Acamprosate calcium

THERAPEUTICS

Brands
- Campral EC

Generic?
Yes

Class
- Neuroscience-based nomenclature: pharmacology domain – glutamate; mode of action – unclear
- Alcohol dependence treatment; glutamate multimodal (Glu-MM)

Commonly Prescribed for
(bold for BNF indication)
- **Maintenance of abstinence in alcohol-dependence** (moderate-severe condition in combination with psychosocial interventions)

How the Drug Works
- Theoretically reduces excitatory glutamate neurotransmission and increases gamma-aminobutyric acid (GABA) to increase abstinence
- Binds to and blocks certain glutamate receptors, including metabotropic glutamate receptors
- Acts as a functional glutamatergic NMDA antagonist
- 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
- Treatment duration of longer than 6 months suggested
- Has demonstrated efficacy in trials lasting between 13 and 52 weeks

If It Works
- Increases continuous/cumulative abstinence from alcohol

If It Doesn't Work
- Evaluate for and address contributing factors
- Consider switching to another agent, e.g. naltrexone or disulfiram
- Consider augmenting with naltrexone

Best Augmenting Combos for Partial Response or Treatment Resistance
- Naltrexone
- Augmenting therapy may be more effective than monotherapy
- Use in combination with individual psychological interventions (CBT, behavioural therapy, social network/environment-based therapies)

Tests
- Baseline urea and electrolytes, liver function (including gamma-glutamyl transferase)
- Follow-up blood tests: liver function to check on recovery and to increase motivation

SIDE EFFECTS

How Drug Causes Side Effects
- Theoretically, behavioural side effects are 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
- Diarrhoea, nausea
- Anxiety, depression

Common or very common
- GIT: abdominal pain, diarrhoea, flatulence, nausea, vomiting
- Other: sexual dysfunction, skin reactions

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

Weight Gain


- Reported but not expected

Acamprosate calcium (Continued)

Sedation

- Reported but not expected

What to Do About Side Effects

- Wait
- Adjust the 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

DOSING AND USE

Usual Dosage Range

- Adult (body weight <60 kg): 666 mg in the morning, and 333 mg at midday and at night time
- Adult (body weight ≥ 60 kg): 666 mg 3 times per day

Dosage Forms

- Tablet 333 mg

How to Dose

*Maintenance of abstinence in alcohol dependence:

- Patients should begin treatment as soon as possible after achieving detoxification
- Some evidence suggests can be started during detoxification for neuroprotection
- Recommended dose is 666 mg 3 times daily, titration is not required

Dosing Tips

- Provide psychosocial intervention in combination with acamprosate treatment to increase the chances of success
- Stop if drinking persists 4 to 6 weeks after starting the drug
- Stay under supervision at least monthly for 6 months, then less frequently if taking more than 6 months
- 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 the 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

- Acute overdose can lead to persistent diarrhoea

Long-Term Use

- Should be prescribed for 6 months or longer (licensed for 1 year)
- Has been studied in trials for up to 1 year

Habit Forming

- No

How to Stop

- Taper not necessary

Pharmacokinetics

- Bioavailability reduced when taken with food
- Terminal half-life about 20–33 hours
- Excreted mostly unchanged via kidneys

Drug Interactions

- Does not inhibit hepatic enzymes, and this is unlikely to affect plasma concentrations of drugs metabolised by those enzymes
- Is not hepatically metabolised 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 behaviour (suicidality)
- Use cautiously in individuals with known psychiatric illness
- Continued alcohol abuse – risk of treatment failure

Do Not Use

- If the patient has severe renal impairment
- If the patient has severe hepatic impairment
- If there is a proven allergy to acamprosate

SPECIAL POPULATIONS

Renal Impairment
- For moderate impairment, recommended dose is 333 mg 3 times per day
- Contraindicated in severe impairment

Hepatic Impairment
- Dose adjustment not generally necessary
- Avoid in severe liver impairment

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
- 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 about 3 times the human dose (rabbit studies)
- Pregnant women needing to stop drinking may consider behavioural therapy before pharmacotherapy
- Not generally recommended for use during pregnancy, especially during first trimester
- Alcohol is a confirmed teratogen and therefore acamprosate use during pregnancy may be considered beneficial in some cases

Breastfeeding
- No evidence of safety
- Long half-life increases the risk of accumulation in the breastfed infant
- Low levels anticipated in milk due to low oral absorption
- Benefit of the mother abstaining from alcohol to the infant may outweigh the risk to the infant of acamprosate

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages
- Individuals who have recently abstained from alcohol
- For the chronic, daily drinker
- It works as well as naltrexone for maintenance of abstinence from alcohol

Potential Disadvantages
- Individuals who are not abstinent at time of treatment initiation
- For binge drinkers
- Naltrexone works slightly better for reducing cravings for alcohol and heavy drinking

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
- Studies have found that acamprosate works best when used in combination with psychosocial support since the drug facilitates a reduction in alcohol consumption as well as full abstinence
- Over 3 to 12 months it increases the number of people who do not drink at all and the number of days without alcohol
- It appears to work as well as naltrexone for maintenance of abstinence from alcohol, however, naltrexone works slightly better for reducing cravings for alcohol and heavy drinking
- Some evidence suggests that acamprosate is neuroprotective (it protects neurons from damage and death caused by the effects of alcohol withdrawal, and possibly other causes of neurotoxicity)

Suggested Reading

De Witte P, Littleton J, Parot P, et al. Neuroprotective and abstinence-promoting effects of acamprosate: elucidating the mechanism of action. CNS Drugs 2005;19(6):517–37.

