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Opioid Antagonism Does Not Directly Block Aberrant Alcohol/Opioid Craving Behavior but Indirectly Induces "Psychological Extinction"

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Abstract

The epicenter of the second but worst opioid epidemic driven in-part by Big Pharma (now being fined) with disastrous deaths due to overdose is so overwhelming the total societal cost reaching an unimaginable amount north of one - trillion. This epidemic has crippled so many communities across America with dismal outcomes in spite of utilization of MAT such as Buprenorphine combinations. There is argument that one reason for failure is underutilization, in-part due to high addiction liability. Moreover, simply the idea of treating one narcotic with another narcotic, even with some special properties including partial agonism at Mu receptors, seems counter intuitive. Understanding the nature of addiction liability has led to the increasing utilization of narcotic antagonism. One –major problem is compliance and as such the long-acting Naltrexone injectable (e. g. Vivitrol®) has been developed with varying results. One issue is the misbelief that naltrexone molecules actually block opioid craving behavior via direct neurobiological mechanisms. This fallacy has led to false claims of the benefits of narcotic antagonism. We hereby point out that in fact the primary benefit is simply "psychological extinction". Understanding the psychopharmacological profile mandates the continued search for better treatments including the induction of genetically guided (GARS) precision pro-dopamine regulation and subsequent potential induction of dopamine homeostasis. We believe this is a more laudable goal to have in the treatment /clinical toolbox.

Keywords: Opioids; Opioid Use Disorder (OUD); Narcotic Antagonism; Vivitrol®; Genetic Addiction Risk Score (GARS); Pro-Dopamine Regulation (KB220) And Dopamine Homeostasis

Introduction

Each year, more than 1.5 million Americans seek treatment for quantity of alcohol consumption in those who do drink, and have alcohol -related problems. In 1994, naltrexone became only the. second drug approved for treating alcoholism by the U.S. Dopamine along with other chemical messengers like serotonin, cannabinoids,

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endorphins, acetylcholine and glutamine, play significant roles in brain reward processing. There is an American opiate/opioid epidemic that is devastating. According to the Center for Disease Control and Prevention (CDC), at least 127 people, young and old, are dying every day in America due to narcotic overdose. Heroin overdose is on the rise across America and it is alarming. The Food and Drug Administration (FDA) has approved a number of Medication-Assisted Treatments (MAT) for the treatment of alcoholism, opiate, and nicotine dependence, but nothing for psychostimulant and cannabis abuse. While these pharmaceuticals have important relevance in the short-term induction of "psychological extinction," and possible endorphinergic activation at very low doses, there should be caution in the long-term. In this paper we will focus on the use of Naltrexone as an opioid antagonist. Caution is important because its use favors blocking of dopaminergic function. The two institutions devoted to alcoholism and drug dependence (NIAAA and NIDA) realize that MAT including naltrexone in any form, are not optimal and continue to seek better treatment options. This article focuses on an ignored major problem in the addiction field. It is even more disturbing when you factor in the impact the opioid crisis has had on medical services now required that has reached an unprecedented 3,000% increase geared to assist OUD patients. The number of OUD patients rose from ~217,000 in 2007 to ~7 million in 2014 and as such required an inordinate amount of Medicare services.

We are encouraging clinicians to realize that post- Opioid Use Disorder (OUD) is a neurotoxic issue driven by opioid induced impairment of brain reward circuitry and attenuated neurotransmitter signaling that ultimately leads to unwanted associated sequalae that includes depression, sleep disturbances, sensation seeking, lack of satisfaction and impulsivity. If left untreated by suggesting that post - short-term recovery only includes attending 12 - steps and other fellowship programs without attempts at epigenetically manipulating compromised brain neurochemistry through potential pro-dopamine regulation, relapse will inevitably occur. It is additionally important for primary care specialists and addiction clinicians to also be cognizant that OUD is like a "double edge sword "having a bio-directional effect on the brain reward circuitry. Besides having differential effects on neurotransmitter function whereby acute administration/intake of psychoactive drugs results in heightened dopaminergic activity, the opposite occurs following chronic abuse (hypodopaminergia). Naltrexone does not reduce opioid or alcohol craving via direct pharmacological activity, it only induces "psychological extinction". In terms of the "double edge sword" concept, it is even more important to understand that based on certain reward gene polymorphisms which sets up a high risk for all RDS behaviors drug and none drug, as well as environmentally induced epigenetic insults on chromatin (methylation and acetylation) ultimately influences this post–recovery protracted abstinence which could take years to recover.

