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# Moxidectin as a Neuromodulator, A Review

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## 1. Abstract

Very little is known about the pathophysiology of mood and alcohol use disorders and their treatment is equally lackluster. Consequently, new molecular targets are often being explored. The development of novel drugs poses significant challenges, prompting the investigation of already established compounds in different therapeutic areas as an interesting alternative. One of such new targets in depression is the positive allosteric modulation of GABA-A receptors, which has recently had a new drug approved by the FDA for the treatment of postpartum depression, brexanolone. Moxidectin, an antiparasitic drug, has the capability to modulate mammalian GABA-A and P2X4 purinergic receptors in doses above the standard endectocidal. Due to this capability and its favorable safety profile, it has been tested as a neuromodulator in murine models of depression, alcohol use disorder, and Parkinson's disease in recent years. This review aims to synthesize the findings of papers published between 2012 and 2022 on the neuromodulatory and neuropharmacological properties and effects of moxidectin. All papers consistently showed moxidectin as possessing promise in the treatment of alcohol use disorder and depression and anxiety disorders in mice models with a favorable safety profile. The in vitro studies corroborated these findings and better elucidated the mechanism of action of this compound.

## 2. Keywords

Alcohol Use Disorder; Depression; Drug Repositioning; Macrocyclic Lactones; GABA-A

## 3. Moxidectin as a Neuromodulator, a Review

In 1938 a gram-positive bacterium named *Streptomyces cyaneogriseusnoncyanogenus*was isolated from Australian red sand by scientists of the Glaxo Group from England and scientists of American Cyanamid from the USA. The bacterium produced a chemical named Nemadectin. After undergoing modifications in its structure, the semisynthetic compound now known as Moxidectin (MOX) was created. It was first marketed in 1990 as an injectable endectocide for cattle (Campbell, 2012). Moxidectin is the most popular Milbemycin, a subgroup of the Macrocyclic Lactones (ML). The ML are a group of pharmaceuticals used mainly for external and internal parasite control. For its wide use and success in human and animal medicine its developers were awarded the Nobel Prize in Physiology or Medicine in 2015.

Moxidectin was approved for human use by the FDA in 2018 for onchocerciasis, popularly known as "River Blindness" (FDA, 2023). In veterinary practice it is commonly used as an endectocide in livestock and in the prevention of *Dirofilaria immitis* in dogs (Ménez et al., 2012).

Another widely known ML is Ivermectin (IVM), part of the Avermectins (AVM) subgroup. IVM is derived from *Streptomyces avermectinius*, a Japanese soil dwelling bacterium (Spampanato et al., 2018). We highlight the existence of AVM because MOX and IVM research often goes hand in hand and, even though we focus this paper on the former, the latter will appear often as a point of reference or comparison.

ML have as their main mechanism of action the targeting of glutamate-activated chloride channels, an ionotropic channel, essential for muscular control of invertebrates. This activation leads to flaccid paralysis of the parasites and eventual death. These channels are not found in mammals (Rodrigues-Alves et al., 2008). Therefore, they are interesting antiparasitic compounds for their minimal side effects to their users while maintaining potent effect on invertebrates. However, new studies have demonstrated their ability to allosterically bind and modulate mammalian nervous system ionotropic receptors, namely the γ-aminobutyric acid type A (GABA-A), glycine, nicotinic α7 and P2X4 purinergic receptors (Spampanato et al., 2018). These effects are rarely observed when the drug is utilized in its standard endectocidal dose.

The intricacies of the brain remain a mystery. Very little is known

about its functioning and even less about the pathophysiology of some disorders that affect it. Major depressive and alcohol use disorders have in common their high toll on public health and relative inefficacy of treatment (Getachew &Tizabi, 2019; Huynh et al., 2017). As for Major Depressive Disorder (MDD), the main theory, monoaminergic imbalance or of low serotonin, remains influential as an explanation of its pathophysiology and represents the basis of the most common treatment option: serotonin replacement therapy, utilizing SSRIs and other associated classes, although there is no empirical evidence to support that MDD is linked to or caused by serotonin depletion (Moncrieff et al., 2023). Currently, other targets are being explored in the attempt to develop new, more efficient, therapies.

