ACAMPROSATE

THERAPEUTICS

Brands • Campral
see index for additional brand names

Generic? Not in USA

Class
- Neuroscience-based Nomenclature: glutamate multimodal (Glu-MM)
- Alcohol dependence treatment

Commonly Prescribed for
(bold for FDA approved)
- **Maintenance of alcohol abstinence**

How the Drug Works
- Theoretically reduces excitatory glutamate neurotransmission and increases inhibitory gamma-aminobutyric acid (GABA) neurotransmission
- Binds to and blocks certain glutamate receptors, including metabotropic glutamate receptors
- Because withdrawal of alcohol following chronic administration can lead to excessive glutamate activity and deficient GABA activity, acamprosate can act as "artificial alcohol" to mitigate these effects

How Long Until It Works
- Has demonstrated efficacy in trials lasting between 13 and 52 weeks

If It Works
- Increases abstinence from alcohol

If It Doesn't Work
- Evaluate for and address contributing factors
- Consider switching to another agent
- Consider augmenting with naltrexone

Best Augmenting Combos for Partial Response or Treatment Resistance
- Naltrexone
- Augmentation therapy may be more effective than monotherapy
- Augmentation with behavioral, educational, and/or supportive therapy in groups or as an individual is probably key to successful treatment

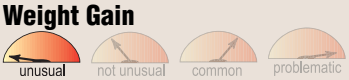
Tests
- None for healthy individuals

SIDE EFFECTS

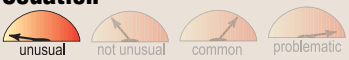
How Drug Causes Side Effects
- Theoretically, behavioral side effects due to changes in neurotransmitter concentrations at receptors in parts of the brain and body other than those that cause therapeutic actions
- Gastrointestinal side effects may be related to large doses of a drug that is an amino acid derivative, increasing osmotic absorption in the gastrointestinal tract

Notable Side Effects
- Diarrhea, nausea
- Anxiety, depression

Life-Threatening or Dangerous Side Effects
- Suicidal ideation and behavior (suicidality)

Weight Gain


- Reported but not expected

Sedation


- Reported but not expected

What to Do About Side Effects
- Wait
- Adjust dose
- If side effects persist, discontinue use

Best Augmenting Agents for Side Effects
- Dose reduction or switching to another agent may be more effective since most side effects cannot be improved with an augmenting agent

ACAMPROSATE (continued)

DOSING AND USE

Usual Dosage Range
- 666 mg three times daily (>60 kg)
- 666 mg two times daily (<60 kg)

Dosage Forms
- Tablet 333 mg

How to Dose
- Patient should begin treatment as soon as possible after achieving abstinence
- Recommended dose is 666 mg three times daily; titration is not required

Dosing Tips
- Providing educational materials and counseling in combination with acamprosate treatment can increase the chances of success
- Patients should be advised to continue treatment even if relapse occurs, and to disclose any renewed drinking
- Although absorption of acamprosate is not affected by food, it may aid adherence if patients who regularly eat three meals per day take each dose with a meal
- Adherence with three times daily dosing can be a problem; having patient focus on frequent oral dosing of drug rather than frequent drinking may be helpful in some patients

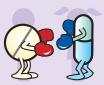
Overdose
- Limited available data; diarrhea

Long-Term Use
- Has been studied in trials up to 1 year

Habit Forming
- No

How to Stop
- Taper not necessary

Pharmacokinetics
- Terminal half-life 20–33 hours
- Excreted unchanged via the kidneys



Drug Interactions
- Does not inhibit hepatic enzymes, and thus is unlikely to affect plasma concentrations of drugs metabolized by those enzymes
- Is not hepatically metabolized and thus is unlikely to be affected by drugs that induce or inhibit hepatic enzymes
- Concomitant administration with naltrexone may increase plasma levels of acamprosate, but this does not appear to be clinically significant and dose adjustment is not recommended

Other Warnings/Precautions
- Monitor patients for emergence of depressed mood or suicidal ideation and behavior (suicidality)
- Use cautiously in individuals with known psychiatric illness

Do Not Use
- If patient has severe renal impairment
- If there is a proven allergy to acamprosate

SPECIAL POPULATIONS

Renal Impairment
- For moderate impairment, recommended dose is 333 mg three times daily
- Contraindicated in severe impairment

Hepatic Impairment
- Dose adjustment not generally necessary

Cardiac Impairment
- Limited data available

Elderly
- Some patients may tolerate lower doses better
- Consider monitoring renal function