Extinction theory

Extinction is a behavioral phenomenon observed in both operant and classical conditioned behavior, which manifests itself by fading of non-reinforced conditioned response over time. For example, after Pavlov's dog was conditioned to salivate at the sound of a metronome, it eventually stopped salivating to the metronome after the metronome had been sounded repeatedly but no food came. It is noteworthy, that many theories have tried to explain this psychological phenomenon. Myers and Davis research involving fear extinction in rodents has concluded that multiple mechanisms may be at work depending on the timing and circumstances in which the extinction occurs [1].

Certainly, the role of neurotransmitters especially at the mesolimbic brain region including the VTA, amygdala, hippocampus and prefrontal cortex are all involved. Amano., *et al.* [2] found that extinction of a conditioned fear response is linked to synaptic inhibition in the fear output nerve cells of the central amygdala that project to the pain centers like the periaqueductal gray that controls what has been termed " freezing behavior".

Interestingly, the brain region most extensively implicated in learning extinction is the infralimbic cortex (IL) of the medial prefrontal cortex (PFC). According to Do-Monte., *et al*. [3] the IL is important for the extinction of reward- and fear-associated behaviors, while the amygdala has been strongly implicated in the extinction of conditioned fear. Moreover, in adolescents both the posterior cingulate cortex [PCC] (a known area for relapse) and the temporalparietal junction [TPJ] have been identified as regions that may be associated with impaired extinction [4].

Historical perspective of opioid antagonism

It is noteworthy that in the early 70's Blum's laboratory [5] was first to show the benefits of naloxone or narcotic antagonists in the treatment of alcohol dependence published in Nature. This seminal work along with later research served as the basis to use Naltrexone (DuPont) in treatment for both opioid and alcohol dependence. Since 2006 based on many studies globally, Alkermes has retained the market for Vivitrol® as an extended release injectable approved by the FDA.

In fact, naltrexone is a relatively weak antagonist of κ- and δ-receptors and a potent μ-receptor antagonist, dosages of naltrexone that effectively reduce opioid and alcohol consumption also strongly block μ-receptors, but down- regulates meso-limbic dopamine release. While these studies show benefit especially in the short term there is ongoing evidence that the retention and compliance on Vivitrol® is not sufficient to characterize adherence as high [6]. Specifically in a meta –analysis, of 22 randomized, controlled trials, only 3 (14%) met criteria for high levels of adherence assurance, 5 (23%) met medium adherence assurance criteria,

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and 14 (64%) met low adherence criteria. Moreover, the Spearman correlation between risk ratios for return to heavy drinking (for naltrexone vs. placebo) and the level of adherence assurance (low vs. medium vs. high) was significant (r = -.62, p = .025). The completion of the study of opioid treatment with extended release Vivitrol (XR-NTX) was associated with superior outcomes and less likely relapse (defined as daily use), with a much greater time to relapse despite higher rates of concurrent non-opioid substance use like cocaine. In terms of long-term extended release injectable (XR-NTX) for opioid dependence there was a higher compliance in Opioid Use Disorder (OUD) than for Alcohol Use Disorder (AUD), but after completion of study most participants discontinued treatment with XR-NTX largely due to "feeling cured" and "wanting to do it on my own" rather than external barriers such as cost or side effects [7].

In 2004, Blum's laboratory tested the hypothesis that combining narcotic antagonistic, amino-acid therapy (KB220) consisting of an enkephalins inhibitor (D-phenylalanine) and neurotransmitter precursors (L-amino- acids) might promote neuronal dopamine release and enhance compliance in methadone patients rapidly detoxified with the narcotic antagonist naltrexone [8].