Drug development is a lengthy, costly, and therefore risky, process. Finding new uses for already established compounds, known as drug repositioning, is an alternative to speed up the exploration and development of new therapeutic strategies (Jarada et al., 2020).

ML are currently being explored as neuromodulators in mammals in various murine models of disorders utilizing doses many times higher than the endectocidal. In this paper, we have selected articles that explore the effects and profile of moxidectin as a neuromodulator.

The search prompt "(moxidectin) AND (neur* OR depression OR anxiety OR brain OR behavior OR alcohol use disorder)" was inputted into PubMed, with the timeframe set between 2012 and 2022, resulting in 185 studies. Four (4) studies were excluded for quoting MOX but not experimenting on or exploring it; twenty-four (24) studies used MOX as an agent for some other disorder not in the scope of this study, such as an antitumor agent, or analyzed its toxicology profile in a way that was not deemed relevant to this study; in one hundred and thirty-five (135) studies the MOX was analyzed as an endectocide; fifteen (15) studies explored its effects on wildlife, food and environmental contamination. After applying the eligibility and exclusion criteria, seven (7) papers were selected and included in this review.

## 4. Discussion

### 4.1. Pharmacological profile

P-glycoprotein (P-gp), coded by the MDR1/ABCB1 gene, is a plasma membrane efflux pump belonging to the ATPbinding cassette (ABC) transporters family (Ménez et al., 2012). It can be found in the small intestine, blood-brain barrier (BBB), hepatocytes, kidney proximal tubule (International Transporter Consortium et al., 2010) and at low levels in the myocardium (Couture et al., 2006). It performs functions of aiding in absorption, such as in the small intestine; excretion, such as in the production of bile and urine (Wessler et al., 2013); and protective, as in the BBB, where it efficiently restricts the entry and actively disposes of compounds, being vital for homeostasis and protecting the Central Nervous System (CNS) from harmful compounds (Ménez et al., 2012). P-gp is a semi-specific protein, however, with the capability of affecting some compounds but not others (Ménez et al., 2012).

Tests with equimolar doses of IVM and MOX in P-gp deficient mice show that these compounds tend to accumulate in the CNS, with IVM possessing a higher ratio of brain-to-blood concentration than MOX in all times tested (Ménez et al., 2012).

To exert any effect, therapeutic or toxic, a compound has to reach its target. Since MLs tend to accumulate in the CNS, efflux pumps are vital to hinder toxic effects (Spampanato et al., 2018). P-gp, which has affinity to IVM, is one of these pumps. IVM overdoses in humans are mainly characterized by extended coma and hypotension (Chung et al., 1999). Severe signs of neurotoxicity and potential lethality can be observed in P-gp deficient dogs with a standard therapeutic dose (0.2 mg/kg). This polymorphism is rare in humans, but very common on Collie-like dog breeds. Interestingly, MOX is not toxic to these animals and showed less affinity (10-fold) to P-gp than IVM (Ménez et al., 2012).

Models of P-gp deficient mice show that the s.c. LD50 for IVM is 0.40 mg/kg or 0.46 μmol/kg, with literature depicting 27–34 μmol/kg for wild-type mice. For MOX, the LD50 was 1.47 mg/kg or 2.3 μmol/kg in P-gp deficient mice, with literature depicting 70–131 μmol/kg in wild-type mice. The onset of toxicological signs started at 6 h for IVM and 4 h for MOX. The lethality for both compounds happened between 8 and 12 h post administration (Ménez et al., 2012). These above stated LD50 differences between wild-type and P-gp deficient animals indicate that, although MOX possesses less affinity to P-gp, there still is some level of efflux. Furthermore, the concentration of these compounds in the CNS does not seem to be directly correlated to their toxicity. At the LD50 the concentration of MOX in the brain was 830 *versus* IVM's 270 pmol/g. Assuming the toxicity is GABA-A mediated, this suggests that these compounds show different GABA-A activation profiles (Ménez et al., 2012).

