

# Alcohol Antagonists

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**What is an alcohol antagonist?** An alcohol antagonist is a drug that specifically blocks the effects of alcohol. If you take an alcohol antagonist and then drink a bunch of alcohol, it should theoretically prevent you from getting drunk, or it should at least reduce your level of drunkenness.

**Reminder: What is a receptor antagonist?** A receptor antagonist is a drug that binds to a receptor but does not send any signal. A receptor antagonist can block other ligands from binding. In this way, an antagonist can block the effects of agonists, whether those agonists are drugs or neurotransmitters.

Some alcohol antagonists are receptor antagonists, but many are not. Do not be confused.

Alcohol has many different mechanisms of action, so there are many different classes of alcohol antagonists.

## GABA<sub>A</sub> antagonists:

The GABA<sub>A</sub> receptor complex has separate binding sites for several different classes of drugs. The GABA<sub>A</sub> receptor complex is shaped like a donut with a number of dimples (depressions) where drugs can bind. The center donut hole is a chloride ion channel. The GABA<sub>A</sub> receptor complex binds the neurotransmitter GABA in one location, it binds barbiturates in a second location, it binds benzodiazepines in a third location, it binds neurosteroids in a fourth location, and it binds picrotoxin in a fifth location. Alcohol binds in a sixth location that is adjacent to the benzodiazepine binding site.

### GABA binding site antagonists:

**Bicuculline** – This is an alkaloid found in several different plants. It causes stimulation, anxiety, and seizures. Bicuculline is used to simulate epilepsy in animals.

### Barbiturate site antagonists:

**Bemegride** (a.k.a. **megimide**) – This drug is occasionally used to reverse barbiturate overdose. It causes stimulation, anxiety, and seizures. Barbiturate overdose causes death by respiratory failure, because the patient just stops breathing. Barbiturate overdose is a popular means of suicide and lethal injection, because it is very peaceful. Although bemegride is the specific antidote to barbiturate overdose, it is not commonly used anymore because of side effects. Today, barbiturate overdose is treated by mechanically ventilating the patient until the barbiturates have worn off. Bemegride can also be used to stimulate breathing in the absence of barbiturate overdose. For instance, bemegride can increase respiratory rate in opioid overdose patients.

### Benzodiazepine site antagonists:

**Flumazenil** – This drug is occasionally used to reverse benzodiazepine overdose, reverse benzodiazepine sedation after surgery, and relieve drowsiness in patients with

a disease called primary hypersomnia. Flumazenil causes stimulation, anxiety, and seizures. Benzodiazepine overdose almost never causes death, unless the patient has also taken other drugs such as opioids or alcohol. Because benzodiazepine overdose is generally non-fatal, flumazenil is usually not necessary.

Ethanol site antagonists:

**Ro 15-4513** – This drug is a benzodiazepine receptor partial inverse agonist. It causes stimulation, anxiety, and seizures. Ro 15-4513 binds in the benzodiazepine binding cleft, but it has an azido group sticking out that occupies the ethanol binding cleft. Most benzodiazepine ligands do not interfere with ethanol binding, but Ro 15-4513 does interfere with ethanol binding because of this bulky azido group that displaces ethanol. *In vitro*, Ro 15-4513 **competitively inhibits ethanol binding to the GABA<sub>A</sub> receptor complex**. *In vivo*, Ro 15-4513 inhibits the sedation caused by alcohol but does not interfere with the anxiety relief caused by alcohol.

Among the 4 drugs discussed so far, Ro 15-4513 is unique. Bicuculline, bemegride, and flumazenil all work by causing stimulation which counteracts the sedation caused by ethanol. Ro 15-4513 actually prevents ethanol from binding to its molecular target. However, ethanol has many molecular targets, and Ro 15-4513 only blocks one of them.

Ro 15-4513 is a much more effective alcohol antagonist than flumazenil, which is interesting because Ro 15-4513 is a less potent stimulant. This is because Ro 15-4513 only binds to a few types of benzodiazepine receptor, whereas flumazenil binds to (and blocks) almost all types.

Ro 15-4513 was originally investigated as a possible treatment for alcohol overdose. It was abandoned because it tends to cause seizures, and also because it has a very short half-life.

