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A historical perspective on clonidine as an alpha-2A receptor agonist in the treatment of addictive behaviors: Focus on opioid dependence

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Abstract

Clonidine operates through agonism at the alpha-2A receptor, a specific subtype of the alpha-2-adrenergic receptor located predominantly in the prefrontal cortex. By inhibiting the release of norepinephrine, which is responsible for withdrawal symptoms, clonidine effectively addresses withdrawal-related conditions such as anxiety, hypertension, and tachycardia. The groundbreaking work by Gold *et al.* demonstrated clonidine's ability to counteract the effects of locus coeruleus stimulation, reshaping the understanding of opioid withdrawal within the field. In the 1980s, the efficacy of clonidine in facilitating the transition to long-acting injectable naltrexone was confirmed for individuals motivated to overcome opioid use disorders (OUDs), including physicians and executives. Despite challenges with compliance, naltrexone offers sustained blockade of opioid receptors, reducing the risk of overdose, intoxication, and relapse in motivated patients in recovery. The development of clonidine and naltrexone as treatment modalities for OUDs, and potentially other addictions, including behavioral ones, underscores the potential for translating neurobiological advancements from preclinical models (bench) to clinical practice (bedside), ushering in innovative approaches to addiction treatment.

Keywords: Behavioral addictions; Clonidine; Opioid use disorder; Substance use disorder; Naltrexone; Locus coeruleus

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1. Introduction

Clonidine is a well-researched molecule patented in 1961 but was not used medically until 1966.[1] Catapres is a brand name for clonidine, which is used to treat high blood pressure, as well as, off-label, attention deficit hyperactivity disorder (ADHD),[2,3] withdrawal from substances such as opioids, alcohol and nicotine, menopausal flushing, and selected painful conditions.[2,3] Administration of clonidine can be oral, transdermal, or by injection with an onset of action within 1 h. Most side-effects are reversible when withdrawn.[4]

To design a comprehensive review, our team searched PubMed, MEDLINE, Cochrane Library, and references from relevant articles for publications dating from June 1, 2014, to August 1, 2020. We searched for the Medical Subject Headings terms "Opioid-Related Disorders," or "Analgesics, Opioid" and "Substance Withdrawal Syndrome." This work is worthy of a thorough review as current reviews of clonidine often overlook much of the laboratory and clinical discovery work focusing on 2014 – 2020.[5]

2. Pharmacokinetics and pharmacodynamics of clonidine

Importantly, clonidine crosses the blood-brain barrier.[6] Gold *et al.*[7] demonstrated that clonidine's molecular mechanism of action occurs due to its agonism at the alpha-2A receptor, a subtype of the alpha-2 adrenergic receptor, found primarily within the prefrontal cortex (PFC). Alpha-2A adrenergic receptors inhabit the presynaptic cleft of the neuron and, when activated by an agonist, inhibit downstream neurons. The stimulation of alpha-2 receptors arrests the secretion of the neurotransmitter norepinephrine (NE).

While usually not severe, common side effects of clonidine include dry mouth, dizziness, headaches, and sleepiness. However, in rare cases, severe adverse effects include heart arrhythmias, confusion, and even hallucinations. Clonidine should be avoided during pregnancy or breastfeeding because it crosses the placental barrier and is present in breast milk. Moreover, if abruptly stopped, withdrawal reactions could occur. Clonidine, first patented in 1961, was the 79th most commonly prescribed pharmacologic agent in the United States and by 2017, with over 10 million prescriptions.[8]

Following oral ingestion, the drug is absorbed into the bloodstream very promptly and almost completely, with peak concentrations in human plasma within 60 – 90 min.[9] It is important to emphasize that clonidine is lipid-soluble to some extent. The partition coefficient logarithm (log P) is equal to 1.6.[10] It is well-known that the optimal log P for a drug to enter the central nervous system through the blood-brain barrier is 2.0.[11]

Approximately one-fifth of an oral dose will not be absorbed and is excreted in the feces, while under half of the absorbed dose will be metabolized by the hepatic tissue into inactive metabolites, with the rest excreted unchanged

by the kidneys. Moreover, the half-life of clonidine varies widely, between 6 and 23 h, depending on kidney function.[11]

