18-Methoxycoronaridine (18-MC)

Experimentation with ibogaine, an extract of *Tabernanthe iboga* (a shrub native to Western Africa), at doses of 40 mg/kg administered intravenously has shown some promise in mitigating the physiological processes of addiction. Many different addictive substances (including cocaine, methamphetamine, alcohol, heroin, and nicotine) were self-administered by rats in a study performed by Glick et al. conducted in 2000. After ensuring 'addictive behaviours' were present, ibogaine administration resulted in marked decrease of self-administration of these compounds. Both single dosing and repeated dosing attenuated this effect with variable duration (often between 24 hours and several weeks). These rodents were also subject to acute opioid withdrawal (by administering Naloxone (Narcan) or Naltrexone (Vivitrol) for induction) which seemed to be somewhat attenuated by administering ibogaine.

So obviously the potential for ibogaine as a therapy was there, but there were some glaring issues:

1) The drug produces some hallucinogenic/stimulant effects and was outlawed in the 70s by the FDA (Schedule 1)
2) The drug has noticeable and serious adverse effects: full-body tremors, damage to cerebellar tissue, bradycardia

The goal from this point was to use ibogaine as a starting point to develop medications that had similar addiction therapy potential while minimizing the relatively serious adverse effects. Initial compounds (such as R-Coronaridine) reduced the tremor and self-administration of drug, but also prevented the self-administration of water in rats which were not conditioned to use an addictive substance (i.e. the therapy was not selective for addictive compounds). Further development produced **18-methoxycoronaridine (18-MC)** which also demonstrated no tremor activity and had the added benefit of not inducing cerebellar damage (due to reduced sigma-2 receptor binding compared to ibogaine), reducing heart rate (due to reduced muscarinic receptor binding compared to ibogaine), or altering self-administration of water.

Addiction Study Design: Female rats were taught to self-administer IV 10 microlitres of morphine, 50 microlitres of cocaine, 10% oral ethanol, 4 micrograms per millilitre oral nicotine, or water (control rats) by pressing a bar to signal self-administration should occur (exactly how is outlined in a previous paper). This action was conditioned on a strict schedule until the behaviour was learned. Administration of varying doses of intra-peritoneal ibogaine or 18-MC was performed 15-30 minutes prior to the normally conditioned time for self-administration.

Addiction Study Results: Ibogaine or 18-MC was administered in doses of 0 mg/kg (control), 10/20/40 mg/kg doses. The results were a dose-dependent decrease in the self-administration of cocaine, morphine, or nicotine depending on the trial. Significant decreases in self-administration of all drugs were noted in both the 20 and 40 mg/kg dosing regimens. There appeared to be a relatively similar effect of both 18-MC and ibogaine given at equivalent doses (aside from low dose 18-MC/ibogaine in the nicotine trial where ibogaine was more effective in attenuating self-administration). Ibogaine also had the unfortunate activity of lowering water intake in a dose-dependent matter as well (i.e. it was not selective for the addictive drugs). 18-MC did not alter the intake of water in the control rodents. For exact percent reductions in self-administration of each test compound at each 18-MC or ibogaine dose see figure 1 on the next page.

Notably, the 40 mg/kg dosing for both 18-MC and ibogaine produced lasting results for a minimum of 24 hours. 18-MC still had statistically significant reductions in morphine intake 3 days post-administration and statistically significant reductions in cocaine intake 2 days post-administration. Ibogaine demonstrated similar effects over 2 day periods for both morphine and cocaine compared to baseline. What was even more notable was that both ibogaine and 18-MC were no longer present in significant concentrations in the rodents at this time, meaning that the effect was not explainable due to drug presence alone (although the presence of an active metabolite was not investigated). Further, repeated treatments (weekly/bi-weekly) of 18-MC further extended this period of reduced self-administration without affecting the control rats' self-administration of water. For exact percent reductions in self-administration of each test compound over time see figure 2 on the next page.