Children and Adolescents
- Safety and efficacy have not been established

Pregnancy
- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter

categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- In animal studies, acamprosate demonstrated teratogenicity in doses approximately equal to the human dose (rat studies) and in doses approximately 3 times the human dose (rabbit studies)
- Pregnant women needing to stop drinking may consider behavioral therapy before pharmacotherapy
- Not generally recommended for use during pregnancy, especially during first trimester

Breast Feeding

- Unknown if acamprosate is secreted in human breast milk, but all psychotropics are assumed to be secreted in breast milk
- Recommended either to discontinue drug or bottle feed

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Individuals who have recently abstained from alcohol
- For the chronic daily drinker

Potential Disadvantages

- Individuals who are not abstinent at time of treatment initiation
- For binge drinkers

Primary Target Symptoms

- Alcohol dependence

Pearls

- Because acamprosate serves as "artificial alcohol," it may be less effective in situations in which the individual has not yet abstained from alcohol or suffers a relapse
- Thus acamprosate may be a preferred treatment if the goal is complete abstinence, but may not be preferred if the goal is reduced-risk drinking

Suggested Reading

Anton RF, O'Malley SS, Ciraulo DA, et al. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. JAMA 2006;295(17):2003–17.

Kranzler HR, Gage A. Acamprosate efficacy in alcohol-dependent patients: summary of results from three pivotal trials. Am J Addictions 2008; 17:70–6.

Rosner S, Leucht P, Soyka M. Acamprosate supports abstinence, naltrexone prevents excessive drinking: evidence from a meta-analysis with unreported outcomes. J Psychopharmacol 2008;22:11–23.

AGOMELATINE

THERAPEUTICS

Brands • Valdoxan
see index for additional brand names

Generic? No

Class

- Neuroscience-based Nomenclature: melatonin multimodal (Mel-MM)
- Agonist at melatonergic 1 and melatonergic 2 receptors
- Antagonist at 5HT2C receptors

Commonly Prescribed for

(bold for FDA approved)

- Depression
- Generalized anxiety disorder

How the Drug Works

- Actions at both melatonergic and 5HT2C receptors may be synergistic and increase norepinephrine and dopamine neurotransmission in the prefrontal cortex; may resynchronize circadian rhythms that are disturbed in depression
- No influence on extracellular levels of serotonin

How Long Until It Works

- Daytime functioning, anhedonia, and sleep can improve from the first week of treatment
- Onset of full therapeutic actions in depression is usually not immediate, but often delayed 2–4 weeks
- May continue to work for many years to prevent relapse of symptoms

If It Works

- The goal of treatment is complete remission of current symptoms as well as prevention of future relapses
- Treatment most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine is stopped
- Continue treatment until all symptoms are gone (remission)
- Once symptoms are gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite

If It Doesn't Work

- Many patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Consider increasing dose as early as 2 weeks after initiating treatment if response is insufficient (decision on dose increase has to be balanced with a higher risk of transaminase elevation; any dose increase should be made on an individual patient benefit/risk basis and with strict respect of liver function tests monitoring)
- Consider switching to another agent or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer

Best Augmenting Combos for Partial Response or Treatment Resistance

- SSRIs (excluding fluvoxamine), SNRIs, bupropion, reboxetine, atomoxetine (use combinations of antidepressant with caution as this may activate bipolar disorder and suicidal ideation)
- Modafinil, especially for fatigue, sleepiness, and lack of concentration
- Mood stabilizers or atypical antipsychotics for bipolar depression, psychotic depression, or treatment-resistant depression
- Benzodiazepines

Tests

- Liver function tests before initiation of treatment and then at 3 weeks, 6 weeks, 12 weeks, 24 weeks, and thereafter when clinically indicated
- When increasing the dose, liver function tests should be performed at the same frequency as when initiating treatment
- Liver function tests should be repeated within 48 hours in any patient who develops raised transaminases

AGOMELATINE (continued)

SIDE EFFECTS

How Drug Causes Side Effects

- Adverse reactions usually mild to moderate and occur within the first 2 weeks of treatment
- Actions at melatonergic receptors and at 5HT2C receptors could contibute to the side effects described below

Notable Side Effects

- Nausea and dizziness are most common
- Other adverse reactions are somnolence, fatigue, insomnia, headache, anxiety, diarrhea, constipation, upper abdominal pain, vomiting, hyperhidrosis
- Increase of transaminase levels

Life-Threatening or Dangerous Side Effects

✻ Rare hepatitis, hepatic failure

- Theoretically rare induction of mania (class warning)
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24) (class warning)

Weight Gain

- Occurs in significant minority
- In clinical studies, weight changes were similar to those in placebo
- Cases of weight decrease have been reported

