Guideline Watch (April 2007): Practice Guideline for the Treatment of Patients With Substance Use Disorders, 2nd Edition

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Since the publication in May 2006 of APA's *Practice Guideline for the Treatment of Patients With Substance Use Disorders,* 2nd Edition (1), results have been reported for a multisite randomized, controlled trial evaluating the efficacy of medication, behavioral therapies, and their combinations for treatment of alcohol dependence in nonspecialty treatment settings (the COMBINE study, 2). In addition, two novel pharmacotherapies have been approved for use in the treatment of nicotine dependence (varenicline) and alcohol dependence (intramuscular naltrexone). This watch describes these developments.

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Treatment of nicotine dependence with varenicline

Varenicline is a novel pharmacotherapy that has selective partial agonist activity at neuronal nicotinic acetylcholine receptors (nAChR), specifically the brain α4β2 nAChR, which has been implicated in the development of nicotine dependence via its effect on mesolimbic dopamine release (3). Varenicline binds with very high affinity (Ki = .06 nM) but has low intrinsic activity at α4β2 nAChR sites (4), such that it will competitively block exogenous nicotine binding (preventing subjective and neurochemical effects of cigarette "cheating" and relapses that can sustain nicotine addiction). At the same time, it provides low-level receptor stimulation sufficient to relieve nicotine craving and withdrawal syndrome during nicotine abstinence.

The results of five multisite randomized, controlled trials consistently demonstrated superior ef-

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ficacy of varenicline versus placebo for 6-month smoking abstinence rates as well as retention in smoking cessation treatment, with the odds of successfully quitting smoking with varenicline being 3 to 4 times that with placebo intervention (reviewed in 2007 by the Cochrane Collaboration, 5). An additional multisite trial (6) randomized successful quitters to either an additional 12 weeks of varenicline relapse prevention treatment or to placebo and reported superior outcomes for the varenicline maintenance group both during study drug treatment (OR=2.48) and up to 1 year after completion of study drug intervention (OR=1.34); however, temporary relapse during the withdrawal of varenicline treatment was noted, similar to that observed in studies of smoking cessation using other nicotine replacement therapies. Three of the above trials also compared varenicline treatment with buproprion SR treatment at standard dosing (150 mg b.i.d.) and found that smokers receiving varenicline were 1.5 times more likely to have successfully quit smoking at 1-year follow-up than were smokers receiving bupropion SR (who also compared favorably to the placebo group). A limitation of these studies is that all were funded by the pharmaceutical manufacturer.

Varenicline was approved by the U.S. Food and Drug Administration (FDA) in May 2006 for prescription-only treatment of nicotine dependence. Varenicline dosing is initiated 1 week prior to the desired quit date and is facilitated by starter packs that have blister-packed doses with titration instructions for the first month of treatment (0.5 mg daily for 3 days, followed by 0.5 mg b.i.d. for 4 days, followed by increases as tolerated to a target dose of 1 mg b.i.d.). Varenicline is taken with food and a full glass of water to minimize the most common adverse response, nausea, which is usually transient and dose dependent. Other common side effects are headache and sleep disturbances. Varenicline undergoes minimal metabolism; 92% is excreted unchanged in urine. When varenicline is prescribed to patients with moderate to severe renal impairment, reductions in dose and close monitoring are indicated.

Varenicline is an effective and well-tolerated pharmacotherapy to aid patients who are engaged in behavioral treatment for smoking cessation. Although the majority of research has involved a 12-week course of varenicline, extending treatment beyond this recommended duration may be appropriate in certain populations, e.g., for heavy smokers or those with multiple prior failed attempts to stop smoking. More research is needed to determine the role of varenicline in treating individuals with co-occurring psychiatric disorders as well as to determine its relative efficacy compared with already established pharmacotherapies, i.e., bupropion and alternate nicotine replacement therapies (nicotine patch, gum, inhaler, nasal spray, or lozenge). Given its high potency and partial agonist activity at central nicotinic acetylcholine receptors, varenicline should not be combined with alternate nicotine replacement therapies.