2.1. The off-label use of clonidine to treat opioid withdrawal syndrome

The off-label use of clonidine to ease symptoms associated with abrupt withdrawal from long-term use of opioids, alcohol, benzodiazepines, and nicotine[12,13] is the main topic of this review. Clonidine can alleviate opioid withdrawal symptoms by reducing the sympathetic nervous system response, including tachycardia, hypertension, sweating, hot and cold flashes, anxiety, and general restlessness. These sedating effects of clonidine may also aid smokers in quitting. However, side effects can include insomnia, exacerbating an already common feature of opioid withdrawal.[14] Clonidine induces a reduction in blood pressure in both normotensive and hypertensive patients but may also induce hypotension and postural hypotension during opioid withdrawal. Notably, clonidine may also reduce the severity of neonatal abstinence syndrome for infants with maternal substance use disorder.[15,16] Although off-label clonidine has been replaced clinically by buprenorphine and other treatments,[16] it may improve the Network Neurobehavioral Score in neonatal intensive care units for neonatal withdrawal syndrome.[17]

2.2. Better outcomes for impaired health professionals: Why?

Opioid use disorder (OUD) is common and generally untreated. Medications and medication-assisted recovery have gained support as it is evidence-based, safe, and useful.[18] Nevertheless, most adults with OUD do not receive outpatient treatment to address their addiction and remain untreated.[19] At present, outcomes for impaired health professionals[20] and others with OUD are markedly different, even when receiving the same treatments. Relapse to OUD and treatment discontinuation are common among most patients but not among impaired physicians.[21] The fear of overdose, slip, or relapse, which can result in death, may differ due to the fear of losing licensure requirements as professional and mandated requirements to be drug-free.[22] The treatment procedures, follow-up, and case management available to physicians through impaired health professional programs, including group therapy, caduceus meetings, medication, and particularly random urine testing, contribute to their successful recovery.[22] The usual goal of treatment for OUD is being alive and taking the opioid agonist or antagonist medication. Urine testing confirmed OUD outcomes for impaired physicians at 80%, with most tested drug-free and functioning at premorbid levels at 5-year follow-ups.[23] These outcomes are significantly better than those reported for non-health professionals, who are rarely studied for at least 6 months. The characterization of OUD treatment outcomes includes treatment discontinuation, dropouts, relapses, overdoses, and numbers of hospital visits.[24] Return to premorbid functioning socially, jobwise, and in other spheres are not investigated as thoroughly as it is for physicians. Physician outcomes focus on full recovery and return to work.[25] Thus, OUD treatment tends to replace opioids with medications such as buprenorphine and methadone.

Physicians and other health professionals are likely to opt for detoxification from opioids and placement on long-acting injectable naltrexone.[26] The frequent choice of clonidine may be related to licensure and drug-free job regulations. Clonidine's choice may also relate to changes in perception and cognitive functioning felt on chronic opioids compared to the effects of detoxification and abstinence or detoxification and naltrexone. In the highest-risk group of physicians with OUDs, such as anesthesiologists, the decision to treat with naltrexone may be directed by the physician health program itself.[27] In this case, clonidine may be incorporated in post-assessment detoxifications.

Clonidine is widely used today as an adjunct treatment for opioid withdrawal, OUD-related craving, and anxiety, and in the transition to naltrexone for treating physicians, executives, and other patients with OUDs.[28] The neurochemical mechanisms of clonidine, especially related to catecholaminergic activity involving NE and dopamine, provide promising treatments to reverse opioid-induced changes in the locus coeruleus (LC) and boost dopaminergic recruitment across this brain region to attenuate NE hyperactivity.[28,29]

Although the United States Food and Drug Administration (FDA) approved lofexidine,[30] which has a higher affinity and specificity for alpha-2A adrenergic receptors, induces less hypotension and other serious side effects than clonidine, and does not reinforce opioid dependence, the high cost of lofexidine has kept clonidine ahead of lofexidine prescriptions for OUD detoxification.[31]

2.3. Opioid withdrawal: Clinical syndrome and pathophysiology

Despite effective treatment for opioid addiction, including buprenorphine (suboxone) and methadone, most patients still relapse into opioid misuse, often resulting in overdoses during these slips and relapses. Acute precipitants, such as stress, exposure to drug-associated cues, or the use of an initially small amount or priming dose of a drug, can trigger relapses, shorter lapses, and episodes of craving. Treatments that buffer the effects of these acute triggers might improve buprenorphine maintenance outcomes.