GABA<sub>B</sub> antagonists:

**Saclofen** – This drug is used only in experiments. Saclofen is structurally related to baclofen, which is the classic GABA<sub>B</sub> agonist.

Opioid receptor antagonists:

Ethanol causes the release of endogenous opioids (e.g. beta-endorphin). Remember that opioids are very important in the **liking pathway**, meaning that opioids cause pleasure.

**Naltrexone** – The FDA has approved naltrexone (as pills) for alcohol dependence. If a recovering alcoholic takes naltrexone and then slips up and drinks a glass or two of liquor, the naltrexone will block the positive feelings usually induced by alcohol. The alcoholic may then reconsider their actions, and they may decide to stop drinking. Without naltrexone, the first two drinks usually lead to ten more drinks and a full relapse.

Naltrexone blocks ethanol-induced pleasure, but it does not block ethanol-induced sedation, ataxia, or nausea. Naltrexone still qualifies as an alcohol antagonist because it blocks one specific effect of alcohol. Naltrexone could be called a *selective* alcohol antagonist.

### Dopamine receptor antagonists:

Ethanol causes the release of dopamine in the nucleus accumbens. Remember that dopamine in this location is absolutely critical to the **wanting pathway**, which leads to addiction.

**Haldol (haloperidol)** – This is a potent D<sub>2</sub> receptor antagonist, it is widely prescribed as an antipsychotic. Normal rats will self-administer ethanol, but rats treated with Haldol will not. This seems to indicate that taking Haldol along with alcohol will block the learning processes that lead to addiction, at least in rats and at certain doses. Injecting a dopamine receptor antagonist directly into the nucleus accumbens will inhibit self-administration while minimizing other side effects.

Like naltrexone, Haldol is a *selective* alcohol antagonist. Haldol does not block most of the effects of ethanol, and it will actually increase the level of drowsiness. However, Haldol selectively blocks the effect of ethanol on the wanting pathway.

Dopamine antagonists can prevent a rat from learning to self-administer alcohol, but what if the rat has already learned to self-administer? In this case, the dopamine antagonist is much less effective. This means dopamine antagonists are only mildly effective for human alcoholics. Dopamine antagonists also cause serious side effects, such as tardive dyskinesia.

### 5-HT<sub>3</sub> serotonin receptor antagonists:

5-HT<sub>3</sub> serotonin receptors are involved with nausea and vomiting. Serotonin induces feelings of fullness and nausea, especially when serotonin binds to and activates 5-HT<sub>3</sub> receptors. Ethanol also binds to and activates 5-HT<sub>3</sub> receptors. Specifically, ethanol has been shown to bind to 5-HT<sub>3A</sub> receptors, and ethanol stabilizes the open configuration of the 5-HT<sub>3</sub> ion channel. The 5-HT<sub>3</sub> ion channel conducts sodium ions, so it is excitatory. Ethanol and serotonin both cause nausea and vomiting by stimulating the 5-HT<sub>3</sub> receptor. (Ethanol also causes nausea by creating acetaldehyde in the stomach lining, and other effects.)

**Zofran (ondansetron)** – Ondansetron is a highly selective 5-HT<sub>3</sub> antagonist. Ondansetron is widely used to prevent chemotherapy-induced nausea and vomiting. Ondansetron is also used to prevent nausea and vomiting caused by other things such as radiation therapy, surgery, and viral gastroenteritis (norovirus and rotavirus, “the stomach bug”).

As you would expect, ondansetron functions as a selective alcohol antagonist that selectively blocks the nausea. However, ondansetron doesn't just block alcohol-induced nausea. Low doses of ethanol cause locomotor stimulation in rats (they run around more), and this response shows sensitization. This means that after repeated ethanol doses, the rats actually run around even more. Sensitization is the opposite of tolerance. Ondansetron blocks ethanol-induced locomotor sensitization. This may indicate that ondansetron can block alcohol addiction, much like Haldol (a dopamine antagonist). Limited human trials have also shown that ondansetron is helpful for recovering alcoholics. Ondansetron reduces the urge to drink alcohol and also reduces the anxiety that alcoholics feel when they don't drink.

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