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APA Guideline for Alcohol Use Disorder

Fewer than 1 in 10 Americans with a diagnosis of alcohol use disorder receives any treatment, and receipt of evidence-based care is even less common. According to a guideline on the pharmacological treatment of the disorder from the American Psychiatric Association (APA), naltrexone and acamprosate are first-line drug treatments for moderate-to-severe alcohol use disorder. This recommendation reflects a moderate degree of confidence that the benefits of these drugs outweigh the harms. Disulfiram, topiramate, and gabapentin may also have greater benefits than harms and may be appropriate in patients who have not experienced response with first-line medications. The guideline recommends against treating alcohol use disorder with antidepressants or prescribing benzodiazepines except for acute alcohol withdrawal.

The guideline, which is based on evidence from clinical trials, expert opinion, and patient values and preferences, ranks the level of confidence that the benefit of a treatment outweighs its harms. Harms included not only adverse effects, but direct and indirect costs of the intervention. In addition to treatment, assessment of patients' alcohol use disorder is discussed.

Assessment: The APA recommends that patients with suspected alcohol use disorder be assessed for use of tobacco and misuse of other substances, including prescription medications. Alcohol use should be assessed with a quantitative behavioral measure, and patients should be assessed for co-occurring conditions that may influence the choice of pharmacotherapy. Patients should have a documented, comprehensive, person-centered treatment plan that includes evidence-based nonpharmacological and pharmacological treatments. Additional suggestions, based on lower quality evidence, include use of physiological biomarkers to identify ongoing high levels of alcohol use, as well as documented discussions of risks of continued alcohol use and treatment goals (e.g., abstinence, reduction of alcohol use).

Treatment: Naltrexone or acamprosate are recommended in patients with moderate or severe alcohol use disorder who prefer pharmacotherapy or have not experienced response with nonpharmacological treatments alone. Both drugs have shown positive effects overall,

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although they have not shown a statistically significant benefit in all studies or for all outcomes. Benefits are generally small, but the harms of treatment with these drugs are considered minimal in patients without contraindications. Acamprosate should not be used in patients with renal impairment, and naltrexone should not be used in those with acute hepatitis or hepatic failure. Both drugs should be avoided in pregnant women. Lower quality evidence also suggests that disulfiram may be used in patients who have a goal of achieving abstinence, can understand the risks of alcohol consumption while taking the drug, and either prefer it or have not had response with naltrexone or acamprosate. Disulfiram efficacy is mainly supported by open-label trials, but effect sizes have been medium to large. Topiramate has had moderate effect sizes in alcohol use disorder, but harms include cognitive dysfunction, dizziness, and weight loss. Gabapentin has a small beneficial effect and minimal harms, but the strength of evidence is low.

The APA notes that "Practice Guidelines are assessments of current scientific and clinical information provided as an educational service and should not be considered as a statement of the standard of care or inclusive of all proper treatments or methods of care and are not continually updated and may not reflect the most recent evidence. They are not intended to substitute for the independent professional judgment of the treating provider."

Reus V, Fochtmann L, Bukstein O, Eyler A, et al: The American Psychiatric Association practice guideline for the pharmacological treatment of patients with alcohol use disorder. *American Journal of Psychiatry* 2018;175 (January):86–90. From the APA Practice Guideline Working Group.

Common Drug Trade Names*: acamprosate—*Campral*; disulfiram—*Antabuse*; gabapentin—*Neurontin*; naltrexone—*ReVia*; topiramate—*Topamax

Asenapine Maintenance in Bipolar I Disorder

In a manufacturer-sponsored randomized withdrawal study, asenapine (*Saphris*) prevented recurrence of a mood episode in patients with bipolar I disorder who initially experienced response to the drug. No new safety concerns became apparent during the trial.