2.4. Definitions of withdrawal

Withdrawal from a substance is characterized in the Diagnostic and Statistical Manual for Mental Disorders, 5th edition (DSM-5), as "a substance-specific problematic behavioral change, with physiological and cognitive concomitants, that is due to the cessation of, or reduction in, heavy and prolonged substance use." The International Classification of Diseases, 10th edition, defines withdrawal as "a group of symptoms of variable clustering and severity occurring on absolute or relative withdrawal of a psychoactive substance after persistent use of that substance." The characteristic clinical signs of opioid withdrawal syndrome include hypertension, tachycardia, mydriasis, piloerection (goosebumps), lacrimation, rhinorrhea, yawning, insomnia, nausea, vomiting, and diarrhea.[32] The progression of opioid withdrawal is primarily influenced by the half-life of the specific opioid involved. Opioids characterized by short half-lives, such as heroin (with a half-life of 3 – 5 h), prompt the onset of withdrawal symptoms within approximately 12 h after the last dose. Conversely, discontinuation of opioids with longer half-lives, such as methadone (with a half-life of up to 96 h), may lead to withdrawal symptoms emerging 1 – 3 days following the last dose. Moreover, the duration of the withdrawal syndrome typically aligns with the half-life of the opioid. For instance, heroin withdrawal typically spans 4 – 5 days, while methadone withdrawal can extend from 7 to 14 days and, in certain cases, persist for several weeks. Other than alpha-2 receptor agonists, other agents, such as pro-dopamine regulators, may be useful adjuncts to intervene in heightened NE activity during opioid withdrawal.

2.5. Development of the locus coeruleus noradrenergic hyperactivity theory

In 1977, Gold's group tested clonidine in humans with OUD after opioid discontinuation and the emergence of withdrawal signs and symptoms as a test of the LC noradrenergic hyperactivity theory.[33,34] These clinical scientists chose clonidine over other available alpha-2 adrenergic agonists because clonidine was widely used worldwide and considered safe, effective, and approved by the FDA for hypertension. During that period, the WHO was concerned about any medication that reversed opioid withdrawal in laboratory investigations. In the experiments, clonidine acutely reversed opioid withdrawal, including neonatal opioid withdrawal distress, reduced naloxone-precipitated withdrawal distress, facilitated rapid and ultra-rapid opioid detoxification, and provided an option for impaired health professionals and others interested in a drug-free treatment. Clonidine also improved the transition from opioid agonist to naltrexone and enhanced treatment outcome success rates for both naltrexone and buprenorphine.[35-38]

Gold's group conducted a series of studies on LC stimulation and ablation in rodents at the College of Medicine, University of Florida, in the early 1970s, and later at Yale in the late 1970s and early 1980s. These studies led Gold and his associates to hypothesize that the nucleus LC might be responsible for some opioid withdrawal syndrome symptoms. They continued this work with rats and non-human primates at Yale in the Aghajanian and Redmond laboratories. Specifically, they stimulated the LC and produced hypertension, tachycardia, and other signs of opioid withdrawal, including piloerection (bristling) in animals that had never been exposed to opioids.[39] This LC electrical stimulation produced signs, symptoms, and behaviors similar to those induced by the alpha-2 adrenergic antagonists yohimbine and piperoxane.[40] They could reverse the effects of electrical stimulation with morphine, and this effect could be reversed again with the opioid antagonist naloxone.[41] Moreover, these researchers could reverse the effects of yohimbine and piperoxane with clonidine.[42] They were also able to pre-empt the effects of these agents by lesioning the nucleus LC.[39]

As a known alpha-2 adrenergic receptor agonist, clonidine was first tested in rodents and non-human primates and ultimately in humans in cases of both precipitated and naturally occurring opioid withdrawal by Gold's group in the 1970s. This work (Gold *et al*., 1982), recognized by the American Psychiatric Association with the Foundations Fund Annual Award and Prize, represents the first true translation of basic science into discoveries that help patients in psychiatry.[43]

2.6. Mechanisms in withdrawal symptomatology

The noradrenergic hyperactivity theory for opioid withdrawal changed the field in many ways.[34,42] First, it provided the first neuroanatomy of opioid withdrawal, which could be tested, and identified the roles of alpha-2 adrenergic and opioid inputs. This allowed for a better understanding of both opioid and non-opioid treatments or withdrawal reversal methods. Second, it enabled physicians to explore and develop new opioid, mixed opioid, and non-opioid treatments, including pharmaceuticals and nutraceuticals.[44,45-50] Third, it introduced a new class of treatments, such as lofexidine, guanfacine, and others, which use the same mechanism of action–alpha-2 adrenergic agonist stimulation and inhibition of the nucleus LC.[31,43,51] These treatments could potentially exhibit better side effect profiles and other advantages.[36,52]

2.7. Summary of empirical research

Several behavioral and biochemical studies[53] support Gold's hypothesis that naloxone-precipitated withdrawal can be attenuated by targeting the LC. Subsequent studies demonstrated that clonidine reduced morphine withdrawal-induced increases in regional cerebral metabolic rates for glucose, irrespective of the distribution of alpha-2 adrenergic receptors. Clonidine acts primarily at the LC and central amygdala, and it may also have importance in other regions.[54]

