outcome or dependent measures vary from study to study depending on the treatment goals set. For example, in Canada, moderation of alcohol intake is an acceptable goal in human studies of mildly to moderately dependent individuals. Abstinence is considered the preferred goal for individuals who are highly dependent. In the United States, however, abstinence is the preferred goal for all levels of dependence. Although abstinence is explicitly advised and preferred in many studies, drinking during treatment is often recorded to monitor “slips” (any return to drinking) and relapses (5 drinks for men or 4 for women in 1 sitting).

**Serotonin Reuptake Inhibitors and Alcohol Consumption**

Correlational studies of alcohol-dependent individuals suggest that brain serotonergic activity is inversely related to ethanol consumption. Abstinent alcoholics have been shown to have reduced cerebrospinal fluid (CSF) 5-HIAA levels, low platelet 5-HT content, and low tryptophan availability in plasma, suggesting decreased central serotonergic function. In addition, although results are mixed, blunted neuroendocrine responses have been documented in detoxified alcoholics administered m-chlorophenylpiperazine, MK212, and fenfluramine, suggesting reduced responsivity of the serotonergic system.

An inverse relationship between serotonergic activity and alcohol consumption is also partially supported by studies examining the impact of serotonergic agonists on ethanol intake. Although administration of 5-HIAA precursors had no effect on alcohol intake, several selective serotonin reuptake inhibitors have been employed with some success. Tables 1 through 3 summarize studies examining the effect of SSRIs on alcohol consumption and craving.

The first SSRIs available for testing were zimelidine and viqualine. Although research on these agents suggested that they reliably reduced alcohol consumption, the appearance of significant adverse effects led to a withdrawal of these agents from the market. Fluoxetine, fluvoxamine, citalopram, paroxetin, and sertraline were all subsequently introduced. Using the IC50 ratio to measure the in vitro competitive inhibition of SSRIs, citalopram emerges as the most potent and selective of the available serotonin reuptake inhibitors (Table 4).

Several studies have assessed the effect of fluoxetine treatment (40–80 mg/day) on alcohol consumption and craving in heavy drinkers and in alcohol-dependent sub-
The effect of 4 weeks of fluoxetine (40 or 60 mg/day) on alcohol consumption and craving was assessed in 29 men with mild-to-moderate alcohol dependence (Figures 1 and 2). Significant reductions in drinks per day and drinks per drinking day were evident without any significant change in percentage of days abstinent. Gorelick and Paredes administered fluoxetine (up to 80 mg/day) or placebo to 20 alcohol-dependent male inpatients for 4 weeks, and alcohol consumption was measured using a fixed-interval drinking decision paradigm (see Figure 1). Fluoxetine reduced craving and requests for alcohol during the first week, but no significant effect of fluoxetine was evident during the subsequent 3 weeks of treatment. Other studies suggest no significant effect of similar doses of fluoxetine in alcohol-dependent subjects seeking treatment.22,28

Table 2. Citalopram and Alcoholism: Placebo-Controlled Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Drinker (N)</th>
<th>Dose</th>
<th>Treatment Duration</th>
<th>Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naranjo et al,</td>
<td>Mild to moderate (39)</td>
<td>40 mg/d</td>
<td>2 weeks</td>
<td>Δ drinks/d</td>
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<tr>
<td>198721</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naranjo et al,</td>
<td>Heavy (16)</td>
<td>40 mg/d</td>
<td>1 week</td>
<td>Δ abstinence</td>
</tr>
<tr>
<td>199224</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Naranjo et al,</td>
<td>Mild to moderate (62)</td>
<td>40 mg/d</td>
<td>1 week</td>
<td>Δ drinks/d</td>
</tr>
<tr>
<td>199525</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tiilhonen et al,</td>
<td>Dependent (62)</td>
<td>40 mg/d</td>
<td>12 weeks</td>
<td>Δ abstinence</td>
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<tr>
<td>199626</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Angelone et al,</td>
<td>Dependent (81)</td>
<td>20 mg/d</td>
<td>16 weeks</td>
<td>Δ abstinence</td>
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<tr>
<td>199827</td>
<td></td>
<td></td>
<td></td>
<td>Δ craving</td>
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Table 3. Studies of the Effects of SSRIs on Alcohol Craving