Methods: Study participants were adults with bipolar I disorder, currently experiencing a manic or mixed episode. Following taper and discontinuation of previous psychotropic medications, all patients received open-label monotherapy with 5 or 10 mg asenapine b.i.d. for 12–16 weeks. Response criteria were Young Mania Rating Scale (YMRS) and Montgomery-Asberg Depression Rating Scale (MADRS) scores of ≤12 for 5 consecutive visits. Patients who met these criteria for 8 weeks went on to the second phase of the study, in which they received randomly assigned, double-blind asenapine or placebo for 26 weeks. The primary study outcome was time to recurrence of a mood episode, defined as either initiation of a non-study medication to treat mood symptoms, YMRS or MADRS score of ≥16, need for psychiatric hospitalization, or study discontinuation because of a mood event. There were no prespecified key secondary endpoints, but time to recurrence of specific types of mood episode was analyzed post hoc.

Results: A total of 549 patients began the open-label phase. Of these, 296 discontinued treatment during this phase because of adverse events (n=91), lack of efficacy (n=45), or other reasons. Thus 253 patients who met response criteria entered the randomized withdrawal phase. Mean patient ages were 41 years in the placebo group and 43 years in the asenapine group, and 45% of participants were men. The majority of patients (78%) entered the randomized phase in a manic episode as opposed to a mixed episode (22%). Medication compliance was nearly 100% during the second phase.

Asenapine was associated with a longer time to mood episode recurrence than placebo, both overall and for mania and depression individually. Among the asenapine-treated patients, 11 experienced any mood episode recurrence, compared with 42 in the placebo group (hazard ratio [HR],* 0.22; p<0.0001; number needed to treat [NNT],* 5). Manic episodes affected 5 and 24

patients in the asenapine and placebo groups, respectively (HR, 016; p<0.0001; NNT, 7). Depressive episode recurrence was also significantly less likely with asenapine than with placebo, although the effect was smaller than for manic episodes: 5 patients versus 13 patients (HR, 0.35; p=0.045; NNT, 16). Occurrence of mixed episodes did not differ significantly between the groups (HR, 0.10; NNT, 32), but the number of patients experiencing these episodes was small: 1 in the asenapine group and 5 in the placebo group.

Of the prespecified adverse events of interest, during open-label treatment, 18% of patients experienced somnolence/sedation/hypersomnia, 10% had clinically significant weight gain, 10% extrapyramidal symptoms, 10% oral hypoesthesia/dysgeusia, and 8% akathisia. Few patients had lab abnormalities. There were no significant differences between asenapine and placebo in adverse events of interest during the second study phase.

Discussion: Asenapine is currently FDA approved for acute treatment of bipolar mania and acute and maintenance treatment of schizophrenia. This trial confirms the known safety and tolerability profile of asenapine. The observation that it may prevent depressive episodes is noteworthy because few atypical antipsychotics are effective in bipolar depression.

Study Rating*—17 (100%): This study met all criteria for a randomized controlled trial.

Szegedi A, Durgam S, Mackle M, Yu S, et al: Randomized, double-blind, placebo-controlled trial of asenapine maintenance therapy in adults with an acute manic or mixed episode associated with bipolar I disorder. *American Journal of Psychiatry* 2018;175 (January):71–79. From Allergan, Jersey City, NJ; Merck, Whitehouse Station, NJ; and Forest Research Institute, Jersey City, NJ. **Funded by Forest Laboratories. All 7 study authors disclosed financial relationships with commercial sources, including Allergan, Merck, or Forest Laboratories.**

***See reference guide.**

Ghrelin Agonist for Anorexia Nervosa

In a preliminary placebo-controlled study, the investigational ghrelin receptor agonist relamorelin was associated with accelerated gastric emptying and modest weight gain in women with anorexia nervosa.

Background: There are currently no approved agents to stimulate gastric motility in anorexia nervosa, although pro-kinetic agents such as erythromycin or metoclopramide (*Reglan*) are used off-label. These agents' adverse effects may preclude long-term use. Ghrelin is a hormone produced in the stomach that stimulates appetite and gastric motility. Relamorelin is an agonist of the ghrelin receptor, or growth hormone secretagogue receptor 1a (GHS-R1a).

Methods: Study participants were 22 adult women who met DSM-5 criteria for anorexia nervosa and who had gastrointestinal symptoms, such as fullness, bloating, and constipation, thought to be caused by delayed gastric emptying. All were outpatients during the study, and none were receiving hyperalimentation therapy, tube feedings, or agents to reduce gastric motility. At the baseline study visit, participants were randomized and taught to self-administer subcutaneous injections. Patients then self-administered 100 µg relamorelin or placebo subcutaneously every morning for 4 weeks and returned to the clinic for weekly evaluations.