Research conducted on non-human primates has revealed that the noradrenergic LC may play a role in various aspects of the brain's alarm function, encompassing attentiveness, arousal, anxiety, fear, and terror, along with their physiological manifestations. These investigations involved comparing the outcomes of electrically stimulating the LC with minute electrodes to the effects induced by other agents or conditions capable of modulating LC activity. The findings suggested that endogenous morphine-like substances and opioids serve to inhibit the activation of the LC system, and the onset of opioid withdrawal syndrome arises from the reactivation of this LC-noradrenergic system.[35] Clonidine, which suppressed noradrenergic LC activity in low doses, was therefore postulated to suppress opioid withdrawal signs and symptoms. Many signs of opioid withdrawal produced through electrical or chemical stimulation of the nucleus LC increase noradrenergic activity and the concentration of the noradrenergic metabolite 3-methoxy-4-hydroxy-phenyl glycol within the brain. Clonidine, an alpha-2 adrenergic agonist, can inhibit signs of opioid withdrawal in animals and humans.[55]

Clonidine likely attenuates opioid withdrawal syndrome due to the reduction of noradrenergic neuronal activity originating in the LC. However, alpha-2 adrenergic receptors located throughout the body and other mechanisms may also play a role. In a series of studies, Gold's group explored the LC alpha-2 adrenergic receptor selectivity and the neuroanatomical and pharmacological anti-withdrawal action of clonidine (Table 1). Confirmation of this hypothesis in rats, monkeys, and human subjects has added to the understanding of the mechanisms of opioid action and withdrawal.

Moreover, a double-blind, placebo-controlled, and cross-over trial from Taylor *et al.*[53] found that clonidine eliminated the symptomology of opioid withdrawal for 240 – 360 min in 11 hospitalized OUD subjects. In the longer term, the same patients, in an open pilot study of the effects of clonidine taken for 1 week, also experienced the elimination of opioid abstinence symptoms. These data suggest that opioid withdrawal is due to increased neuronal activity in areas regulated by alpha-2 adrenergic and opioid receptors, like the LC. The early clinical studies, combined with more direct observations in rodents and non-human primate studies, are consistent with the hypothesis that in humans, brain NE systems become hyperactive during opioid withdrawal and that clonidine suppresses this hyperactivity of NE systems.[29]

3. Modern architectural analysis of treatment for OUD: Inducing "dopamine homeostasis" to treat protracted withdrawal

In the United States, a national opioid epidemic[4] has prompted the recommendation of three FDA-approved medications for the prevention and treatment of OUD: methadone, buprenorphine, or naltrexone. There is ample evidence of their efficacy; however, these medications are under-prescribed.[18] The objective here is to briefly review and synthesize data from the available medical literature on these FDA-approved medications and provide a framework to demonstrate the optimal approach for outpatient management of OUD.

Clonidine and lofexidine have improved and refined the medical approach to opioid withdrawal states while transitioning opioid-dependent adults to extended-release injection naltrexone.[56] Opioid agonists like methadone, mixed agonists like buprenorphine, and the combination of buprenorphine with naltrexone and clonidine are now used to treat OUD.[57] The authors assessed the efficacy of two outpatient opioid detoxification methods and relapse prevention in a trial transition induction to extended-release (XR)-naltrexone. A 7-day detoxification regimen utilizing naltrexone with a single day of buprenorphine administration was followed by a gradual increase in oral naltrexone doses, supplemented with clonidine and other medications. Similarly, a buprenorphine-assisted detoxification protocol involved a 7-day tapering of buprenorphine, followed by a week-long interval before initiating XR-naltrexone, in accordance with official prescribing guidelines. The combination of naltrexone treatment and adjunctive clonidine facilitated complete withdrawal for 38 out of 40 methadone-dependent patients within a span of 4 – 5 days. Naltrexone dosing typically commenced at 1 mg/day and was incrementally raised to 50 mg/day over a 4-day period for most patients. Clonidine administration helped mitigate the intensity of naltrexone-induced withdrawal symptoms. Significant reductions in blood pressure were observed without instances of syncope, and although certain symptoms persisted, including anxiety, anorexia, insomnia, restlessness, and muscular aching, they were either substantially alleviated

