See article by Higuchi

Acamprosate, Alcoholism, and Abstinence

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Pathological alcohol use affects more than 2 billion people and accounts for nearly 6% of all deaths worldwide.[1] Alcohol use disorder can also significantly undermine the diagnosis and treatment of comorbid psychiatric disorders. Thus, abstinence from alcohol and all other nonprescribed drugs is widely accepted as the primary and necessary criterion for recovery in dependent individuals. There are 3 medications approved for the treatment of alcohol dependence by the US Food and Drug Administration (FDA): disulfiram, naltrexone (oral and long-acting injectable), and acamprosate; acamprosate recently received approval from regulatory authorities in Japan. Although each drug works through different mechanisms, treatment effects for each medication are optimized when patients are abstinent at treatment initiation.[2]

Acamprosate has a novel mechanism of action that acts to support abstinence by restoring homeostasis in *N*-methyl-D-aspartate–mediated glutamatergic neurotransmission that becomes dysregulated in alcohol dependence and withdrawal.[3] Additionally, polysomnography and clinical data indicate that acamprosate reverses alcohol-related changes in sleep architecture, which may yield added value when treating patients with comorbid psychiatric disorders characterized by sleep disturbance, such as posttraumatic stress disorder and anxiety and depressive disorders. A recent sex-specific, individual patient data meta-analysis[4] found acamprosate to have a significant effect compared with placebo in improving rates of abstinence and no heavy drinking in both women and men with alcohol dependence, despite women having a history of significantly more anxiety, depression, suicide attempts, drug abuse, and interpersonal loss and greater hepatic impairment than men. The side effect and tolerability profiles of acamprosate were likewise comparable between men and women, and acamprosate was associated with significantly higher rates of treatment completion and medication compliance than placebo among both men and women.[4] The neuromodulatory approach exemplified by acamprosate is supported by recent positive findings showing that gabapentin, a calcium channel/γ-aminobutyric acid–modulating drug, improved rates of abstinence and no heavy drinking while decreasing alcohol-related disturbances in sleep, mood, and craving relative to placebo in men and women with alcohol dependence.[5] Importantly, neither acamprosate nor gabapentin are appreciably metabolized in the liver, and both have been shown to be safe in patients taking concomitant medications and in those with hepatic impairment. This is an important distinction relative to disulfiram and naltrexone, which each have a "black box" warning for hepatotoxicity.

In this issue of *JCP*, Higuchi, on behalf of the Japanese Acamprosate Study Group,[6] reports positive findings for rates of complete abstinence in a 24-week randomized controlled trial of acamprosate (1,998 mg/d orally) conducted across 34 centers in Japan and involving 327 patients with alcohol dependence. Patients were significantly more likely to maintain complete abstinence over the 24-week study when treated with acamprosate (47.2%) relative to placebo (36.0%), with a difference of 11.3% (95% CI, 0.6%–21.9%) in rates of abstinence between treatment conditions. These rates are comparable to those reported in recent meta-analyses of acamprosate randomized controlled trials, which found numbers needed to treat to prevent a return to any drinking of 7.5[2] and 12[7] and an odds ratio of 1.9 (95% CI, 1.6–2.3) for rate of complete abstinence.[4] Posttreatment follow-up studies have shown the effects of acamprosate to be sustained for periods up to 1 year after the last dose.[2,3]

A unique aspect of the Higuchi[6] study is that, per customary treatment of alcohol dependence in Japan, all patients initially received 2 months of inpatient treatment encompassing detoxification and rehabilitation phases and began acamprosate treatment at the time of inpatient discharge. The efficacy of acamprosate in maintaining abstinence relative to placebo after such an extended abstinent interval is consistent with meta-analyses finding that efficacy is greater with abstinence of longer duration at treatment initiation, with studies typically specifying 5 days of abstinence (range, 0–21 days) prior to acamprosate treatment.[2]