Results: The study participants had a mean age of 29 years and were at about 80% of their ideal body weight on average. Nine of 12 patients in the placebo group and all 10 in the relamorelin group were receiving long-term outpatient therapy, which continued during the study. Mean baseline gastric emptying time was about 87 minutes.

A total of 20 patients were included in the intent-to-treat analysis; the other 2 patients, both in the active treatment group, withdrew from the study because of increased hunger and had no available outcome data. Patients in the relamorelin group gained more weight than the placebo group (1.9 lbs vs 0.08 lbs; p<0.07). At 4 weeks, 7 of 8 patients in the relamorelin group and 6 of

12 patients in the placebo group gained weight (88% vs 50%). Mean gastric emptying time after 4 weeks was 58 minutes with relamorelin and 85 minutes with placebo (p=0.03). Patients in both groups reported similar effects on hunger, measured with a visual analog scale. Changes in self-reported gastric symptoms did not differ between the groups.

Discussion: Based on these results, relamorelin may have a role in the nutritional rehabilitation of patients with anorexia nervosa and additional study appears to be warranted. It should be noted that in the present study, 3 patients discontinued relamorelin because of increased hunger (although 1 remained in the study), suggesting that not all patients with anorexia nervosa may tolerate the ghrelin agonist.

Fazeli P, Lawson E, Faje A, Eddy K, et al: Treatment with a ghrelin agonist in outpatient women with anorexia nervosa: a randomized clinical trial. *Journal of Clinical Psychiatry* 2018; doi 10.4088/JCP.17m11585. From Massachusetts General Hospital, Boston; and other institutions including Motus Therapeutics, Boston. **Funded by Motus Therapeutics. One study author disclosed a financial relationship with Motus Therapeutics; the remaining 9 authors declared no competing interests.**

Metabolic Effects of Newer SGAs

Despite recent evidence, ziprasidone does not appear to have a more benign metabolic profile than the second-generation antipsychotics aripiprazole or quetiapine in patients with first-episode psychosis.[1]

Background: Among SGAs, aripiprazole and ziprasidone have been proposed to have relatively neutral metabolic effects, and a previous study by these investigators showed more benign effects of ziprasidone after 12 weeks of treatment.[2] The present study was conducted to compare the effects of the 3 drugs during patients' first year of antipsychotic treatment.

Methods: Patients were participants in a larger study of first-episode non-affective psychosis, conducted at a regional hospital in Spain. To be eligible for the study, patients (n=198; mean age, 32 years) were required to be aged 15–60 years, to have at least moderately severe psychotic symptoms, and to be antipsychotic-medication-naive. Participants were randomly assigned to receive open-label treatment with 5–30 mg/day aripiprazole, 100–600 mg/day quetiapine, or 40–160 mg/day ziprasidone. Medication doses were adjusted as clinically indicated to target the lowest effective dose. Patients were followed clinically for 1 year. Those who did not experience response to their initial antipsychotic after 6 weeks and those who had significant adverse effects were switched to another agent. The study's main outcomes were changes in weight and metabolic parameters after 1 year.

Results: About 5% of the study subjects were obese (body mass index [BMI] ≥30) at study entry. Nine individuals with baseline outlier values for ≥1 of the laboratory parameters were excluded from the analysis, and 33 patients (17 in the quetiapine group, 6 in the ziprasidone group, 10 in the aripiprazole group) were lost to follow-up or refused evaluation at 1 year; thus 165 were included in the analysis. Of these patients, about 40% were still receiving their initial medication (18% for quetiapine, 43% for ziprasidone, 62% for aripiprazole). Reasons for the switch were inefficacy (22%), adverse effects (15%), and nonadherence (10%). Patients in the ziprasidone group were significantly more likely to receive a prescription for an antidepressant during the year than others (31% vs 18% for quetiapine and 11% for aripiprazole; p=0.03).