Sedation (Somnolence)

- Occurs in significant minority
- Generally transient
- May be more likely to cause fatigue than sedation

What to Do About Side Effects

- Wait
- Wait
- Stop if transaminase levels reach 3 times the upper limit of normal
- Switch to another drug

Best Augmenting Agents for Side Effects

- Often best to try another antidepressant monotherapy prior to resorting to augmentation strategies to treat side effects
- Many side effects are time-dependent (i.e., they start immediately upon dosing and upon each dose increase, but go away with time)
- Many side effects cannot be improved with an augmenting agent
- Therotically activation and agitation may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of agomelatine (class warning)

DOSING AND USE

Usual Dosage Range

- 25–50 mg/day at bedtime

Dosage Forms

- Tablet 25 mg

How to Dose

- Initial 25 mg/day at bedtime; after 2 weeks can increase to 50 mg/day at bedtime

Dosing Tips

- If intolerable anxiety, insomnia, agitation, akathisia, or activation occur upon either dosing initiation or discontinuation, consider the possibility of activated bipolar disorder and switch to a mood stabilizer or an atypical antipsychotic

Overdose

- Drowsiness and epigastralgia; fatigue, agitation, anxiety, tension, dizziness, cyanosis, or malaise have also been reported

Long-Term Use

- Treatment up to 12 months has been found to decrease rate of relapse

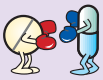
Habit Forming

- No

How to Stop

- No need to taper dose

Pharmacokinetics
- Half-life 1–2 hours
- Metabolized primarily by CYP450 1A2



Drug Interactions
- Use of agomelatine with potent CYP450 1A2 inhibitors (e.g., fluvoxamine) is contraindicated
- Tramadol increases the risk of seizures in patients taking an antidepressant (class warning)

Other Warnings/ Precautions
- Use with caution in patients with hepatic injury risk factors, such as obesity/ overweight/non-alcoholic fatty liver disease, diabetes, patients who drink large quantities of alcohol and/or have alcohol use disorder, or who take medication associated with risk of hepatic injury. Doctors should ask their patients if they have ever had liver problems
- If symptoms or signs of potential liver injury (dark urine, light-colored stools, yellow skin/eyes, pain in upper right belly, sustained new-onset and unexplained fatigue) are present, agomelatine should be discontinued immediately
- Use caution in patients with pretreatment elevated transaminases (> the upper limit of the normal range and <3 times the upper limit of the normal range)
- Discontinue treatment if serum transaminases increase to 3 times the upper limit of normal; liver function tests should be performed regularly until serum transaminases return to normal
- Agomelatine should be administered at bedtime
- Use with caution in patients with bipolar disorder unless treated with concomitant mood-stabilizing agent
- When treating children off label (an unapproved use), carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Whenever possible, warn patients and their caregivers about the possibility of activating side effects, and advise them to report such symptoms immediately
- Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use
- If patient has hepatic impairment
- If patient has transaminase levels >3 times the upper limit of normal
- If patient is taking a potent CYP450 1A2 inhibitor (e.g., fluvoxamine, ciprofloxacin)
- If patient is taking an MAO inhibitor (MAOI)
- If patient has galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption
- If there is a proven allergy to agomelatine

SPECIAL POPULATIONS

Renal Impairment
- Drug should be used with caution

Hepatic Impairment
- Contraindicated

Cardiac Impairment
- Dose adjustment not necessary

Elderly
- Efficacy and safety have been established (< 75 years old)
- Dose adjustment not necessary
- Should not be used in patients age 75 years and older
- Should not be used in elderly patients with dementia

Children and Adolescents
- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient's chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
- Safety and efficacy have not been established and it is not recommended

Pregnancy
- Controlled studies have not been conducted in pregnant women
- Not generally recommended for use during pregnancy, especially during first trimester

- Must weigh the risk of treatment (first trimester fetal development, third trimester newborn delivery) to the child against the risk of no treatment (recurrence of depression, maternal health, infant bonding) to the mother and child
- For many patients this may mean continuing treatment during pregnancy

Breast Feeding

- Unknown if agomelatine is secreted in human breast milk, but all psychotropics are assumed to be secreted in breast milk
- Therefore, breast feeding or drug needs to be discontinued
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstituted late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Patients with lack of energy, anhedonia, anxious comorbidity, and sleep-wake disturbances
- Patients particularly concerned about sexual side effects or weight gain