The outcomes of the majority of acamprosate randomized controlled trials are positive. However, given that the mechanism of action of acamprosate targets neuroadaptations specific to drinking cessation and alcohol dependence, it is not surprising that the negative trials were typically those in which the appropriate pharmacologic target for acamprosate was absent—for example, admission criteria did not require patients to be abstinent at treatment initiation, did not require patients to meet dependence criteria, or permitted a mild variant of the disorder such that alcohol withdrawal was not deemed necessary.[2,3] Negative as well as positive trials are useful in identifying factors associated with response to a given treatment. The meta-analysis evidence base suggests that patients meeting criteria for alcohol dependence of relatively greater severity, that is, who required detoxification, and who were abstinent at treatment initiation may experience the greatest benefit from acamprosate,[2] regardless of sex or

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history of psychopathology.[4] The absence of differential sex effects is important, in that some studies have found a lack of naltrexone efficacy in women with alcohol dependence. Identification of phenotypes and genotypes associated with acamprosate response may further optimize treatment effect size; for example, an association has recently been reported between acamprosate treatment response and polymorphisms in candidate genes in glycine and glutamate neurotransmission pathways.[8]

The primary outcome selected by Higuchi,[6] the rate of complete abstinence over the 24-week study, is consistent with recent FDA guidance indicating that a categorical outcome with clinical relevance is more informative than analyses of group means, which are difficult to interpret with regard to clinical relevance.[5] The outcome reported by Higuchi is easily interpreted: a patient has an 11.3% greater likelihood of being entirely abstinent for 6 months when treated with acamprosate relative to placebo. Higuchi's study is also parsimonious in its design; it is designed to collect high-quality data specific to the primary outcome, including biochemical validation with liver function test data and corroboration from a significant other. The study did not involve lengthy ancillary assessments requiring contact with multiple specialists on each patient visit, which may inflate placebo response and decrease generalizability to treatment settings. The methods used in Higuchi's study are highly transferable to clinical practice and relevant to treatment of a disorder that requires comprehensive behavioral changes and compliance with a thrice-daily dosing regimen. Keeping a daily diary of dosing, abstinence or drinking, and the circumstances associated with a drinking episode for review at patient visits may facilitate treatment outcome. Advising patients to place a week's supply of acamprosate in an over-the-counter pill dispenser indicating day and time of dose can facilitate compliance and parallel the blister cards used in the Higuchi study. As in many earlier acamprosate studies, patients received the concomitant psychosocial treatment typical of the participating clinical site, further enhancing the generalizability of the findings.

Higuchi used *ICD-10* criteria for alcohol dependence that closely parallel those of *DSM-IV*, and these criteria will likely be maintained in the upcoming *ICD-11*. However, *DSM-5* has essentially merged the criteria for alcohol abuse and dependence into a single entity of alcohol use disorder that requires only 2 of 11 criteria be met for diagnosis, a threshold that does not capture the neuroadaptations targeted by acamprosate. The *DSM-5* severity modifier of moderate or greater for alcohol use disorder (at least 4 positive criteria) may be used to approximate the *DSM-IV* and *ICD-10* criteria for alcohol dependence, as the approved indication for all current medications is alcohol dependence, and not alcohol use disorder.

A nationwide pharmacy survey[9] suggested that fewer than 9% of the 8.4 million afflicted Americans fill a prescription for an FDA-approved medication for alcohol dependence; these prescriptions were provided primarily by psychiatrists, and acamprosate was the most commonly prescribed medication. Alcohol misuse costs the American economy about $223.5 billion annually.[1] Pharmacoeconomic studies in Europe and the United States report a cost-savings benefit of prescribing acamprosate in conjunction with psychosocial treatment relative to nonpharmacologic treatments alone.[3] The study by Higuchi[6] is consistent with findings from meta-analyses showing that acamprosate combined with psychosocial treatment has superior efficacy for supporting abstinence relative to psychosocial treatments administered in conjunction with placebo.[2,4,7] These effect sizes are also similar to those found for remission rates in recent meta-analyses of trials of antidepressant treatment of major depressive disorder, with a similar association found between greater baseline symptom severity and treatment response.[10] The extensive evidence base for acamprosate shows it to be a safe and well-tolerated medication. Clearly, there is a critical need for the development of more effective medications for the treatment of alcohol dependence and a need for expanded utilization of existing treatments with established safety and efficacy.

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Additional information: Clinicians can access the patient educational and self-help materials and the therapist's manual developed for the first US acamprosate study at www.alcoholfree.info.

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