Over two decades ago, a rapid method to detoxify either methadone or heroin dependent subjects utilizing naltrexone sparked interest in many treatment centers throughout the United States, and worldwide. However, when Blum's group coupled naltrexone with enkephalinase –inhibition and precursor amino-acids, results were dramatic in terms of significantly enhancing compliance to continue taking naltrexone.

The average number of days of compliance calculated on 1000 patients, without amino-acid therapy, using this rapid detoxification method is only 37 days. In contrast, the 12 subjects tested, receiving both the Naltrexone and amino-acid therapy were relapse-free or reported taking the combination for an average of 262 days ($p < 0.0001$) [8]. Thus, coupling amino-acid therapy and enkephalins inhibition, while blocking the delta-receptors with a narcotic antagonist even if weak, may be quite promising as a novel method to induce rapid detox in chronic methadone patients. This may also have important ramifications in the treatment of both opiate and alcohol-dependent individuals; enhanced compliance with Vivitrol® and especially as a relapse prevention tool. It may also be interesting to further test this hypothesis both in a larger cohort and with the sublingual combination of the partial opiate mu receptor agonist buprenorphine. In terms of buprenorphine and dopaminergic function, acute doses increase dopamine release, whereas, chronic administration leads to reduced dopamine release (Figure 1). However, with naltrexone it was found that in human's dopamine release increased over an 8-day period but dissipated over time. In animal studies the opioid antagonist naltrexone has been shown to attenuate the subjective effects of amphetamine. However, the mechanisms behind this modulatory effect were unknown up until April 2017, when Nitya Jayaram-Lindström and associates [9] hypothesized that naltrexone would diminish the striatal dopamine release induced by amphetamine, which is considered an important mechanism behind many of its stimulant properties. They used positron emission tomography and the dopamine D2-receptor radioligand [11] raclopride in healthy subjects to study the dopaminergic effects of an amphetamine injection after pretreatment with naltrexone or placebo. In a rat model, they used micro dialysis to study the modulatory effects of naltrexone on dopamine levels after acute and chronic amphetamine exposure. In healthy humans, naltrexone attenuated the subjective effects of amphetamine, confirming previous results. Amphetamine produced a significant reduction in striatal radioligand binding, indicating increased levels of endogenous dopamine. However, there was no statistically significant effect of naltrexone on dopamine release. The same pattern was observed in rats, where an acute injection of amphetamine caused a significant rise in striatal dopamine levels, with no effect of naltrexone pretreatment. However, in a chronic model, naltrexone significantly attenuated the dopamine release caused by reinstatement of amphetamine. Collectively, these data suggest that the opioid system becomes engaged during the more chronic phase of drug use, evidenced by the modulatory effect of naltrexone on dopamine release following chronic amphetamine administration. The importance of opioid-dopamine interactions in the reinforcing and addictive effects of amphetamine is highlighted by these findings and may help to facilitate medication development in the field of drug dependence especially as it also relates to buprenorphine / naloxone combinations.

Figure 1: Buprenorphine Effects on Dopaminergic (DA) Release [9].

It is our contention that while narcotic antagonism holds a special place in the treatment of Substance Use Disorder (SUD), certain statements about for example naltrexone's pharmacological profile related to drug and alcohol craving behavior is misleading. Simply, naltrexone in any form does not directly affect alcohol or opioid seeking behavior, as claimed by pharmaceutical manufactures and many certified addiction specialists. Instead, the real fact is that any

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attenuation of drinking or drug seeking behavior is due to "psychological extinction" [10]

Opioid Antagonists to Reduce Craving Behavior: "Fools Gold"

There is a widespread misunderstanding about how and when opioid antagonists such as naltrexone, naloxone and even nalmefene suppress the craving for alcohol and opioids. The preclinical and clinical evidence reviewed by Sinclair's group [10] exquisitely show that craving is not reduced simply by the presence of the antagonists in the brain. Instead, these agents work by the mechanism of "psychological extinction". It is generally accepted that alcohol intake (drinking), seems to be learned through reinforcement and involves the opioid peptide pathway. In fact, alcohol drinking while under the influence of a narcotic antagonist blocks the wanted reinforcement and as such initiates the process of extinction of the drinking behavior and craving. There is no direct effect of narcotic antagonists to reduce craving behavior.