After 1 year of follow-up, there were no differences among the 3 medication groups in any metabolic outcome. There was no change from baseline in mean fasting glucose and insulin levels or in the HOMA index of insulin resistance. Overall, patients had statistically significant increases in fasting total and LDL cholesterol and triglycerides, averaging 16 mg/dL, 13 mg/dL, and 20 mg/dL, respectively (p<0.001 for all). The triglyceride/HDL index increased by 0.4 points, and patients gained an average of about 15 lbs and 2.4 points in BMI (p<0.001 for all).

The proportion of patients with hypercholesterolemia and hypertriglyceridemia increased, to 40% and 14%, respectively. A secondary analysis according to gender showed that the weight gain in patients taking aripiprazole was significantly greater in women than men.

Discussion: These results suggest that none of the SGAs can be considered metabolically neutral. Results of short-term studies have suggested that ziprasidone has the most benign metabolic profile. The present results indicate that this assumption should be re-evaluated as the differences among agents that appear after 3 months of treatment may disappear after 1 year.

[1]Vazquez-Bourgon J, Perez-Iglesias R, Ortiz-Garcia de la Foz V, Pinilla P, et al: Long-term metabolic effects of aripiprazole, ziprasidone, and quetiapine: a pragmatic clinical trial in drug-naïve patients with a first-episode of non-affective psychosis. *Psychopharmacology* 2018;235 (January):245–255. From the University Hospital Marques de Valdecilla-IDIVAL, Santander, Spain; and other institutions. **Funded by the Instituto de Salud Carlos III; and other sources. The authors declared no competing interests.**

[2]Perez-Iglesias R, et al: Comparison of metabolic effects of aripiprazole, quetiapine and ziprasidone after 12 weeks of treatment in first treated episode of psychosis. *Schizophrenia Research* 2014;159:90–94.

Common Drug Trade Names*: aripiprazole—*Abilify*; quetiapine—*Seroquel*; ziprasidone—*Geodon

Low-Grade Infection and Antidepressant Resistance

In a nationwide retrospective cohort study from Taiwan, a history of frequent low-grade upper respiratory infections was associated with increased incidence of depression and also contributed to patients' refractoriness to antidepressant drugs.

Methods: Two independent cohorts of patients were identified from the Taiwan National Health Insurance Research Database: Cohort 2002 (followed between 2002 and 2011) and Cohort 2004 (followed between 2004 and 2011). Cohort members were medically healthy adults who had any recorded history of low-grade infections, defined as common upper airway infections. Patients were stratified based on the frequency of repeated low-grade infections (RLGI), and depression diagnoses were compared between the RLGI positive (top tertile of frequency) and negative groups (lowest tertile of frequency). The treatment responsiveness analysis was based on the period from 1 year before to 1 year after the depression diagnosis. Patients' depression was defined as easy-to-treat (requiring no antidepressants or a single antidepressant), intermediately difficult-to-treat (requiring 2 drugs), and difficult-to-treat (not responsive to ≥2 antidepressants in adequate doses for ≥60 days each).

Results: The analysis included >78,000 patients in Cohort 2002 and >49,000 in Cohort 2004. The RLGI groups within the 2 cohorts had an average of 5–7 low-grade infections per year at baseline. Depression onset was more frequent in persons with RLGI in both the 2002 and 2004 cohorts, with hazard ratios* of 1.37 and 1.91, respectively ($p<0.001$ for both hazard ratios after adjustment for gender, age, and income). Responsiveness to antidepressant medications differed significantly according to RLGI status (see table), with significantly higher rates of difficult-to-treat depression among those with recurrent infections.

Depression Symptom Responsiveness by RLGI Status

	2002 Cohort		2004 Cohort	
	RLGI	**No RLGI**	**RLGI**	**No RLGI**
Number in cohort	489	328	238	115
Easy to treat	67.5%	75.9%	67.2%	83.5%
Intermediate	21.1%	16.5%	21.0%	12.2%
Difficult to treat	11.5%	7.6%	11.8%	4.3%

Discussion: Many types of pathogen, both viral and bacterial, can trigger short-term depression for a period following infection. Conceivably, repeated infections could activate the immune system and elevate proinflammatory cytokines, leading to depression via multiple mechanisms, among them an activation of stress pathways by cytokines.