Table 1. Key facts

Clonidine.
Locus coeruleus stimulation promotes the release of norepinephrine.
Reduces the severity of withdrawal from opioid use.
Narcotic replacement therapy
Methadone-synthetic opioid and buprenorphine (Subutex) are agonists.
Suboxone; buprenorphine/naloxone is an agonist/antagonist.
Buprenorphine and methadone maintenance are equally effective in retaining patients in substance abuse treatment and in reducing illicit opioid use.
Narcotic replacement therapies have high treatment compliance.
Reduce overdoses and Emergency Department treatment-seeking.
Subutex and suboxone induction and maintenance are available in outpatient or physician offices.
Disadvantages buprenorphine
Chronic blockade of opioid receptors has anti-reward effects, increasing relapse potential when coupled with a narcotic antagonist
Does not activate the areas of the brain associated with relapse in some studies.
Possible lack of effectiveness in patients who require high methadone doses.
Locks people into addiction and also causes a "zombie" like effect.
There is evidence of potential suicide ideation and accompanied depression.
Even in the injectable form of delivery, there is poor compliance.
Naltrexone
Naltrexone is an opioid antagonist.
Provides chronic opioid receptor blockade and prevents overdose and opioid intoxication.
Agonists are better at this than antagonists unless in mandated impaired physician programs with monitors.
The main issue with naltrexone is poor compliance, but it can be assisted with Pro-dopamine regulation like KB220 variants or other modalities like rTMS.
Positive effects of treatment
All forms of treatment are significantly less costly and more effective than no treatment.
Reduction or abstinence in illicit opioid use.
Reduction in the severity of withdrawal from opioid use.
Retention in treatment for persons enrolled in opioid withdrawal or opioid cessation programs.
Harm reduction
Summary Points
• The adverse effects of OUD include (fatal overdose, infectious disease transmission, elevated health care costs, public disorder, and crime) and the available treatments.
• The alpha-2-adrenergic receptor a subtype of the alpha-2-adrenergic receptor secretes norepinephrine (NE).
• NE causes the symptoms of withdrawal.
• Withdrawal-symptoms include hypertension, tachycardia, and anxiety.
• Clonidine is a molecular agonist of the alpha-2A receptor.
• Gold *et al.*[7] found that clonidine can reverse the effects of locus coeruleus stimulation.
• This noradrenergic hypothesis for opioid withdrawal changed the field.
• Successful comprehensive treatment programs that used clonidine to transition to long-acting injectable naltrexone for impaired physicians and other very motivated patients with OUDs were confirmed in the 1980s.
• The naltrexone, despite poor compliance, provides chronic opioid receptor blockade that prevents overdose, opioid intoxication, and subsequent re-addiction in recovered in motivated patients.
• The development of clonidine and naltrexone as treatment agents for OUD demonstrates that neurobiological advances could be translated from rodents to non-human primates to man into new effective clinical approaches.
• The traditional narcotic substitution therapies, like methadone maintenance, provide agonistic activity but do not target or block delta or mu receptors. The combination treatment of narcotic antagonism and mu receptor agonist therapy (even at minimal doses of naloxone) seems parsimonious but may induce anti-reward
• Clinical studies indicate that buprenorphine maintenance is as effective as methadone but less cardiac adverse effects maintenance in retaining patients in substance abuse treatment and in reducing illicit opioid use.
• Clinical studies indicate that buprenorphine maintenance is as effective as methadone maintenance in retaining patients in substance abuse treatment and in reducing illicit opioid use.
• The negative effect on reward circuitry is that chronic blockade of opioid receptors, even with partial opioid agonist action, may ultimately block dopaminergic activity, causing anti-reward effects and increasing relapse potential.
• Based on initial results with large populations receiving D2 agonist therapy with KB220, a safe, non-addicting, natural dopaminergic receptor agonist that potentially up-regulates instead of down-regulating dopaminergic receptors could be a co-therapy for long-term treatment to prevent relapse rather than the combination of buprenorphine/naloxone alone.
• Futuristic frontline modalities should include genetic addiction risk testing, which could lead to precision medicine by matching polymorphisms in risk alleles with medications or nutraceuticals.

Abbreviations: rTMS: repetitive transcranial magnetic stimulation; OUD: Opioid use disorder.

or resolved entirely by the time of discharge. The use of clonidine for opioid detoxification may pave the way for naltrexone maintenance in many clinical settings and might also succeed with patients receiving methadone doses up to 50 mg/day.[56]

This development of clonidine and naltrexone as a treatment for opioid addiction demonstrates the translation of neurobiological advances into new and effective clinical approaches. Naltrexone provides a chronic opioid receptor blockade, which prevents opioid intoxication and subsequent re-addiction in recovery. This sequential use of naltrexone for opioid receptor blockade, in conjunction with clonidine to treat withdrawal symptomatology during rehabilitation, represents a viable and effective treatment for opioid addiction in motivated patients.

