Pharmacotherapy, Pharmacogenomics, and Alcohol Dependence: Serotonin Receptors and Potential Agents

George A. Kenna, PH.D., B.S.Pharm., is Fellow in Community Health, Center for Alcohol and Addiction Studies (CAAS), Brown University, Providence, RI, and Clinical Pharmacist, Kent County Memorial Hospital, Warwick, RI. John E. Mcgeary, PH.D., is Postdoctoral Fellow in Community Health, CAAS. Robert M. Swift, M.D., PH.D., is Associate Chief of Staff for Research and Education, Providence VA Medical Center, Providence; Associate Director, CAAS; and Professor of Psychiatry, Brown Medical School, Providence.

Abstract
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Alcoholics and experimental animals that consume large amounts of alcohol have comparatively lower levels of serotonin than nonalcoholics.[88] Considerable experimental evidence suggests that serotonin plays a crucial role in the impulsivity and craving often seen in alcoholics[89] and is at least partly responsible for alcohol dependence.[90,91] Hypotheses for a relationship between serotonin and alcoholism[91] note (1) the impulsive use of alcohol associated with hyposerotoninergic levels and increased dopaminergic activity,[90] (2) the possible relationship between symptoms of anxiety and hyposerotoninergic states leading to the use of alcohol to self-medicate,[93] (3) the ability of alcohol to increase serotoninergic activity in the hyposerotoninergic brain,[94] (4) the interaction of serotonin with dopamine in contributing to the rewarding properties of alcohol, and (5) the possibility that medications that affect serotonin might have an effect on appetitive behaviors through the renin-angiotensin system.[92]

Differences in the response to alcohol may also be related to subtypes of serotonin receptors. The pharmacology of serotonin and its many receptors has been found to contribute to alcohol consumption in animal studies.[88] Moreover, in humans, in addition to and operating concurrently with dopamine release, alcohol has many actions on the brain through serotoninergic systems.[9] However, to complicate matters, there are many types of serotonin receptors. 5-HT1A-receptors may be associated with alcohol consumption, intoxication, and the development of tolerance; 5-HT2-receptors have been found to contribute to reward systems; and 5-HT3-receptors are implicated in the development of reinforcement through synaptic projections to the mesolimbic dopaminergic system.[88] Alcohol increases brain levels of serotonin affecting these receptors. In addition, the concentration of the serotonin metabolite 5-hydroxyindoleacetic acid may be lower in the cerebrospinal fluid of individuals with suicidal ideation, impulsivity, and depression, as well as alcoholism, suggesting some potential for dysregulation of serotonin.[95,96]

Perhaps because of the multiplicity of types of serotonin receptors, studies of serotoninergic medications have provided mixed results. For example, although buspirone is a D2-receptor antagonist, its primary action is as a 5-HT1A-receptor partial agonist that exhibits anxiolytic properties. Studies have found that groups receiving buspirone, while also suffering from coexisting anxiety disorders, scored significantly better than placebo recipients on alcohol-use

measures.[97-99] When these anxiety disorders were controlled for, however, buspirone was not superior to placebo,[49] rendering efficacy for alcohol dependence treatment alone questionable.[55,100] Ritanserin, a 5-HT2-receptor antagonist, also failed to clearly demonstrate usefulness as a pharmacotherapy for alcohol dependence in a double-blind, placebo-controlled trial.[101]

The findings of clinical trials of specific serotonin-reuptake inhibitors (SSRIs) are also uncertain.[55] Despite reductions in drinking in animal studies[102] and some limited human studies,[51,102,103] SSRIs have not reduced drinking or any other measures of alcohol consumption in most double-blind, placebo-controlled studies. However, frequencies of genetic variation in the serotonin transporter differ between persons with alcohol dependence and those with comorbid alcohol dependence and depression, suggesting that patients with this comorbidity may constitute an important subpopulation that might respond differently to treatment.[104] Recent research suggests that SSRIs do not appear to be an efficacious approach to treating heterogeneous groups of alcoholics,[105] since subtypes of alcoholics may respond differently to SSRIs. Although Kranzler et al.[50] observed that fluoxetine hydrochloride 60 mg was no better than placebo in reducing alcohol consumption, two types of alcoholics, A and B, responded differentially to fluoxetine: While the type A alcoholics drank the same amount as the group receiving placebo, the type B alcoholics drank significantly more than those receiving placebo. Persons with type A alcoholism have a later onset of dependence (after 25 years of age), few pathological problems, and few drinking-related problems and childhood risk factors. Type B alcoholism, an early-onset form occurring before the age of 25, involves a more severe psychopathology, antisocial and impulsive tendencies, childhood risk factors, and significant problems with alcohol.

In a follow-up to the Kranzler et al study, Pettinati and colleagues[52] used sertraline hydrochloride 200 mg and classified subjects as having early-onset or late-onset alcoholism. This study confirmed that those with early-onset alcoholism actually drank significantly more when taking SSRIs, but, unlike the Kranzler et al.study, also found that those with late-onset alcoholism drank significantly less.

It appears that a subgroup of alcohol-dependent individuals who lack certain predisposing factors, such as family history, may achieve some success with SSRIs.