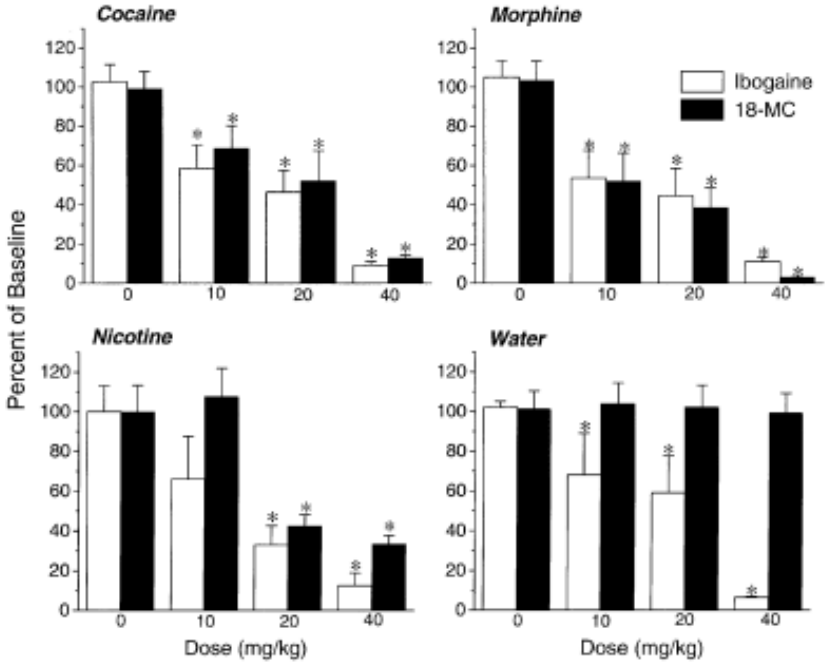

FIGURE 2. Comparison of the dose-response effects of intraperitoneally administered ibogaine and 18-MC (40 mg/kg, ip, 30 min earlier) on the self-administration of cocaine (top, left), morphine (top, right), nicotine (bottom, left), and water (bottom, right). Each bar represents the mean (±SEM) of at least 6 rats. *Asterisks* indicate significant differences ($p < 0.05$) from vehicle (0 mg/kg).

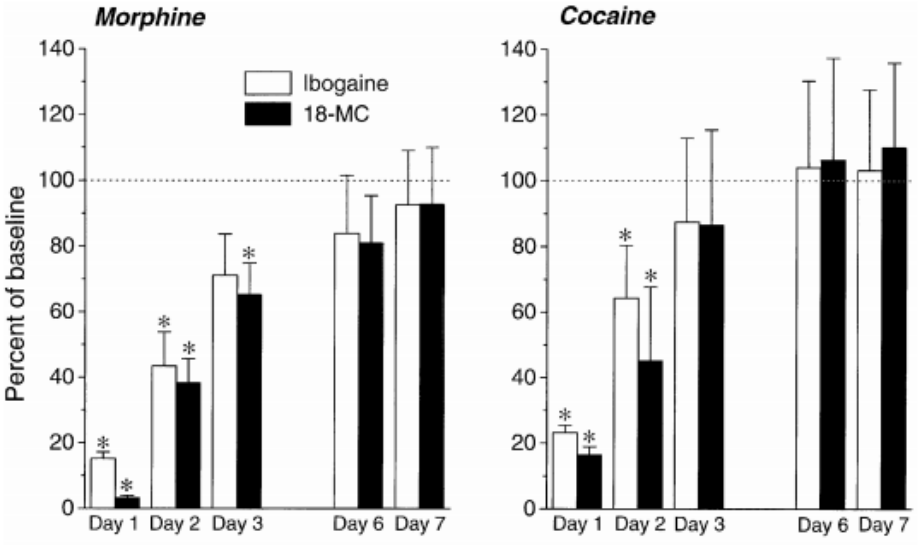

FIGURE 3. Comparison of the aftereffects of pretreatment (30 min prior to day 1 testing) with either ibogaine or 18-MC (40 mg/kg, ip) on the self-administration of morphine (left) and cocaine (right). Each bar represents the mean percent of baseline levels of responding (±SEM) of at least 6 rats. Dotted lines represent the mean baseline level of responding. *Asterisks* indicate significant differences ($p < 0.05$) from baseline.

Opioid Withdrawal Study Design: Using a similar conditioning system as before, morphine addicted rats were treated with naltrexone to induce acute opioid withdrawal. Classical signs of withdrawal in the rodents include weight loss, teeth chattering, diarrhea, and many motor effects. Treatment rats were given 10/20/40 mg/kg peritoneal IV of ibogaine or 18-MC 30 minutes prior to inducing withdrawal effects.