<table>
<thead>
<tr>
<th>Study</th>
<th>SSRI (N)</th>
<th>Dose</th>
<th>Treatment Duration</th>
<th>Parameters</th>
</tr>
</thead>
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<tr>
<td>Naranjo et al,</td>
<td>Citralopram (16)</td>
<td>40 mg/d</td>
<td>1 week</td>
<td></td>
</tr>
<tr>
<td>199221</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angelone et al,</td>
<td>Citralopram (81)</td>
<td>20 mg/d</td>
<td>16 weeks</td>
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<tr>
<td>199428</td>
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<tr>
<td>Naranjo et al,</td>
<td>Fluvoxamine (81)</td>
<td>150 mg/d</td>
<td>16 weeks</td>
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<td>199421</td>
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</tr>
<tr>
<td>Tiihonen et al,</td>
<td>Fluoxetine (16)</td>
<td>60 mg/d</td>
<td>2 weeks</td>
<td></td>
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<tr>
<td>199625</td>
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Table 4. Relative Uptake Inhibition of SSRIs: Rat Brain Synaptosomes In Vitro

<table>
<thead>
<tr>
<th>SSRI</th>
<th>5-HT</th>
<th>Norepinephrine</th>
<th>Dopamine</th>
<th>Norepinephrine</th>
<th>5-HT</th>
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<tbody>
<tr>
<td>Citalopram</td>
<td>1.8</td>
<td>6100</td>
<td>40,000</td>
<td>3400</td>
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<tr>
<td>Sertraline</td>
<td>0.19</td>
<td>160</td>
<td>48</td>
<td>840</td>
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</tr>
<tr>
<td>Paroxetine</td>
<td>0.29</td>
<td>81</td>
<td>5100</td>
<td>280</td>
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<tr>
<td>Fluvoxamine</td>
<td>3.8</td>
<td>620</td>
<td>42,000</td>
<td>160</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>6.8</td>
<td>370</td>
<td>5000</td>
<td>54</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Hyttel et al.22 All values shown are IC50 values: the lower the value, the higher the affinity. Abbreviations: 5-HT = serotonin, SSRI = selective serotonin reuptake inhibitor.

Table 4. Relative uptake inhibition of SSRIs: Rat brain synaptosomes in vitro.

Figure 1. Clinical Trials Examining Percentage Change in Alcohol Consumption With Fluoxetine

Figure 2. Clinical Trials Examining Percentage Increase in Abstinent Days With Fluoxetine

Figure 3. Clinical Trials Examining Percentage Change in Abstinence With Citalopram

medication had a significant effect on relapse severity relative to placebo-control subjects. However, increased rates of continuous abstinence were found in both drug groups compared with placebo. Only citalopram reduced craving for alcohol throughout the study. Despite these

among heavy drinkers.

among early-stage problem drinkers.
positive results with fluvoxamine, the frequency of adverse events may limit the usefulness of this medication.

In a series of studies by Naranjo et al., citalopram (40 mg/day) produced short-term reductions in alcohol consumption and alcohol craving in subjects with mild-to-moderate dependence (Figures 3–5). In another study of severely alcohol-dependent subjects, 12 weeks of citalopram treatment (titrated up to 40 mg/day) produced significant reductions in alcohol consumption, as measured by subject and relative report as well as by γ-glutamyltransferase levels. However, in a 12-week treatment study of mildly to moderately dependent men and women, no significant benefit of citalopram on alcohol consumption or craving was evident beyond the first week of treatment.

Much of the treatment efficacy research uses change in mean alcohol consumption as the primary dependent variable. Using these measures, overall reductions of 15% to 20% from baseline drinking levels are consistently reported. For each SSRI, the dose required to reduce alcohol consumption falls within a fairly narrow range. Increasing the SSRI dose increases the incidence of side effects but does not increase the effect size.