TREATMENT OF ALCOHOL DEPENDENCE

Oral naltrexone, a mu-opiate receptor antagonist, was first approved by the FDA in 1984 for treatment of opioid dependence and in 1994 for treatment of alcohol dependence (7, 8). Outcomes, however, are frequently compromised by medication nonadherence (9). The use of long-acting injectable naltrexone is described in the May 2006 guideline (1) as potentially promoting adherence; however, it had not yet been approved by the FDA when the guideline went to press. This once-monthly formulation was associated with significant improvements in medication exposure and drinking outcomes in one large (N=624) manufacturer-sponsored multisite randomized, controlled trial (10). Drinking outcomes in this predominantly male study population were improved for treatment-seeking outpatients whether or not they were drinking at the time of medication initiation. However, patients with lead-in abstinence showed greater improvement in reduction of heavy drinking compared with those who were drinking at the time of initiating treatment. Tolerability was acceptable compared to placebo, with dose-dependent short-term increases in nausea, dizziness, fatigue, appetite disturbance, and injection site pain, and no evidence of hepatoxicity. In April 2006, the FDA approved a depot formulation of naltrexone that has a microsphere-based drug delivery system and that is administered intramuscularly (via gluteal injection) and has demonstrated bioavailability for up to 4 weeks. Some considerations for optimal prescribing include the medication's cost-effectiveness for at-risk populations (the monthly cost for injectable naltrexone is estimated to be substantially greater than the cost for a 30-day supply of oral naltrexone, not including costs for refrigerated storage of injection kits and nurse administration of injections) and side effects not observed with the oral formulation (i.e., injection site reactions such as tenderness, inability to remove medication once injected if not well tolerated by the patient, eosinophilic pneumonia). Evidence of efficacy is lacking in patients not seeking treatment for alcohol dependence (e.g., court-mandated or incarcerated individuals) as well as in those having co-occurring se-

vere mental disorders. Injectable naltrexone is contraindicated in patients with blood coagulation disorders, severe hepatic or renal impairment, prior allergic reaction to oral naltrexone, or respiratory or gastrointestinal motility disorders and in patients likely to require opioid therapy for pain disorders.

Additional advances in our knowledge of the treatment of alcohol dependence have come from the COMBINE study, a large (N=1,383, with 428 women and 955 men) multisite randomized, controlled trial sponsored by the National Institute on Alcohol Abuse and Alcoholism of pharmacotherapies and behavioral intervention alone or in combination, with and without specialized adjunctive substance use behavioral counseling (2). Because the majority of patients with alcohol use disorders are seen in primary healthcare settings rather than specialized settings for the treatment of substance use disorders, a major contribution of this trial was its attempt to mimic the duration and intensity of visits associated with primary care interventions. Outpatients at 11 academic centers who met criteria for a primary diagnosis of alcohol dependence were invited to participate in 16 weeks of outpatient treatment aimed at reducing drinking, with a research follow-up assessment 1 year after completion of treatment. To be eligible for the study, patients had to be in good medical health, have no co-occurring psychiatric symptoms requiring pharmacotherapy, and have no co-occurring substance use in the past 90–180 days with the exception of nicotine or cannabis use. At baseline patients had patterns of heavy drinking with more than 14 drinks per week for women or more than 21 drinks per week for men, and at least 2 heavy drinking days (4 or more drinks per day for women, 5 or more drinks per day for men) per month. Patients were required to demonstrate a minimum of 4 days of abstinence from drinking prior to randomization into the study treatment.