The gamma-aminobutyric acid is one of the main inhibitory neurotransmitters. It acts mainly on two receptors, GABA-A, ionotropic and GABA-B, metabotropic. The GABA-A receptor is a pentameric receptor composed of varying combinations of subunits, with 19 different types of subunits already identified (α1–6, β1–3, γ1–3, δ, ε, θ, π and ρ1–3) (Farrant & Nusser, 2005).

Most GABA-A receptors are found at the synaptic junction; however, they have also been encountered throughout the neuronal surface independent of synaptic contact, both by electron microscopy and electrophysiological tests. Their concentration, however, diminishes the further away the site is from a GABA-releasing site (Nusser et al., 1995).

Receptors of different subtypes, i.e. composed of different combinations of subunits, seem to populate different areas of the neuron, where, for example, receptors expressing the gamma subunit are present mainly in synapses and delta-containing receptors in extra synaptic areas. Different combinations of subunits give specific characteristics to the receptor, such as sensitivity to benzodiazepines, conferred by the presence of the gamma subunit with certain alpha subunits. GABA-A receptors' main function is to open chloride channels, leading to chloride influx and cellular hyperpolarization, resulting in inhibitory postsynaptic currents (Zorumski et al., 2013).

Trying to better understand the different effects MOX and IVM have over mammalian GABA-A receptors, *Xenopus laevis* oocytes expressing rat α1β2γ2 GABA-A receptors were exposed to saline containing 0.05 μM–1 mM GABA and the tested compounds. The results showed that at low receptor occupancy (EC10) both IVM and MOX were able to potentiate GABA receptors demonstrating that both compounds can act as positive allosteric modulators of the mammalian GABA-A receptor. At a concentration averaging 0.5 μM, however, IVM caused almost twice the maximal potentiation of the GABA-A receptor than MOX, indicating that IVM's potentiating response is much greater than MOX's at that concentration (Ménez et al., 2012).

The shape of the GABA-potentiation curves was also different between the compounds, with IVM having a Hill slope of 1.52±0.45 and MOX of 0.34±0.56. "A Hill coefficient greater than one for IVM suggests positive cooperativity, i.e., once one molecule is bound to the receptor, the affinity of the receptor for the molecule increases", while a coefficient under one suggests negative cooperativity. This data indicates that at sublethal concentrations, IVM's action can potentiate GABA-A receptors at a greater extent than MOX, contributing to its higher toxicity (Ménez et al., 2012).

IVM has a higher and faster penetration rate into the brain and lower toxicity threshold than MOX. Both compounds are able to allosterically modulate GABA-A receptors; but at higher concentrations MOX is less potent than IVM (Ménez et al., 2012). Moxidectin, then, possesses lower neurotoxicity and a more favorable margin of safety over IVM, especially at higher concentrations. This would contribute to a safer long-term use of MOX over IVM for preventing accumulation of the compound in the CNS, both in healthy and in p-gp deficient patients, leading to a diminished likelihood of coma due to the overstimulation of GABA-A receptors (Huynh et al., 2017).

It is of note that the concomitant use of two or more pharmaceuticals that depend on P-gp for removal from the brain

may lead to an exhaustion of the protein. Therefore, MOX seems to again be safer in comparison to IVM in multi-drug scenarios due to its lower dependence on P-gp for removal from the CNS, diminishing the likelihood of adverse effects and/or intoxication (Huynh et al., 2017).

Live CA1 hippocampal pyramidal neurons from brain slices of young-adult male and female Sprague-Dawley rats and CD-1 mice's miniature inhibitory postsynaptic currents (mIPSCs) were recorded with a whole cell patch-clamp configuration. Statistical differences on tonic currents were observed in the concentrations of 100 nM, 300 nM, and 1 μM of MOX, while the concentration of 10 nM presented no such differences. No effect was found in phasic currents in any of the concentrations tested. The EC50 for tonic currents found was 152nM (Spampanato et al., 2018).