Interindividual variability in response to SSRIs is large, with reductions in alcohol consumption ranging from 10% to more than 70% (Figure 6). In addition, gender may affect response to citalopram treatment, with men exhibiting larger reductions in alcohol consumption than women. The extent of drinking also appears to affect response. For example, Balldin et al. found no significant overall effect of 40 mg/day of citalopram in a 5-week trial. However, an analysis of responders revealed that citalopram significantly reduced alcohol consumption in a subgroup of heavy drinkers who had lower baseline drinking values (between 60 and 100 g of alcohol/day). Such heterogeneity suggests that only a subgroup of alcohol-dependent individuals have 5-HT dysfunction. Given the large interindividual variability in response to treatment, a significant research challenge is to identify which subject variables distinguish, a priori, SSRI responders from nonresponders.

Kranzler et al. examined the hypothesis that individuals with the greatest probability of serotonergic dysfunction may be the most responsive to interventions that increase serotonergic activity (Figure 1). The effect of 12 weeks of fluoxetine or placebo and cognitive-behavioral therapy on drinking was examined in alcohol-dependent subjects who were subdivided on the basis of probable 5-HT dysfunction. Individuals were classified as type A or type B alcoholics according to Babor’s typology. Type B alcoholics were characterized by behavioral profiles that suggest reduced serotonergic function, including early onset and greater severity of alcohol problems, greater psychopathology, high familial risk factors, and poorer prognosis. Results of this study indicated that type B subjects had poorer outcomes in the fluoxetine condition than in the placebo condition. Kranzler et al. suggest that in this subgroup of type B patients SSRIs may, through their agonist effect, serve as a conditioned stimulus, increasing rather than decreasing alcohol consumption. Similar findings have recently been reported with sertraline.

Figure 4. Clinical Trials Examining Percentage Reduction in Alcohol Craving With Citalopram, Fluoxetine, or Fluvoxamine

Figure 5. Clinical Trials Examining Percentage Change in Drinks Per Day With Citalopram

Figure 6. Alcohol Consumption in Women and Men After Treatment With Citalopram

*a Adapted from Naranjo et al.
study, type B alcoholics receiving sertraline (200 mg/day) exhibited less favorable drinking outcomes than those receiving placebo treatment, while the opposite was true for type A alcoholics. Studies examining the relationship between subject variables and response to treatment will improve our ability to predict which individuals are likely to respond to serotonergic interventions.

Several studies strongly suggest that reduced serotonin function is associated with more severe course of alcohol dependence and disturbances of affect. A subgroup of individuals with early onset of alcoholism and a more severe course of illness (i.e., Cloninger’s type 2 alcoholics)\(^4\) are more likely to exhibit behavioral characteristics such as impulsivity, aggressiveness, and suicidality.\(^3\) Biochemical measures in individuals with this behavioral profile indicate reduced serotonergic function. For example, low levels of 5-HIAA in CSF have been associated with aggressive behavior as well as early onset of alcoholism.\(^3\),\(^4\) Furthermore, low levels of tryptophan are associated with depressive and aggressive tendencies in subjects with early onset (<20 years of age) of alcohol problems. These subjects were also more likely than individuals with a later onset of alcohol problems (>20 years of age) to exhibit risk-taking and antisocial behavior and to have a family history of alcoholism.\(^4\) Buydens-Branchey et al.\(^1\) hypothesized that early onset of alcohol problems may be related to an underlying serotonergic dysfunction that becomes apparent only with additional insult to the system. Alternatively, individuals with onset of alcohol abuse after the age of 20 years may possess mechanisms to compensate for the alcohol-induced imbalance in serotonin.

The precise relationship between 5-HT function and alcohol dependence is unclear. Chronic alcohol consumption itself has been associated with disturbances in central serotonergic activity. Reduced availability of serotonin transporters in the raphe nucleus has been reported after 3 to 5 weeks of abstinence, and this reduction has been attributed to the cumulative toxic effects of alcohol.\(^4\) The binding potential of the radioligand correlated significantly with lifetime alcohol consumption, reflecting changes in serotonergic function inversely related to chronicity of alcohol abuse.\(^4\) Similarly, increases in number and reduction in affinity of \(^{[3]}\)H-paroxetine binding in platelets associated with chronic alcohol use and changes in serotonergic activity were reversed among abstinent individuals.\(^4\) Reductions in 5-HT neurotransmission associated with withdrawal can be reduced by acute alcohol administration. This finding and the results of several other studies suggest that compensatory reductions in 5-HT levels and blunted 5-HT neurotransmission are part of the adaptation to chronic alcohol exposure.\(^4\) Thus, whether or not serotonergic dysfunction is directly implicated in the genesis of alcohol dependence, changes in response to alcohol exposure suggest that serotonergic agents may be helpful in treatment.