Kiefer F, Jahn H, Tarnaske T, et al. Comparing and combining naltrexone and acamprosate in relapse prevention of alcoholism: a double-blind, placebo-controlled study. Arch Gen Psychiatry 2003;60:92–9.

Kranzler HR, Soyka M. Diagnosis and pharmacotherapy of alcohol use disorder: a review. JAMA 2018;320(8):815–24.

Lingford-Hughes AR, Welch S, Peters L, et al. BAP updated guidelines: evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and comorbidity: recommendations from BAP. J Psychopharmacol 2012;26(7):899–952.

Maisel NC, Blodgett JC, Wilbourne PL, Humphreys K, Finney JW. Meta-analysis of naltrexone and acamprosate for treating alcohol use disorders: when are these medications most helpful? Addiction 2013;108(2):275–93.

Mann K, Kiefer F, Spanagel R, et al. Acamprosate: recent findings and future research directions. Alcohol Clin Exp Res 2008;32(7):1105–10.

Mason BJ, Heyser CJ. The neurobiology, clinical efficacy and safety of acamprosate in the treatment of alcohol dependence. Expert Opin Drug Saf 2010;9(1):177–88.

Nutt DJ. Doing it by numbers: a simple approach to reducing the harms of alcohol. J Psychopharmacol 2014;28(1):3–7.

Pilling S, Yesufu-Udechuku A, Taylor C, et al. Diagnosis, assessment, and management of harmful drinking and alcohol dependence: summary of NICE guidance. BMJ 2011;342:d700.

Plosker GL. Acamprosate: a review of its use in alcohol dependence. Drugs 2015;75(11):1255–68.

Agomelatine

THERAPEUTICS

Brands
- Valdoxan

Generic?
Yes

Class
- Neuroscience-based nomenclature: pharmacology domain – melatonin, serotonin; mode of action – agonist and antagonist
- Agonist at melatonin 1 and melatonin 2 receptors
- Antagonist at 5HT2B and 5HT2C receptors

Commonly Prescribed for
(bold for BNF indication)
- **Major depression**
- Generalised anxiety disorder

How the Drug Works
- Actions at both melatonin and 5HT2C receptors may be synergistic and increase noradrenaline and dopamine neurotransmission in the prefrontal cortex; may resynchronise 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 is 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 at least 6–9 months for the first episode of depression or >12 months if relapse indicators present
- If >5 episodes and/or 2 episodes in the last few years then need to continue for at least 2 years or indefinitely

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 non-responders, 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; dose increases should be made on an individual patient benefit/risk basis and with mandated liver function tests monitoring)
- Consider switching to another agent or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider diagnosis or whether there is a co-morbid condition (e.g. medical illness, substance abuse, etc.)
- Some patients may experience lack of consistent efficacy due to the diagnosis actually being of a bipolar disorder, and require antidepressant discontinuation and consideration of a mood stabiliser or bipolar depression treatment

Best Augmenting Combos for Partial Response or Treatment Resistance
- SSRIs (excluding fluvoxamine), SNRIs, bupropion (use combinations of antidepressants with caution as this may activate bipolar disorder and suicidal ideation or agitation)
- Mood stabilisers or atypical antipsychotics for bipolar depression, psychotic depression, or treatment-resistant depression
- Modafinil, especially for fatigue, sleepiness, and lack of concentration
- Benzodiazepines

Tests
- Liver function tests before initiation of treatment and then at 3, 6, 12, and 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

SIDE EFFECTS

How Drug Causes Side Effects
- Adverse reactions usually mild to moderate and occur within the first 2 weeks of treatment
- Actions at melatonin receptors and at 5HT2C receptors could contribute to the side effects described below

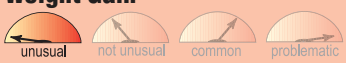
Notable Side Effects
- Nausea and dizziness

Common or very common
- CNS: anxiety, dizziness, drowsiness, headaches, sleep disorders
- GIT: abdominal pain, constipation, diarrhoea, nausea, vomiting, weight changes
- Other: back pain, fatigue

Uncommon
- Aggression, altered mood, blurred vision, confusion, hyperhidrosis, movement disorders, paraesthesia, skin reactions, suicidal tendencies, tinnitus

Rare or very rare
- Angioedema, facial oedema, hallucination, hepatic disorders, urinary retention