In order to provide some convincing evidence concerning the rationale related to the notion that for example, naltrexone induces a reduction of alcohol craving behavior having psychological extinction as an indirect clinical rather that a direct pharmacological outcome, seems prudent. Sinclair's group [10] points out that naloxone administration to rat's lever pressing for ethanol resulted in no observed reduction in lever pressing behavior for alcohol reward at the beginning of the first session. Based on the work of Lee., et al. [11] and others prescribing naltrexone to abstinent alcoholics has not delayed significantly the resumption of drinking. Simply, both rodents and humans that are administered opioid antagonists show little to no effect initially [12]. The general consensus is that in the presence of a narcotic antagonist both craving and drinking decrease progressively as a function of the number of sessions. In fact, most of the mean variation in the rate of drinking is explained by the theoretical extinction curve. The importance here is that the effect of drinking reduction continues long-after the antagonist has been catabolized. Thus the primary effect of the antagonist on craving behavior and actual ethanol intake is not directly due to the drug at all but rather extinction. Certainly, from animal experimentation it is too difficult to prove that direct anti-craving effects are present following naltrexone. However, even in humans it must be noted that if there is such effects it is too small to be clinically relevant.

In a number of published and unpublished experiments from Sinclair's group [11] in Helsinki it has been adequately observed that there is no significant effect of naloxone, naltrexone or nalmefene following the first dose of any of these agents to rodents. Simply, there is no evidence to show a decrease in the behavior of initiating alcohol intake after the first administration of an antagonist (Figure 2).

Figure 2: Extinction of voluntary alcohol drinking to male Wistar rats with one hour daily access to 10% alcohol solution and continual access to food and water. Prior to alcohol sessions, the rats ate measured amounts of a cocoa-flavored sucrose paste. These 7 rats then received 10 mg/kg nalmefene in the paste before each of the next 5 sessions. *p<0.05; **p<0.01 relative to 7 controls given only the vehicle [10,11].

Other work revealed [10,11], that rats of the high-drinking AA line given 1 mg/kg naltrexone (NTX) or vehicle orally with a stress-free procedure just before 1 h of access to 10% ethanol daily for 8 days and again, 8 h later on the first 7 days. Forebrain homogenate binding studies using 0.03 - 6.00 nM [3H] naloxone were conducted from 1 to 4 days following treatment. NTX significantly suppressed alcohol intake, with the effect becoming progressively greater over days and continuing during the post-treatment period. Saturation binding studies in brain homogenate revealed that NTX had increased the B(max) for opioid receptors by 93%, 74%, 49%, and 28%, respectively, from post-treatment days 1 to 4 without altering K(d). B(max) was negatively correlated ($r = -0.510$, $p = 0.008$) with alcohol intake during the preceding hour, but in control rats, it was positively correlated with changes in alcohol intake over time ($r = +0.790$, $p = 0.020$). It is concluded by authors that these results are consistent with the hypothesis that opioid receptors mediate reinforcement from alcohol and that NTX, verifying early work by Blum's group in the 70s,[5] reduces subsequent alcohol drinking by psychological extinction. It was also pointed out that opioid receptor upregulation can develop simultaneously with suppression of drinking and may partially counteract the clinical benefits from NTX in the treatment of alcoholism. Various researchers have noted that patients with higher initial craving appear to derive greatest benefit from naltrexone [13-15]. Naltrexone does not appear to exert an influence compared with placebo on maintaining abstinence or in postponing the first drink in those patients who cannot avoid alcohol. Volpicelli and colleagues [16,17] also observed that naltrexone-treated subjects reported that the subjective "high"

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or euphoria produced by alcohol was significantly less than usual. This is consistent with naltrexone's action in blocking opioid receptors and diminishing pleasurable effects associated with alcohol drinking.