**HYPOTHEZIZED MECHANISMS**

**Craving**

The precise mechanism by which SSRIs reduce consumption has not been fully elucidated. Several hypotheses have been posited to account for drug effects. One hypothesis is that these agents reduce craving for alcohol. To assess the impact of citalopram and fluoxetine on craving or desire to drink, our research team developed an experimental bar paradigm to conduct drinking experiments in humans.\(^2\),\(^4\) A male research assistant was trained to function as a bartender, serving 1 subject per bar session. Participants were primarily heavy drinkers or mildly to moderately dependent subjects who did not want treatment. Each study was characterized by a baseline period, followed by random assignment to drug treatment or placebo. A within-subject crossover design was used, with a 2-week washout period between conditions. After drug treatment, but before washout, subjects participated in the experimental bar session. Prior to commencing the session, subjects were administered a Breathalyzer test to ensure that blood alcohol level was 0. Subjects were given their choice of beverage among a limited selection of liquors. The procedure consisted of offering 18 mini-drinks at 5-minute intervals, with each mini-drink equivalent to 4.2 grams of ethanol. Subjects could refuse to continue drinking. Before each drink, subjects rated their desire for each drink and feeling of intoxication. During outpatient monitoring, self-reported craving and number of drinks consumed were similar in the baseline and placebo phases of the study. However, citalopram treatment significantly reduced alcohol intake and attenuated desire for alcohol (Figure 5).\(^4\)

Administration of fluoxetine using the experimental bar paradigm produced some interesting effects on craving. In the placebo condition, desire to drink increased over the session. However, with predadministration of fluoxetine (60 mg/day), desire to drink was almost completely abolished.\(^2\)

**Reduction of Negative Affective States**

Another line of inquiry relates to the primary action of SSRIs. It has been suggested that SSRIs may indirectly reduce alcohol consumption by improving affect. Fluoxetine has been shown to reduce both alcohol consumption (Figures 1 and 2) and depressive symptoms.\(^2\),\(^4\) In addition, 12 weeks of fluoxetine treatment (20 to 40 mg/day) reduced the rate of relapse in depressed, alcohol-dependent subjects.\(^4\) However, a significant correlation between reductions in depressive symptoms and reductions in alcohol consumption was not found, suggesting that the effect of fluoxetine (60 mg/day) on drinking is independent of its effect on mood.\(^2\) Our own studies, comprising nondepressed alcohol-dependent individuals, have found no correlation between levels of depression and reduction in alcohol consumption.\(^1\),\(^2\)
Side Effects

It has been posited that reductions in alcohol consumption seen early in treatment may be attributed to medication side effects that are often greatest at the beginning of treatment (e.g., nausea and other gastrointestinal side effects). However, some studies document long-term benefits from SSRI treatment, which are difficult to attribute to initial side effects.

Alcohol Sensitizing Reaction

It has been postulated that SSRIs inhibit the metabolism of acetaldehyde, producing a disulfiram-like reaction. Our findings with zimelidine do not support this hypothesis.

Nonspecific Suppression

Human studies have generally shown no significant impact of SSRI treatment on nonalcoholic fluid consumption or nicotine use, suggesting that reductions in alcohol consumption cannot be attributed to nonspecific suppression of consummatory behaviors. Moreover, although reductions in appetite and weight have been reported with SSRI treatment, variations in alcohol consumption did not correlate with changes in body weight.

VARIATIONS IN TREATMENT RESPONSE

As with the treatment response to other drugs, response to SSRI treatment is characterized by wide variation in drinking outcomes. Although some individuals show significant benefit from treatment, others show minimal response. However, we are, at present, unable to predict who will show benefit.