The study suggests that the effect of moxidectin on the profile of observed phasic and tonic currents is by direct potentiation of GABA-activated currents at the extra and peri synaptic GABA-A receptors and not by a presynaptic mechanism (Spampanato et al., 2018).

It is important to highlight that phasic and tonic currents seem to be mediated by different subtypes of the GABA-A receptor. Phasic currents are short-duration high-intensity currents which result from synaptic release of GABA, where tonic currents are non-inactivating and longer-lasting, more associated with the activation of extra and peri synaptic GABA-A receptors which, in CA1 pyramidal neurons, contain the subunit α5. Previous studies showed that MLs have a fivefold increase in selectivity for β3-containing receptors, subunits that naturally pair with α5 subunits (Spampanato et al., 2018). MOX could specifically potentiate tonic GABA currents through α5β3-containing receptors, more commonly found at the extra and peri synaptic spaces (Spampanato et al., 2018), but it is capable of modulating rat α1β2γ2 GABA-A receptors as well (Ménez et al., 2012).

The estimated concentration of MOX 24h after a standard endectocidal dose of 0.2mg/kg in wild-type mice is around 9nM, well below the EC50 found. This concentration, however, would be higher in animals with low or non-functional p-gp and/or higher doses (Spampanato et al., 2018). This finding corroborates the many years in which this compound was used as an endectocide with little to no behavioral effects observed.

## 5. Alcohol Use Disorder

P2X4 receptors are one of the most sensitive purinergic receptors, capable of identifying ATP at nanomolar concentrations. They're widely expressed in central and peripheric neurons and microglia, but are also present in the epithelium and endothelium. The P2X family of receptors is involved in a myriad of functions such as synaptic transmission, muscle contraction, platelet aggregation, inflammation, macrophage activation, cell differentiation and proliferation and neuropathic and inflammatory pain. P2X4, however, is mainly responsible for neurotransmission and has been associated with alcohol-induced responses of microglia, inflammation and neuropathic pain (Suurväli et al., 2017).

Avermectins, such as IVM, have been successful as pharmacotherapeutic drugs in lowering the intake of ethanol in different drinking paradigms in male and female mice. Ivermectin is speculated to be helpful in animal models of Alcohol Use Disorder (AUD) due to its ability to significantly reduce or eliminate the inhibitory effects of ethanol on P2X4 receptors (P2X4R). This effect was observed in vitro and is a common mechanism utilized for the screening of potentially useful drugs for AUD. When P2X4R's effect is reduced or eliminated in animals a significant decrease in alcohol intake is observed (Huynh et al., 2017).

MOX was observed as potent in decreasing the intake of alcohol in both sexes in a dose dependent manner. Doses starting from 1.25 mg/kg were effective, but 2.5 mg/kg MOX was the lowest dose that caused the maximum reduction in ethanol intake, that being a 44% decrease in females and 55% in males. The effect of a single administration lasted between 1 and 2 days, with behavioral effects starting at 4 hours. Doses of 5mg/kg and above impaired food intake, but did not cause significant changes in body weight during the time tested (Huynh et al., 2017).

In a five-day treatment with 2.5 mg/kg, MOX was effective in lowering the ethanol consumption of female mice. There was no interaction between treatment and time, however, meaning the effect found at the first day of treatment remained constant throughout the experiment. There was no impact on water, food intake or body weight in these animals. A drinking-in-the-dark paradigm showed that MOX administration consistently reduced ethanol intake across the testing period. (Huynh et al., 2017).