In summary, many RTCs show clear evidence that over time, but not immediately, NTX is a narcotic antagonist at mu opioid receptors but weaker at delta opioid receptors. There is some controversy that NTX given prior to the first drink of alcohol results in adequate suppression of stimulating alcohol consumption. Clinically, there is anecdotal evidence that people treated with NTX initially claim that they cannot finish a usual full bottle of alcohol. There is the possibility that for some unknown reason NTX stimulates the release of endorphins. While there is no evidence for this fact except at very low doses, it is indeed possible that endospheric activity works to suppress drinking behavior through delta stimulation even in face of the presence of NTX. However, the first drink suppression by NTX is not clearly understood and in some rodent models may not actually occur [10].

It is noteworthy, that Poznanski., *et al.* [18] revealed that with the use of specific opioid receptor antagonists they showed that the naloxone-induced increase in ethanol drinking in HA (high activity) mice is mediated mainly by δ and to a lower extent by μ opioid receptors. The effect of δ-opioid receptor antagonism was abolished in HA mice carrying a C320T transition in the δ-opioid receptor gene (EU446125.1), which impairs this receptor's function. The authors conclude that their results indicate that high activity of the opioid system plays a protective role against ethanol dependence. Therefore, its blockage with opioid receptor antagonists may lead to a profound increase in ethanol consumption. This hypothesis is in agreement with other earlier work on enkephalinergic activity and ethanol consumption as a function of genetics [19].

Survival curve data on NTX reveals significant drop at various times based on severity of opioid dependence. Specifically, Sullivan., *et al*. [20] of 89 randomized participants, 78.7% (70/89) completed 4 weeks, 58.2% (54/89) completed 8 weeks, 47.2% (42/89) completed 12 weeks, and 25.8% (23/89) completed 24 weeks. Accordingly, a Cox proportional hazards regression modeled time to dropout as a function of treatment condition, baseline opioid dependence severity (bags per day of heroin use), and their interaction. Interaction of conditions by baseline severity was significant ($X^2_3 = 9.19$, $p = .027$). For low-severity patients (<6 bags/day), retention was highest in the Behavioral Naltrexone Therapy (BNT) - single-dose injection naltrexone (XRNTX) group (60% at 6 months), as hypothesized. For high-severity (> 6 bags/day) patients, BNT-XR-NTX did not perform as well, due to high early attrition.

Newer strategies of molecular genetic targeted epigenetic repair

Through the work of others involving twin studie [21,22] it is reasonable to conclude that that approximately 50% of the variation in opioid dependence is attributed to genetic factors. While genetics may set up a risk for potential danger of becoming hooked on a particular substance or even behavior, understanding this risk could help prevent an individual from restraining to start to explore and subsequently to abuse. Hurd and O'Brien suggested that having insights into understanding the underpinnings of all addictive behaviors and the neurobiology thereof, could reveal novel genetically guided therapy for OUD [23].

In summary we have provided a schematic to assist the reader to understand the complexity of our proposition. (Figure 3).

Figure 3

Conclusion

Naltrexone blocks opioid receptors in the brain, having efficacy in patients who cannot remain abstinent to reduce their drinking. It is believed that the strong desire to continuingly imbibe is due to the powerful endorphin-mediated reinforcing effects of drinking alcohol. Blum's group investigated the role of, for example, enkephalins and alcohol acceptance in genetically bred rodents. They found that C57/blk mice, alcohol loving, had significantly lower whole brain methionine-enkephalins compared to DBA, alcohol hating, showing significantly higher whole brain methionine-enkephalins [24,25]. It has been claimed that NTX works by, breaking the vicious, self-destructive cycle in alcoholics via psychological extinction. Evidence from RCTs show clearly that especially in people that want to remain abstinent, there is significant prevention of relapse. It has been argued that the recommended time for NTX treatment is between 3 to 6months and then switching to dopaminergic agonistic therapy for potential achievement of dopamine

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homeostasis. Any extension of this recommendation must consider impact on neurotransmitter function especially preventing natural rewards [26,27].

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