3.1. Summary of the clonidine/naltrexone approach to opioid withdrawal

Gold *et al.*[58] summarized experiences with the clonidine/naltrexone approach in motivated OUD patients. Clonidine hydrochloride, an alpha-adrenergic agonist, is a non-opioid medication that, when used in detoxification from opioids, exhibits rapid suppression of the signs and symptoms associated with opioid withdrawal. Studies have demonstrated that clonidine is useful in detoxifying for withdrawal from methadone maintenance patients, achieving zero dosage in <14 days with a high success rate, compared to the usual 3 – 6 months. In a clinical investigation, clonidine suppressed opioid withdrawal symptomatology in patients on doses of up to 75 mg of methadone daily, and shorter-acting narcotics withdrawn in less than a week. To prevent relapse, post-detoxification counseling and the use of the narcotic antagonist, naltrexone, are recommended.[37]

Clonidine's ability to reverse opioid withdrawal syndrome in acute withdrawal and anti-craving studies supported the NE hypothesis and suggested a new use for clonidine.[32,55,59-63] The effectiveness of lofexidine provided further validation for the noradrenaline (NA) hypothesis. Clonidine has been demonstrated to be a potent emergency intervention for acute opioid withdrawal, facilitating detoxification from methadone, heroin, and other opioids. By reversing cognitive, affective, and physiological manifestations of withdrawal, clonidine not only alleviates immediate symptoms but also maintain suppression of their reoccurrence when administered over a period of 10 – 14 days within a detoxification regimen.[55,59]

Clonidine appears most appropriate for clinical application as a transitional intervention bridging opioid dependence and naltrexone therapy. A 10-day outpatient detoxification regimen involving clonidine has proven highly successful in enabling patients to cease opioid use abruptly and maintain abstinence long enough to commence naltrexone treatment. However, the sedative and hypotensive side effects associated with clonidine have constrained its clinical utility, particularly among outpatients, prompting exploration into alternative alpha-2 noradrenergic agonists that may offer similar anti-withdrawal efficacy without the undesirable side effects of clonidine. Initial outpatient evaluations of lofexidine, a structural analog of clonidine, suggest that it could be equally effective for opioid detoxification and potentially more suitable for outpatient management if it lacks the sedation and hypotension occasionally observed with clonidine.[64]

Blum *et al.*[65] developed a protocol that included the neuronutrient KB220Z and other anti-withdrawal agents, such as clonidine, to investigate initial detoxification from OUD in treatment centers, with particularly heavily dependent OUD subjects. Among the 17 subjects in the study, only three were administered buprenorphine/naloxone (Bup/Nx) alongside KB220Z. Initially, in this pilot phase, five patients received 6 days of KB220Z at a dosage of 2 oz twice daily before meals, in conjunction with clonidine, benzodiazepines, and other adjunctive medications such as gabapentin to manage nausea and sleep disturbances. Subsequently, the second protocol involved 12 patients receiving a higher dose of 4 oz every 6 h for 6 days. Only three individuals experienced relapse within the initial 2 weeks, while the remaining 14 subjects remained on KB220Z without requiring additional Bup/Nx for periods ranging from 120 to 214 days.

Due to the inclusion of standard detoxification agents, definitive conclusions regarding the effects of KB220Z cannot be drawn. However, the fact that only three out of 17 subjects needed Bup/Nx is notable. If corroborated by larger, more comprehensive studies, this opioid/opioid detoxification approach could offer a novel strategy for managing withdrawal without relying on addictive opioids. Combining alpha-2 agonist therapy with KB220Z, a pro-dopamine regulator, may emerge as a frontline option alongside other treatment modalities. Notably, neuroimaging studies comparing KB220Z and placebo have demonstrated robust and specific blood oxygen level-dependent dopamine activation in animal models[66] and abstinent heroin addicts,[67] suggesting putative induction of "dopamine homeostasis."

Previously, Blum *et al.* published several articles arguing against the long-term utilization of opioid agonists such as methadone and buprenorphine, except for harm reduction, but did not favor their prophylaxis use.[66-90]

In terms of post-withdrawal treatment options, many articles discuss opioid agonists and narcotic antagonism,

including alpha-2 stimulation with agents such as clonidine and lofexidine. While some of these articles may be somewhat cryptic, they expand understanding of this important topic.[60-62,91,92] Other important novel therapeutic modalities include repetitive transcranial magnetic stimulation,[93-101] exercise,[102-107] and precision addiction management, which couples genetic addiction risk testing[67,69,73,73,76-79,81,82,88,89,108-113] with pro-dopamine regulation.[65,72,72,82,111-121]