The effects of 0.5 and 1 μM concentration of MOX were tested in Xenopus oocytes injected with rat P2RX4 gene accompanied by "behaviorally relevant concentrations of ethanol (25 and 50 mM)". As expected, both doses of ethanol significantly inhibited ATP-gated P2X4R currents. Both doses of MOX produced a comparable degree of potentiation of P2X4R activity. The lower concentration of MOX, however, was only capable of significantly reducing the inhibitory effect of the lower concentration of ethanol. The dose of 1 μM of MOX was capable of eliminating the inhibitory effect of ethanol at both concentrations. Therefore, the concentration of 1 μM of MOX was capable of antagonizing the effects of ethanol on P2X4 receptors (Huynh et al., 2017).

More studies analyzed the effects of MOX on different drinking paradigms, such as adult male Swiss mice, divided into four groups: the control group (saline + saline); alcohol group (saline + alcohol) and moxidectin treatment groups (moxidectin (5 and 10 mg/kg, i.p.) + alcohol respectively) with 10 and 20 mg/kg of moxidectin administered i.p. in the conditioning phase 30 min before the alcohol injections showed significant effect of time, treatment and time x treatment. Post-hoc analysis indicated that MOX at the dose of 10 mg/kg is successful in decreasing the time in the drug-associated chamber, but 5 mg/kg is not (Ekici et al., 2022). One limitation of this study is the short window between MOX and alcohol injections. As one of the previous papers cited, MOX may take 4 hours to reach effect (Huynh et al., 2017), possibly explaining the ample difference between the needed doses to reach efficacy between the studies.

The conditioned place preference test is based on Pavlov's discoveries, where a strong association is formed between contextual stimuli and a psychoactive drug. In the test the animal is repeatedly placed in one of two distinct environments when under effect of a psychoactive and in another environment after receiving none or an inert substance. In a second moment animals are given the chance to move freely between environments. Then, the amount of time spent on each environment is an indicator of the animal's preference for the psychoactive or drug-free state. Animals that spend more time in the drug-associated chamber are said to have acquired incentive salience, reflecting the rewarding properties of the pharmaceutical. Therefore, this test is commonly used to study drug reward processes in rodents and substance addiction as a whole (Napier et al., 2013).

Moxidectin at the dose of 10 mg/kg is successful not only in inhibiting the acquisition of Conditioned Place Preference (CPP), but also in extinguishing and preventing the reinstatement of alcohol induced CPP following a low priming dose of ethanol in mice. GABA agonists (such as sodium oxybate, baclofen, gabapentin, pregabalin and tiagabine) have been shown as capable of reducing alcohol dependance, and that is one of the suggested mechanisms by which MOX could decrease the ethanol-induced CPP (Ekici et al., 2022).

P2X4 (Huynh et al., 2017), GABA-ARs (Ménez et al., 2012), glycine, and nAChRs (Wolstenholme & Rogers, 2005) receptors are all targets ML have been shown to interact with. Notably, all these receptors have been linked to the modulation of the mesolimbic dopamine activity and regulation of ethanol consumption behavior. The effects observed by the administration of MOX should not be read as exclusive to GABA-A or P2X4 receptors, but by cumulative effect on those and possibly others more (Huynh et al., 2017).

## 6. Major Depressive Disorder

Male adult Wistar-Kyoto rats receiving daily doses of either saline or 2.5 mg/kg of MOX i.p. for seven days showed significant differences on multiple species of bacteria in their gut microbiome. The gut

bacteria associated with mood enhancement (e.g. *Bifidobacterium and Lactobacillus*) were increased, while those associated with inflammation (e.g. *Ruminoccus*) were decreased (Getachew et al., 2019).

Inflammatory pathologies, such as diabetes, obesity and infections have high comorbidity with Major Depressive Disorder (MDD). Many clinical and preclinical studies have shown increased levels of pro-inflammatory cytokines in patients with MDD and animals with depressive-like behaviors. Also, treatments that involve pro-inflammatory medication, such as Interferon alpha, have as a side effect highprobabilities of developing MDD (Troubat et al., 2021). A factor highly correlated to increased systemic levels of inflammatory cytokines is a "leaky gut", an increase of intestinal permeability, allowing bacteria or parts of them to cross the intestinal barrier and reach the bloodstream. This is often secondary to an imbalance of the native flora, or dysbiosis (Suneson et al., 2021). Therefore, the increase of gut bacteria associated with mood enhancement and a decrease of inflammation-linked species could explain one of the potential pathways through which MOX produces its antidepressant effect (Getachew et al., 2019).