Opioid Withdrawal Results: Nearly all parameters for opioid withdrawal were reduced in a dose-dependent fashion to some degree compared to baseline withdrawal. Unfortunately some of these behaviours were worsened which was theorized to be due to induction of these effects through alternative (and undiscussed) mechanisms. The exact amount of each unique expressive behaviour required for inclusion as a withdrawal symptom for each rat was not discussed (i.e. how often did a rat have to exhibit flinching for it to be included as a symptom? How often does a control rat flinch?) For exact behavioural alterations see the table below.

TABLE 1. Comparison of the dose-response effects of ibogaine and 18-MC on several signs of acute naltrexone-precipitated withdrawal in morphine-dependent rats

Parameter	Ibogaine (mg/kg)				18-MC (mg/kg)			
	0	10	20	30	0	10	20	40
Weight loss (%)	100.0 ± 5.0	81.3 ± 7.5	90.0 ± 5.0	70.0 ± 8.0	100.0 ± 14.9	70.9 ± 10.6	69.5 ± 5.0	53.2 ± 5.7*
Wet dog shakes	100.0 ± 15.0	97.5 ± 15.0	57.5 ± 8.5*	47.5 ± 2.5*	100.0 ± 22.2	125.3 ± 39.1	3.1 ± 35.8*	8.1 ± 66.0
Flinching	100.0 ± 26.0	76.0 ± 17.0	40.0 ± 15.0	72.5 ± 20.0	100.0 ± 36.5	48.9 ± 23.8	35.7 ± 9.5	63.5 ± 17.5
Grooming	100.0 ± 17.5	35.0 ± 5.5*	12.5 ± 4.5*	2.5 ± 0.3*	100.0 ± 10.6	190.6 ± 51.8	56.5 ± 21.1	103.5 ± 29.4
Teeth chattering	100.0 ± 22.5	27.5 ± 12.5	5.0 ± 1.5*	2.5 ± 2.0*	100.0 ± 14.0	62.0 ± 15.1	53.9 ± 12.1*	28.4 ± 11.8*
Burying	100.0 ± 20.0	80.0 ± 17.5	77.5 ± 16.0	102.5 ± 21.0	100.0 ± 33.3	155.1 ± 34.8	46.4 ± 4.4	5.8 ± 2.9*
Diarrhea	100.0 ± 21.0	34.0 ± 11.0	20.0 ± 9.0*	7.5 ± 5.0*	100.0 ± 20.0	50.0 ± 15.0	75.0 ± 15.0	40.0 ± 10.0*

NOTE: Values are means (±SEM) of at least 6 rats (*$p < 0.05$).

Other notable outcomes: 18-MC and ibogaine were investigated for the attenuation of motor stereotypy (chronic repetition of certain movements which can be seen in acute and chronic opioid or stimulant use). There was considerable variation in the effects of the drugs on these movements. In general, there seemed to be an additive effect to these movements rather than an attenuation which suggests that ibogaine/18-MC may make the rodents more susceptible to movement related effects of the administered drugs. These results were widely variable and would have benefited from further investigation.

So how does 18-MC work? The nucleus accumbens (the so called ‘pleasure centre’ of the brain) is responsible largely for the reward/pleasure sensation derived from enjoyable activities like having sex, eating junk food, or doing drugs (or throwing money at whatever stock /u/416SuitGuy tells you to and doubling up overnight). Normally this area releases large amounts of dopamine in response to pleasurable stimuli. 18-MC reduces the amount of dopamine released in response to opioids (although not cocaine) which essentially makes them less pleasurable. Reduced levels of euphoria in response to opioid use allows patients with opioid use disorders to have largely reduced cravings which in turn allows for easier transition to sobriety. The exact mechanism is still largely unknown. It is theorized that due to 18-MCs short half-life and affinity for adipose tissue that an active metabolite may exist and its slow release from fatty tissues contributes to the prolonged periods of non-craving despite plasma levels of 18-MC being sub-therapeutic. Additionally, as 18-MC lacks the serotonin activity present in ibogaine it is predicted that it will not demonstrate any hallucinogenic activity.