4. Long-term use of opioid agonists engendering antireward

Physicians treat opioid-dependent patients with an office-based maintenance program using buprenorphine, a partial mu-opioid receptor agonist. Basic science predicted[122] and clinical experiences have confirmed that buprenorphine effectively controls opioid withdrawal in OUD treatment, especially in fentanyl use disorders. Patients often prefer opioid replacement with detoxification and abstinence or detoxification and naltrexone. Buprenorphine is more effective than abstinence or placebo for managing opioid addiction; however, if high doses are needed, it may not be superior to methadone. Treatment phases include induction, stabilization, and maintenance. The treatment outcome is comparable to lower doses of methadone. However, the current "standard of care" necessitates the initiation of buprenorphine therapy at the onset of withdrawal symptoms, adjusted to address symptoms and craving severity. The advantages of buprenorphine include some reversal of anhedonia, good availability for office use, and somewhat lower abuse potential. Disadvantages include lack of effectiveness and high cost in patients who would require high methadone doses.

However, as a cautionary note, while short-term therapy with buprenorphine appears very appropriate, this may not be the case for prolonged maintenance therapy. The Bup/Nx combination has acute benefits for the treatment of heroin use disorder (HUD) but not for relapse prevention and may increase the probability of relapse.[123-125] Specifically, opioid agonists, such as methadone and buprenorphine, are clinically effective in reducing withdrawal and craving during heroin detoxification but fail to reduce the likelihood of relapse after detoxification.

Neuroimaging studies have significantly enhanced our comprehension of why methadone or buprenorphine often fall short in reducing the likelihood of relapse. These findings, widely recognized for their reliability, shed light on the neurobiological mechanisms underlying relapse and aid in the development of more effective therapeutic strategies. Mei *et al.*[126] conducted research investigating the immediate impacts of buprenorphine on neurological responses to cues associated with heroin. The functional magnetic resonance imaging (fMRI) investigation provided insights into the neurobiological mechanisms underlying addiction and relapse, as well as the therapeutic effects of buprenorphine. While under the influence of buprenorphine, neurological responses to cues associated with heroin diminished notably in regions including the amygdala, hippocampus, ventral tegmental area, and thalamus. However, no significant changes were observed in the ventral striatum, orbital-prefrontal-parietal cortices, or the cingulate gyrus. This absence of response in the cingulate gyrus underscores its partial role in the process of relapse.

Neuropsychological and functional neuroimaging evidence converges to indicate that the dorsal anterior cingulate cortex (dACC) is dysfunctional in substance abuse. Yücel *et al.*[127] investigated the biochemical and physiological properties of the dACC. Using fMRI and proton magnetic resonance spectroscopy (^{1}H-MRS), researchers investigated the biochemistry and physiological activity of the dorsal anterior cingulate cortex (dACC) during a behavioral control task in 24 individuals with opioid dependence. This group was compared to 24 gender-, intelligence-, age-, and performance-matched healthy subjects. While both groups exhibited comparable levels of activation in the dACC during the task, the opioid-dependent group showed heightened task-related activation in frontal, parietal, and cerebellar regions, alongside reductions in concentrations of N-acetyl aspartate and glutamate/glutamine in the dACC. Moreover, the opioid-dependent group failed to demonstrate the anticipated correlations between dACC activation and behavioral measures of cognitive control. These findings suggest that long-term opioid dependence may result in biochemical and physiological abnormalities in the dACC.

Individuals with OUD may necessitate increased activation of the frontoparietal and cerebellar networks involved in behavioral regulation to achieve normal levels of task performance and behavioral control. Tailoring treatment to the specific needs of patients who are most susceptible to the effects of chronic opioid administration appears prudent. In addition, Mei *et al.*[126] observed an unaltered fMRI response to heroin-related cues in various brain regions, including the ventral striatum, orbital, parietal, lateral, and PFC, indicating a lack of modulation by buprenorphine. This lack of buprenorphine effect on these key brain regions linked to relapse may explain its limited therapeutic effects on relapse.[128] For a review of the effects of opioid agonists on dACC function, see Lin *et al.*,[129] who found positive effects on emotional reactivity

but not reward activity in treatment-resistant mid- and late-life depression. Verdejo-García *et al.*[130] demonstrated a beneficial role of high-dose methadone on dACC biochemistry and linked elevated myoinositol levels to depressive symptoms following buprenorphine treatment. Seah *et al.*,[131] showed in a small sample (N = 4) that group-level analyses revealed buprenorphine significantly activated brain regions, including the thalamus, striatum, frontal, and cingulate cortices, compared to a saline vehicle in awake non-human primates. It is noteworthy that animal studies involving the incubation of cocaine craving have indicated that a novel target for withdrawal is the GluR2-lacking AMPA receptors in the ventral striatum.[132] This notion has received support in humans, whereby Hermann *et al.*[133] revealed a positive correlation between glutamate levels and previous withdrawals, and an increase in glutamate/glutamine with age in contrast to a decrease in controls, indicating a destabilization of the glutamate system in opioid-dependent patients and supporting the glutamate hypothesis of addiction.