MOX has been shown as capable of direct modulation of the CNS, however, therefore further studies were developed to investigate these effects. Adult male Wistar-Kyoto rats who received 2.5 mg/kg MOX i.p. in a single dose showed decreased immobility time in the forced swim test at the 24 hour and 7-day marks when compared to rats that received saline, indicating lower depressive-like behavior. The test was performed again at the 14-day mark, but the results were no longer statistically significant. There was no impact on locomotor activity (Getachew &Tizabi, 2019).

Brains of adult male Wistar-Kyoto rats who received 2.5 mg/kg MOX i.p. 24 hours before tissue collection showed a statistically significant increase of BDNF and decrease of TNF-α in western blot analysis in both cortex and hippocampus (Getachew &Tizabi, 2019).

TNF-α, an inflammatory cytokine, has been previously shown to be increased in patients with MDD and associated with depressive-like behavior in mice (Cheng et al., 2018; Liu et al., 2012).

BDNF, or brain-derived neurotrophic factor, is a neurotrophin that mediates adult hippocampal neurogenesis, neuronal differentiation, growth, plasticity and synaptic development and influences dopaminergic and serotoninergic neurotransmission (Colucci-D'Amato et al., 2020). It has also been associated with MDD, in which patients and animals with depressed mood express less of this protein, while successful treatment tends to rescue it to normal levels (Troubat et al., 2021).

Another factor not discussed by these papers is the previously shown GABA-A modulation of MOX. A new drug called Brexanolone has been approved by the FDA for treatment of postpartum depression (Azhar & Din, 2023). It is a form of a naturally occurring neurosteroid, allopregnanolone, that has been consistently shown to be decreased in postpartum depression, MDD and post-traumatic stress disorder patients in serum and cerebrospinal fluid. It acts as a positive allosteric modulator of GABA-A (Pinna et al., 2022).

We speculate that the positive allosteric modulation of GABA-A receptors may be one of the pathways through which MOX exerts its antidepressive effect.

## 7. Parkinson's Disease

The degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and the ventral tegmental area, results in dopamine depletion in the basal ganglia and its circuitry, leading to Parkinson's disease (PD). All the current pharmacological approaches aim to reestablish the dopamine deficit, be it *via* inhibition of its decarboxylase, supplementation of its precursors or dopaminergic agonists. There is no cure for PD and this line of treatment still has many limitations (Warnecke et al., 2020).

P2XRs are one potential system which could potentially modulate endogenous dopamine levels. The P2X4R subtype is expressed throughout the CNS, including co-localization with the aforementioned dopaminergic neurons in the SNpc and with GABA containing projection neurons in the striatum. P2X4Rs are capable of regulating dopamine release, increasing the expression of dopamine receptors and transporter, and increasing its biosynthesis via tyrosine hydroxylase (Warnecke et al., 2020). There are no selective P2X4R agonists, but MOX and IVM have been shown to be positive modulators, for example on alcohol drinking preference modulated by P2X4Rs (Huynh et al., 2017).

C57BL/6J mice of both sexes submitted to stereotaxic surgery with unilateral lesioning with 6-hydroxydopamine (6-OHDA) and receiving IVM associated with L-DOPA showed statistically significant increases in rotational behavior, therefore a potential treatment option. MOX, also associated with L-DOPA, did not present statistically significant results in either sex in doses of 2.5 and 5 mg/kg. IVM and MOX have been previously reported as possessing no effect on this model when used by themselves (Warnecke et al., 2020) Table 1 and 2.