Life-Threatening or Dangerous Side Effects
- Rare hepatitis, hepatic failure
- Theoretically, rare induction of mania
- Rare activation of suicidal ideation and behaviour (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 25)

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


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

What to Do About Side Effects
- Wait (unless related to liver)
- 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
- Theoretically activation and agitation may represent the induction of a bipolar state, especially a mixed dysphoric state sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabiliser or an atypical antipsychotic, and/or discontinuation of agomelatine

DOSING AND USE

Usual Dosage Range
- Major depression: 25–50 mg/day at bedtime

Dosage Forms
- Tablet 25 mg

How to Dose
- Major depression: initial dose 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 either upon dosing initiation or discontinuation,

consider the possibility of activated bipolar disorder and switch to a mood stabiliser or an atypical antipsychotic

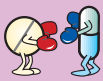
Overdose
- Drowsiness and stomach pain, fatigue, agitation, anxiety, tension, dizziness, cyanosis, or malaise have been reported

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
- Oral bioavailability generally higher in women versus men
- Half-life 1–2 hours
- Metabolised primarily by CYP450 1A2 – dose adjustments may thus be necessary if smoking status changes



Drug Interactions
- Use of agomelatine with potent CYP450 1A2 inhibitors (e.g. fluvoxamine) is contraindicated
- Liver metabolism of agomelatine is induced by smoking
- 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
- Patients should be informed to seek immediate medical review if they experience symptoms related to liver disorder such as abdominal pain, bruising, dark urine, fatigue, jaundice, light-coloured stools, or pruritus
- Patients should be given a booklet with more information on the risk of hepatic side effects
- Use caution in patients with pre-treatment 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
- Use with caution in patients with bipolar disorder or presenting in a hypomanic or manic state unless treated with concomitant mood-stabilising agent
- 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 those below the age of 25

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 MAO inhibitor (MAOI)
- If patient has galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption
- If patient has dementia
- If patient is over 75 years of age
- If there is a proven allergy to agomelatine

SPECIAL POPULATIONS

Renal Impairment
- Drug should be used with caution in moderate to severe impairment

Hepatic Impairment
- Avoid in hepatic impairment or if transaminases exceed 3 times the upper limit of normal

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 aged 75 years and older

Agomelatine (Continued)

- Should not be used in elderly patients with dementia

Children and Adolescents

- Safety and efficacy have not been established and 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 foetal 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

Breastfeeding

- Low levels anticipated in milk
- Extremely limited evidence of safety
- Monitor the infant for drowsiness, feeding difficulties and behavioural effects
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, antidepressants may need to be reinstituted late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Must weigh benefits of breastfeeding with risks and benefits of antidepressant treatment versus nontreatment to both the infant and the mother
- For many patients this may mean continuing treatment during breastfeeding
- Other antidepressants may be preferable, e.g. paroxetine, sertraline, imipramine, or nortriptyline

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Patients with lack of energy, anhedonia, anxious co-morbidity, 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 with depression

Pearls

- Agomelatine tends to be a third-choice antidepressant. It represents a novel approach to depression through a novel pharmacologic profile, agonist at melatonin 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 especially 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

Carvalho AF, Sharma MS, Brunoni AR, et al. The safety, tolerability and risks associated with the use of newer generation antidepressant drugs: a critical review of the literature. Psycother Psychosom 2016;85(5):270–88.

Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet 2018;391(10128):1357–66.

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, Belai'di C, et al. 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.

Stahl SM. Mechanism of action of agomelatine: a novel antidepressant exploiting synergy between monoaminergic and melatonergic properties. CNS Spectrums 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, et al. Antidepressant efficacy of agomelatine: meta-analysis of published and unpublished studies. BMJ 2014;348:g1888 (erratum in BMJ 2014;349:g2496).

Alprazolam

THERAPEUTICS

Brands
- Xanax

Generic?
No, not in UK

Class
- Neuroscience-based nomenclature: pharmacology domain – GABA; mode of action – benzodiazepine receptor agonist (non-selective GABA-A receptor positive allosteric modulator – PAM)
- Benzodiazepine (anxiolytic)

Commonly Prescribed for
(bold for BNF indication)
- **Anxiety (short-term use)**
- Generalised anxiety disorder
- Panic disorder
- 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-centred 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 or muscle spasms – 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 is 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
- Avoid long-term maintenance with a benzodiazepine
- If symptoms re-emerge after stopping a benzodiazepine, consider treatment with an SSRI or SNRI, or consider restarting the benzodiazepine; sometimes benzodiazepines have to be used in combination with SSRIs or SNRIs at the start of treatment for best results

If It Doesn't Work
- Consider switching to another agent or adding an appropriate augmenting agent
- Consider psychotherapy, especially cognitive behavioural psychotherapy
- Consider presence of concomitant substance abuse
- Consider presence of alprazolam abuse
- Consider another diagnosis, such as a co-morbid medical condition

Best Augmenting Combos for Partial Response or Treatment Resistance
- Benzodiazepines are frequently used as augmenting agents for antipsychotics and mood stabilisers 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