The medication therapies that were compared to a placebo control included the mu-opiate receptor antagonist naltrexone (100 mg daily) and the putative glutamate modulator acamprosate (3 gm daily), both of which were administered at doses above the therapeutic standard to maximize efficacy in the event of missed doses. Nonmedication interventions included a standardized medical management intervention and a "combined behavioral intervention." Medication management, designed to be deliverable in primary healthcare settings, consisted of 9 sessions of a 15–20-minute manualized treatment intended to reinforce adherence to medication, abstinence from drinking, and referral to Alcoholics Anonymous. Behavioral therapy involved up to twenty 50-minute sessions, was delivered by a master's level specialist in substance use treatment, and contained elements of evidence-based "best practices" for the treatment of alcohol dependence, including cognitive-behavioral therapy, motivational interviewing and motivational enhancement, and 12-step facilitation. The study design examined the effects of combining pharmacotherapies and specialized behavioral therapies in a 2 (acamprosate vs. placebo) x 2 (naltrexone vs. placebo) x 2 (combined behavioral intervention vs. no combined behavioral intervention) factorial design, resulting in 8 medication treatment groups, all of which also received medication management. The ninth group, combined behavioral intervention without any pills, was added to evaluate the placebo effect of pill taking and medical management intervention combined with behavioral therapy (placebo + combined behavioral intervention vs. placebo without combined behavioral intervention vs. combined behavioral intervention alone). Thus, participants were randomly assigned to 1 of 9 study treatments: (1) acamprosate + combined behavioral intervention + medical management, (2) acamprosate + medical management, (3) naltrexone + combined behavioral intervention + medical management, (4) naltrexone + medical management, (5) acamprosate + naltrexone + combined behavioral intervention + medical management, (6) acamprosate + naltrexone + medical management, (7) placebo + combined behavioral intervention + medical management, (8) placebo + medical management, or (9) combined behavioral intervention alone.

During 16 weeks of treatment, all groups receiving pills and medication management showed significant improvement in percentage of days abstinent (≥74%) compared to baseline (about 25%), indicating that all study interventions, including medication management with placebo pills, were effective in helping participants to achieve the goal of reduced drinking (2). Surprisingly, participants receiving specialized substance use treatment (combined behavioral intervention) without pills or medication management showed the least improvement in percentage of days abstinent during treatment (67%). Only the naltrexone group and the combined behavioral intervention + placebo group further increased percentage of days abstinent (81% and 80%, respectively), and the combination of naltrexone + combined behavioral intervention had no greater benefit than either treatment alone (77%). Acamprosate was well tolerated, but its effects were not different than placebo, with or without combined behavioral intervention, and acamprosate + naltrexone had no further benefit than naltrexone alone. Similar re-

sults were obtained for the percentage of participants who relapsed to at least 1 day of heavy drinking (or were lost to follow-up and presumed to have relapsed) during the 16-week study treatment. Most participants (70% or more) reported at least 1 heavy drinking day, with the combined behavioral intervention without pills group faring the worst (79%), the naltrexone without combined behavioral intervention group faring the best (66%), and no benefit of acamprosate noted, even in number of days until first heavy drinking day (as predicted by prior clinical trials results, 11, 12). At 1-year posttreatment, percentage of days abstinent declined to 60%–68% (still improved from baseline), and interestingly the combined behavioral intervention groups maintained gains better than did groups receiving medication without combined behavioral intervention, including the combined behavioral intervention without pills group. Relapse to heavy drinking was high at 1-year posttreatment for all groups (80%).

The results of the COMBINE study suggest that outpatients with primary alcohol dependence may be effectively treated in nonaddiction specialty settings such as primary healthcare settings. In addition, clinicians without expertise in treating individuals with alcohol dependence may safely prescribe naltrexone to such patients with benefit. This is consistent with evidence of small to moderate benefits of naltrexone from meta-analyses and from a majority of randomized trials conducted in specialty substance use disorder treatment settings (reviewed in the May 2006 guideline, 1). The apparent lack of efficacy of acamprosate in this study may relate to the relatively short period of patient abstinence before treatment initiation. Although requiring further research, these findings are consistent with the evidence reviewed in the guideline (1) that acamprosate may be more effective for patients presenting with sustained abstinence after initial stabilization of drinking. However, there is no evidence from this study to support combining naltrexone and acamprosate. The findings with combined behavioral intervention (alone or in combination with naltrexone) during the initial 16-week course of treatment are less robust than those observed in prior studies, although the maintenance of treatment benefit at 1-year follow-up is more consistent with the generally positive results of behavioral interventions (1). Consequently, patients with alcohol dependence who decline naltrexone may do well when referred for specialized substance use counseling paired with primary care follow-up. Ongoing outpatient treatment and monitoring is recommended for maintaining patient progress in achieving reduced drinking goals, adhering to any prescribed medications, and participating in self-help programs such as Alcoholics Anonymous (AA).

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