## 8. Conclusion

Alcohol use and mood disorders remain elusive in their pathophysiology. The monoaminergic theory of depression, which had been the most accepted for the last decades, has been losing traction not only by the limited results found in its replacement therapy, but also by recent reviews which show that there is no high quality or convincing evidence that depression is associated with, or caused by, lower serotonin concentrations or activity (Moncrieff et al., 2023). Therefore, while no new breakthroughs in its pathophysiology are discovered, new targets and compounds for treatments of this and other mood disorders are urgently needed.

And there we may find moxidectin. The results presented in this paper show the compound as quite safe, by its wide therapeutic margin and under-one Hill coefficient, shows quick effectiveness; especially when compared to standard antidepressants such as SSRIs, which may take up to six weeks to reach maximum effect (Pinna et al., 2022). It is effective in most of the paradigms tested, potentially possessing dual action in mood disorders by direct modulation of the CNS as well as the gut microbiome (Getachew et al., 2019).

Very few studies were found about this subject. This was surprising to our team given how positive the results were. We stimulate further research on this compound as a neuromodulator in more diverse depression-like and drug abuse-like paradigms.

**Table1:** Summary of results found on *In Vitro* studies

| Study | Species | Receptor/Cell type | Concentration | Results |
|---|---|---|---|---|
| Spampanato et al., 2018 | Sprague-Dawley rats | Live neurons from brain slices of CA1 pyramidal neurons of the dorsal hippocampus | 10nM to 1μM | No effect on phasic currents<br>All but 10nM yielded results on tonic currents<br>EC50 for tonic currents was 152nM |
| Huynh et al., 2017 | *Xenopus laevis* | Oocytes injected with rat P2X4R gene | 0.5 and 1 μM concentration of MOX<br>25 and 50 mM of ethanol | Both doses of MOX produced a comparable degree of potentiation of P2X4R activity.<br>But the lower concentration of MOX was only capable of significantly reducing the inhibitory effect of the lower concentration of ethanol. |
| Ménez et al., 2012 | *Xenopus laevis* | Oocytes expressing rat α1β2γ2 GABA-A receptors | 0.0001 to 10 μM | MOX possesses a Hill coefficient of 0.34±0.56 in rat α1β2γ2 GABA channels expressed in Xenopus oocytes |

**Table 2:** Summary of results found on *In Vivo* studies

| Study | Animals | Dose(s) | Pathophys. Model | Tests | Main Results |
|---|---|---|---|---|---|
| Ekici et al., 2022 | Swiss mice, male | 5 and 10mg/kg | AUD | Conditioned Place Preference | 10 mg/kg dose was effective in reverting CPP, 5 mg/kg was not |
| Huynh et al., 2017 | C57BL/6J mice | From 0.65 to 10mg/kg | AUD | Two Bottle Choice, Drinking in the Dark | Doses of 1.25 mg/kg and higher were effective in acute treatment in a dose dependent manner. The dose of 2.5 mg/kg was the lowest dose that achieved the maximum result. Dose of 2.5 mg/kg was tested in a 5-day model and was effective |
| Ménez et al., 2012 | Mdr1ab (-/-) mice | – | P-gp deficiency | LD50 | LD50 of 1.47 mg/kg, or 2.3 µmol/kg. The literature LD50 for wild-type mice is 70 to 131 µmol/kg |
| Warnecke et al., 2020 | C57BL/6J | 2.5 and 5mg/kg | Parkinson's Disease | 6-OHDA unilateral lesioning | No effect by itself or when associated with L-DOPA |
| Getachew et al., 2018 | Wistar-Kyoto rats, male | 2.5 mg/kg, 7d | MDD | Stool bacterial DNA analysis | MOX positively affected the gut microbiome |
| Getachew and Tizabi, 2019 | Wistar-Kyoto rats, male | Single dose, 2.5 mg/kg | MDD | Forced Swim Test | MOX lowered the immobility time in the FST test at the 24 h and 7 d mark. Also increased BDNF and decreased TNF-α |

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