Several lines of research began examining this heterogeneity in an effort to more accurately match alcohol-dependent patients to the treatment modalities that are most likely to be beneficial. Typologies such as Cloninger’s type 1 and type 2 categories of alcoholics have been developed to capture subgroup differences in clinical presentation as well as in prognosis. Identification of pretreatment subject characteristics such as verbal learning ability, cognitive capacity, baseline craving, and severity of alcohol dependence have all been identified as variables that influence response to particular forms of treatment. Unfortunately, the clinical utility of these approaches is limited.

There has also been considerable interest in the contribution of biochemical and genetic factors to alcoholism. More than 16 serotonin receptors have been cloned, and several have been related to impulsive behavior, which may be a predisposing factor in some alcoholics. A genetic polymorphism in the region of the human serotonin transporter promoter has been associated with affective illness, anxiety, and traits related to alcoholism. This polymorphism is designated long (L) and short (S). A higher frequency of the low-activity S variant of the serotonin transporter promoter in severe alcohol dependence has recently been reported. Research is also being conducted to examine other potential trait markers, such as the role of the dopamine D2 receptor gene in severe alcoholism and abnormal adenyl cyclase activity in subgroups of alcoholics. The influence of these factors on treatment outcome and the natural history of alcoholism is unknown.

These issues provided the impetus for the development of a novel research approach utilizing fuzzy logic methodology to identify predictors of treatment response. Fuzzy logic is a knowledge-based discipline used to model systems. For example, it is used to take off, land, and guide airplanes and to determine where elevators will stop.

Fuzzy logic requires changes in the way that we think about variables, which are often treated as dichotomous entities. For example, an individual 18 years or older is routinely classified as an adult, while an individual less than 18 years of age is classified as a nonadult. These cutoff points may be arbitrary and do not capture differences between category members. For example, people aged 18 years and aged 45 years may both be examples of an “adult,” but there may be considerable differences between people of these ages. Fuzzy logic transforms the function that one wants to study into a continuous function, which is then processed by a series of mechanisms to classify that function in fuzzy sets. Unlike dichotomous variables, which force data into discrete categories, this methodology is capable of dealing with imprecision, vagueness, and uncertainty.

These issues are germane to pharmacology and treatment response. Rule bases have traditionally been founded on expert opinion. However, fuzzy logic methodology makes use of input and output data to generate “fuzzy sets” that are used to generate a series of “if-then” rules. This process creates a rule base that is founded on empirical data and inference. For example, in a previous study, citalopram data were modeled to examine which variables predict how subjects will respond to the combination of citalopram and brief psychosocial intervention. A number of input variables such as age, mean daily alcoholic consumption, depression, anxiety, and severity of dependence were examined to determine their impact on the output variable of interest, the extent to which consumption of alcohol decreased. A portion of the data was used to construct a model. The ability of the model to predict responses in the remaining data set was then evaluated by comparing the predicted response generated by the model and the actual observed response. In our initial feasibility study of citalopram, the predicted response and the observed response were superimposable, suggesting that the model was able to accurately predict actual responses.

SUMMARY

As a class, the SSRIs seem to hold significant promise in the treatment of alcohol dependence. Several studies
have documented reductions in drinking in mildly to moderately dependent individuals. The magnitude of the effect is in the order of 15% to 20% and tends to be rather short term. Some studies with more severely dependent subjects suggest that citalopram may also be effective in this population. The effect is not due to toxicity, but is more likely related to the ability of SSRIs to attenuate liking of and craving for alcohol. Paradigms for testing new compounds should therefore incorporate measures to assess craving, desire, and liking of alcohol to clarify the mechanisms by which these drugs exert their effects.

Findings consistently demonstrate reductions in alcohol consumption with SSRIs, although response to treatment is quite variable. Methodologies must be developed to better explain the variability in response to treatment. A significant challenge for researchers is to identify the subjective variables that predict treatment response, providing a basis for guiding alcohol-dependent individuals to the treatment that is most likely to be effective for them. Use of fuzzy logic may improve our ability to predict response to treatment.

Although limited data are available, studies suggest that SSRIs are effective in the treatment of comorbid alcohol dependence and depression. Given the high rate of comorbidity between alcohol dependence and affective disorders, SSRIs represent an important area for future research.

**Drug names:** citalopram (Celexa), duloxetine (Cymbalta), fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft).

**REFERENCES**