

ACAMPROSATE

THERAPEUTICS

**Brands** • Campral

**Generic?** Yes

**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 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 3 times daily (>60 kg)
- 666 mg 2 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 3 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 3 meals per day take each dose with a meal
- Adherence with 3 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 3 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 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.

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from three pivotal trials. *Am J Addictions* 2008; 17:70–6.

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# AGOMELATINE

## THERAPEUTICS

**Brands** • Valdoxan

**Generic?** No

### Class

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

### Commonly Prescribed for

(bold for FDA approved)

- Depression
- Generalized anxiety disorder



### How the Drug Works

- Actions at both melatonergic and serotonin 2C 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 serotonin 2C receptors could contribute 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 CYP1A2

**Drug Interactions**

- Use of agomelatine with potent CYP1A2 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 with 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 CYP1A2 inhibitor (e.g., fluvoxamine, ciprofloxacin)
- If patient is taking an 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

AGOMELATINE (continued)

- 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 pharmacological profile, agonist at melatonergic MT1/MT2 receptors and antagonist at serotonin 2C 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

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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.

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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-HT<sub>2C</sub> 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

**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