Jeng J-S, Li C-T, Chen M-H, Lin W-C, et al: Repeated low-grade infections predict antidepressant-resistant depression: a nationwide population-based cohort study. *Journal of Clinical Psychiatry* 2018; doi 10.4088/JCP.17m11540. From Taipei Veterans General Hospital, Taiwan; and other institutions. **Funded by the Taipei Veterans General Hospital; and the Ministry of Science and Technology. The authors declared no competing interests.**

***See Reference Guide.**

Prazosin in Military PTSD

In a multicenter randomized trial in U.S. military veterans, prazosin was not significantly more effective than placebo at reducing posttraumatic stress disorder-related nightmares. These results contrast those of previous studies with shorter durations and smaller populations that suggested the drug was beneficial for reducing trauma-related nightmares and improving sleep quality and PTSD symptoms.

Methods: The trial, conducted at 12 VA medical centers, enrolled 304 patients (mean age, 52 years; 98% men) with DSM-IV PTSD who had a score of ≥50 on the Clinician-Administered PTSD Scale (CAPS) and recurrent combat-related nightmares following life-threatening events in a war zone. Previous medications and/or psychotherapy were required to be stable for ≥4 weeks before randomization. Among the exclusion criteria were active suicidal ideation and psychosocial instability. Patients were randomized to receive flexible-dose prazosin or placebo for 10 weeks. Prazosin dosage was adjusted to a maximum of 5 mg at mid-morning and 15 mg at bedtime for men and to 2 and 10 mg, respectively, in women. The 3 primary study outcome measures were the CAPS recurrent distressing dreams item, the Pittsburgh Sleep Quality Index, and the Clinical Global Impression (CGI)–Change score. After the 10-week evaluation, double-blind treatment was continued for an additional 16 weeks, with the modification that other treatments could be added or changed as needed. Outcomes were re-assessed at 26 weeks.

Results: A total of 90% of the randomized study patients completed the 10-week evaluation, with no differences in completion rates between the groups. Change from baseline to 10 weeks did not differ between the prazosin and placebo groups for any of the 3 primary study outcomes. Based on CGI-Change scores, patients in both groups showed minimal improvement. Outcomes did not appear to be affected by concurrent antidepressant use. There were no significant between-treatment differences on any of the secondary outcomes including CAPS total scores, Patient Health Questionnaire depression scores, health-related quality of life, or alcohol use. Findings at 26 weeks showed a similar pattern, with no significant differences between the groups and no substantial improvement compared with week 10. Adverse events related to blood pressure-lowering effects were more common with prazosin than placebo. New or worsening suicidal ideation was less common with prazosin than placebo (8% vs 15%; p=0.048).

Discussion: Results of this study contrast with previous randomized trials involving smaller samples of both military and civilian participants. Unlike previous trials, concern about suicidal or violent behavior led the present investigators to exclude patients with psychosocial instability, possibly biasing the sample. The study also had a high threshold for frequency and severity of nightmares, possibly biasing selection toward patients less likely to experience response to prazosin. Despite high levels of symptoms, recruitment criteria ensured that study participants had clinically stable PTSD, potentially making them less likely to experience response. It is also possible that clinicians may have not referred their more vulnerable

patients to the study, preferring to treat them with open-label prazosin. The authors note that the current trial is not the first multicenter, randomized trial involving male military veterans with psychiatric disorders to fail to show efficacy for a treatment that was effective in initial studies and that has been made available within the VA health care system. Similar results have been found with sertraline and trauma-focused psychotherapy, which are considered the first-line pharmacological and psychotherapeutic options for PTSD within the VA system.

Study Rating*—17 (100%): This study met all criteria for a randomized controlled trial.

Raskind M, Peskind E, Chow C, Harris C, et al: Trial of prazosin for post-traumatic stress disorder in military veterans. *NEJM* 2018;378 (February 8):507–517. From the VA Northwest Network Mental Illness Research, Education, and Clinical Center, Seattle, WA; and other institutions. **Funded by the VA. Four of 18 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

Common Drug Trade Names: **prazosin—*Minipress*; sertraline—*Zoloft***

***See Reference Guide.**

Lavender Oil for Subthreshold Anxiety

According to a manufacturer-sponsored meta-analysis, silexan, a standardized extract of lavender oil, reduces subthreshold anxiety symptoms.