Potential Disadvantages

- Patients with hepatic impairment

Primary Target Symptoms

- Depressed mood, anhedonia
- Functioning
- Anxiety within depression

Pearls

- Agomelatine represents a novel approach to depression through a novel pharmacologic profile, agonist at melatonergic MT1 / MT2 receptors and antagonist at 5HT2C receptors acting synergistically
- This synergy provides agomelatine with a distinctive efficacy profile, different from conventional antidepressants with potentially an early and continuous improvement over time
- Agomelatine improves anhedonia early in treatment
- Improves anxiety in major depressive disorder
- May be fewer withdrawals/discontinuations for adverse events than with other antidepressants
- No significant effect on cardiac parameters such as blood pressure and heart rate
- Some data suggest that agomelatine may be specially efficacious in achieving functional remission
- Agomelatine may improve sleep quality by promoting proper maintenance of circadian rhythms underlying a normal sleep-wake cycle

Suggested Reading

DeBodinat C, Guardiola-Lemaitre B, Mocaer E, et al. Agomelatine, the first melatonergic antidepressant: discovery, characterization, and development. Nat Rev Drug Discov 2010;9:628–42.

Goodwin GM, Emsley R, Rembry S, Rouillon F. Agomelatine prevents relapse in patients with major depressive disorder without evidence of a discontinuation syndrome: a 24-week randomized, double-blind, placebo-controlled trial. J Clin Psychiatry 2009;70:1128–37.

Kennedy SH, Avedisova A, Belaïdi C, Picarel-Blanchot F, de Bodinat C. Sustained efficacy of agomelatine 10 mg, 25 mg, and 25–50 mg on depressive symptoms and functional outcomes in patients with major depressive disorder. A placebo-controlled study over 6 months. Neuropsychopharmacol 2016;26(2):378–89.

Khoo AL, Zhou HJ, Teng M, et al. Network meta-analysis and cost-effectiveness analysis of new generation antidepressants. CNS Drugs 2015;29(8):695–712.

Martinotti G, Sepede G, Gambi F, et al. Agomelatine versus venlafaxine XR in the treatment of anhedonia in major depressive disorder: a pilot study. J Clin Psychopharmacol 2012;32(4):487–91.

Racagni G, Riva MA, Molteni R, et al. Mode of action of agomelatine: synergy between melatonergic and 5-HT2C receptors. World J Biol Psychiatry 2011;12(8):574–87.

Stahl SM. Mechanism of action of agomelatine: a novel antidepressant exploiting synergy between monoaminergic and melatonergic properties. CNS Spectr 2014;19:207–12

Stahl SM, Fava M, Trivedi M, et al. Agomelatine in the treatment of major depressive disorder. An 8 week, multicenter, randomized, placebo-controlled trial. J Clin Psychiatry 2010;71(5):616–26.

Stein DJ, Picarel-Blanchot F, Kennedy SH. Efficacy of the novel antidepressant agomelatine on anxiety symptoms in major depression. Hum Psychopharmacol 2013;28(2):151–9.

Taylor D, Sparshatt A, Varma S, Olofinjana O. Antidepressant efficacy of agomelatine: meta-analysis of published and unpublished studies. BMJ 2014;348:g2496.

ALPRAZOLAM

THERAPEUTICS

Brands • Xanax
• Xanax XR
see index for additional brand names

Generic? Yes

Class

- Neuroscience-based Nomenclature: GABA positive allosteric modulator (GABA-PAM)
- Benzodiazepine (anxiolytic)

Commonly Prescribed for

(bold for FDA approved)

- **Generalized anxiety disorder (IR)**
- **Panic disorder (IR and XR)**
- Other anxiety disorders
- Anxiety associated with depression
- Premenstrual dysphoric disorder
- Irritable bowel syndrome and other somatic symptoms associated with anxiety disorders
- Insomnia
- Acute mania (adjunctive)
- Acute psychosis (adjunctive)
- Catatonia

How the Drug Works

- Binds to benzodiazepine receptors at the GABA-A ligand-gated chloride channel complex
- Enhances the inhibitory effects of GABA
- Boosts chloride conductance through GABA-regulated channels
- Inhibits neuronal activity presumably in amygdala-centered fear circuits to provide therapeutic benefits in anxiety disorders

How Long Until It Works

- Some immediate relief with first dosing is common; can take several weeks with daily dosing for maximal therapeutic benefit