Background: Silexan, the active ingredient of a medicinal product manufactured in Germany and licensed in 14 countries, contains an essential oil extracted from lavender flowers. Active substances in silexan cause inhibition of voltage-dependent calcium channels in synaptosomes thought to be important in anxiety and depression. Inhibition of these channels could dampen the excessive stress response associated with anxiety and mood disorders.

Methods: Data were obtained from 3 phase-III clinical trials. A literature and clinical trial registry search for other studies of silexan for anxiety was also conducted, but none were found. The trials were similar in design but targeted different disorders: subthreshold anxiety; restlessness, agitation, and disturbed sleep; and mixed anxiety and depressive disorder. Participants in all studies were required to have a baseline total score of ≥18 on the Hamilton Rating Scale for Anxiety (HAM-A). In all 3 trials, patients received randomly assigned 80 mg/day silexan or placebo for 10 weeks. The primary efficacy outcome was change from baseline to end of treatment in the HAM-A total score. The analysis also assessed treatment response (HAM-A total score decrease of ≥50% or Clinical Global Impression–Improvement [CGI-I] rating of much or very much improved) and remission (HAM-A <10 points at study end).

Results: A total of 697 patients received treatment and were assessed in the 3 trials. Premature withdrawal rates in the pooled studies were 12.6% for silexan and 10.5% for placebo. Silexan was significantly superior to placebo in reducing the mean HAM-A total score from baseline (standardized mean difference* between groups, 0.45; p=0.003). The overall effect of silexan was comparable for the psychic and somatic anxiety subscales of the HAM-A. Differences between silexan and placebo in patient-rated anxiety also favored silexan.

The overall rate of HAM-A response was significantly higher with silexan than with placebo (risk ratio,* 1.47; p=0.002; number needed to treat,* 6). Response based on CGI criteria was also significantly more likely with silexan (risk ratio, 1.69; p<0.001; number needed to treat, 5). Remission was also more likely to occur with silexan (p=0.008; number needed to treat, 8). Silexan also had positive effects on sleep disturbance and health-related quality of life.

Silexan was well tolerated. According to this and other reports, the predominant adverse effects are belching, dyspeptic symptoms, and allergic skin reactions.

Discussion: Although data on the use of silexan in anxiety are sparse, the results of this meta-analysis suggest it may be useful in the treatment of subthreshold anxiety. The authors note, however, that the study results apply only to silexan, not to the many other lavender oil products available.

Study Rating*—18 (100%): This study met all criteria for a systematic review/meta-analysis.

Moller H-J, Volz H-P, Dienel A, Schlafke S, et al: Efficacy of Silexan in subthreshold anxiety: meta-analysis of randomised, placebo-controlled trials. *European Archives of Psychiatry and Clinical Neuroscience* 2017; doi 10.1007/s00406-017-0852-4. From Ludwig Maximilian University, Munich, Germany; and other institutions. **Funded by Dr. Willmar Schwabe GmbH & Co KG, manufacturer of Silexan. All study authors disclosed financial relationships with commercial sources, including 2 with Dr. Willmar Schwabe GmbH & Co KG.**

***See Reference Guide.**

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Hazard Ratio: A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that 1 group has half the risk of the other group.

Number Needed to Treat: Indicates how many patients need to be treated for 1 to benefit. The ideal NNT is 1, where everyone improves with treatment. The higher the NNT value, the less effective the treatment.

Risk Ratio: The risk of an event (or of developing a disease) relative to exposure. Relative risk is a ratio of the probability of the event occurring in the exposed group versus the control (non-exposed) group.

Standardized Mean Difference: The difference between 2 normalized means—i.e. the mean values divided by an estimate of the within-group standard deviation. The standardized mean difference is used for comparison of data obtained using different scales.

Study Rating: A measure of how well a study conforms to quality standards. The study rating uses a checklist system based on the comprehensive Strength of Evidence Report from the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ). The rating checklists are posted at www.alertpubs.com.

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