If It Works

- For short-term symptoms of anxiety – after a few weeks, discontinue use or use on an "as-needed" basis
- For chronic anxiety disorders, the goal of treatment is complete remission of symptoms as well as prevention of future relapses
- For chronic anxiety disorders, treatment most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped
- For long-term symptoms of anxiety, consider switching to an SSRI or SNRI for long-term maintenance
- If long-term maintenance with a benzodiazepine is necessary, continue treatment for 6 months after symptoms resolve, and then taper dose slowly
- If symptoms reemerge, consider treatment with an SSRI or SNRI, or consider restarting the benzodiazepine; sometimes benzodiazepines have to be used in combination with SSRIs or SNRIs for best results

If It Doesn't Work

- Consider switching to another agent or adding an appropriate augmenting agent
- Consider psychotherapy, especially cognitive behavioral psychotherapy
- Consider presence of concomitant substance abuse
- Consider presence of alprazolam abuse
- Consider another diagnosis, such as a comorbid medical condition

Best Augmenting Combos for Partial Response or Treatment Resistance

- Benzodiazepines are frequently used as augmenting agents for antipsychotics and mood stabilizers in the treatment of psychotic and bipolar disorders
- Benzodiazepines are frequently used as augmenting agents for SSRIs and SNRIs in the treatment of anxiety disorders
- Not generally rational to combine with other benzodiazepines
- Caution if using as an anxiolytic concomitantly with other sedative hypnotics for sleep
- Could consider augmenting alprazolam with either gabapentin or pregabalin for treatment of anxiety disorders

Tests

- In patients with seizure disorders, concomitant medical illness, and/or those with multiple concomitant long-term medications, periodic liver tests and blood counts may be prudent

SIDE EFFECTS

How Drug Causes Side Effects

- Same mechanism for side effects as for therapeutic effects – namely due to excessive actions at benzodiazepine receptors

ALPRAZOLAM (continued)

- Long-term adaptations in benzodiazepine receptors may explain the development of dependence, tolerance, and withdrawal
- Side effects are generally immediate, but immediate side effects often disappear in time

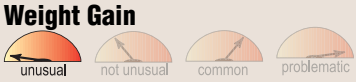
Notable Side Effects

- ✻ Sedation, fatigue, depression
- ✻ Dizziness, ataxia, slurred speech, weakness
- ✻ Forgetfulness, confusion
- ✻ Hyperexcitability, nervousness
- Rare hallucinations, mania
- Rare hypotension
- Hypersalivation, dry mouth

Life-Threatening or Dangerous Side Effects

- Respiratory depression, especially when taken with CNS depressants in overdose
- Rare hepatic dysfunction, renal dysfunction, blood dyscrasias

Weight Gain



- Reported but not expected

Sedation

- Occurs in significant minority
- Especially at initiation of treatment or when dose increases
- Tolerance often develops over time

What to Do About Side Effects

- Wait
- Wait
- Wait
- Lower the dose
- Switch to alprazolam XR
- Take largest dose at bedtime to avoid sedative effects during the day
- Switch to another agent
- Administer flumazenil if side effects are severe or life-threatening

Best Augmenting Agents for Side Effects

- Many side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- Anxiety: alprazolam IR: 1–4 mg/day
- Panic: alprazolam IR: 5–6 mg/day
- Panic: alprazolam XR: 3–6 mg/day

Dosage Forms

- Alprazolam IR tablet 0.25 mg scored, 0.4 mg (Japan), 0.5 mg scored, 0.8 mg (Japan), 1 mg scored, 2 mg multiscored
- Alprazolam IR solution, concentrate 1 mg/mL
- Alprazolam XR (extended-release) tablet 0.5 mg, 1 mg, 2 mg, 3 mg

How to Dose

- For anxiety, alprazolam IR should be started at 0.75–1.5 mg/day divided into 3 doses; increase dose every 3–4 days until desired efficacy is reached; maximum dose generally 4 mg/day
- For panic, alprazolam IR should be started at 1.5 mg/day divided into 3 doses; increase 1 mg or less every 3–4 days until desired efficacy is reached, increasing by smaller amounts for dosage over 4 mg/day; may require as much as 10 mg/day for desired efficacy in difficult cases
- For panic, alprazolam XR should be started at 0.5–1 mg/day once daily in the morning; dose may be increased by 1 mg/day every 3–4 days until desired efficacy is reached; maximum dose generally 10 mg/day

Dosing Tips

- Use lowest possible effective dose for the shortest possible period of time (a benzodiazepine-sparing strategy)
- Assess need for continued treatment regularly
- Risk of dependence may increase with dose and duration of treatment
- For interdose symptoms of anxiety, can either increase dose or maintain same total daily dose but divide into more frequent doses, or give as extended-release formulation
- Can also use an as-needed occasional "top-up" dose for interdose anxiety
- Because panic disorder can require doses higher than 4 mg/day, the risk