There are several limitations to the long-term utilization of methadone and buprenorphine (with and without naloxone) and their associated side effects.[90,109,134-137] Moreover, Chalhoub and Kalivas[138] reviewed the limitations and challenges of the current maintenance and medication-assisted withdrawal strategies commonly used to treat OUD. Using animal models of opioid addiction, they noted the roles of endocannabinoid, orexin, and glutamatergic signaling in the expression and maintenance of addiction-like behaviors and suggested these systems as potential targets to expand therapeutic options for treating OUD. One important aspect related to the effects of chronic buprenorphine use concerns brain glucose metabolism. Walsh *et al.*[139] compared the effect of buprenorphine to a placebo and found that buprenorphine significantly reduced the cerebral glucose metabolism rate and regional cerebral metabolic rate for glucose in 19 of 22 bilateral and four midline regions by up to 32%.

4.1. Locus coeruleus: Beyond drug withdrawal

The locus coeruleus is a compact nucleus situated deep within the brainstem, serving as a pivotal hub for the extensive noradrenergic neurotransmitter system of the brain. The seminal work of Dahlströem and Fuxe[140] in 1964, which unveiled the presence of monoamine-containing neurons in the central nervous system, laid the foundation for subsequent systematic investigations into the structure and functionality of the LC. Recent research has harnessed an impressive array of advanced neuroscience techniques to delve into and understand the intricacies of this enigmatic nucleus, unearthing novel layers of organization and function, particularly pertaining to human behavior. Although all neurons within the LC receive inputs associated with autonomic arousal, subsets of these neurons can encode distinct cognitive processes, potentially through more specialized inputs originating from forebrain regions. As highlighted by Poe *et al.*,[141] the LC exhibits specific patterns, diversity in receptor distributions, and innervation of target areas, suggesting that stimulation (activation) of the LC can exert more nuanced influences on target networks than previously thought.

4.2. Stress

Stressors activate the locus coeruleus-NA (LC-NA) system through corticotropin-releasing factor (CRF), leading to an inclination toward high-tonic activity in LC neurons while reducing their responsiveness to discrete stimuli.[142] Chemogenetic LC activation might mimic acute stress, increasing brain-wide functional connectivity, especially in salience and amygdala networks. Moreover, activation initiates reduced exploratory and enhanced anxiogenic behavior.[143] Interestingly, enkephalin-containing axon terminals converge on some of the same LC dendrites as CRF-containing axon terminals.[144] Furthermore, these enkephalin-type neurons have opposing effects on LC discharge during stress,[145] implying that enkephalin afferents to the LC (acting at mu-opioid receptors) are part of the stress coping and recovery from the opioid system.[146] Importantly, gender is a determinant of LC sensitivity to stress. In animals, the LC neurons of females are more sensitive to CRF and less sensitive to enkephalin than males.[147] Indeed, Brady *et al.*[148] recommended that the higher prevalence of stress-induced psychiatric disorders in females may be partly due to the molecular effects of sex hormones. The interaction of CRF and other neurotransmitters like dopamine may yield anti-stress effects due to the blocking effect on NE. This interaction may have particular relevance for both substance and non-substance behavioral addictions.

4.3. Summary

Clonidine has played a pivotal role in the history of addiction medicine for many reasons. It was the first medication-assisted treatment (MAT) to be discovered and translated from science to practical use in rats, monkeys, and humans. The discovery of clonidine's anti-opioid withdrawal efficacy resulted from understanding LC hyperactivity or release from LC chronic opioid inhibition.[42] Kleber *et al.*[37] demonstrated that clonidine is the first non-opioid medication to reverse opioid withdrawal. Clonidine reduced detoxification distress to the point that naltrexone[149] became a viable alternative to methadone and, ultimately, buprenorphine.

Today's treatment of OUDs often begins with an overdose intervention in an emergency or hospital department, followed by a rapid transition to buprenorphine. Although treatment algorithms for OUD have been well described,[18] they are often one-size-fits-all. Many patients not engaged in this transition from active use to treatment are lost to follow-up, drop out, or continue receiving buprenorphine or methadone for years. Some patients who want to detoxify or switch to monthly naltrexone injections can benefit from using non-opioid medications, such as clonidine or lofexidine, to treat withdrawal symptoms. Non-opioid treatment options are essential for physicians and those at risk for OUDs. Clonidine is important in the transition of physicians from OUDs to naltrexone and the transition of thousands of patients maintained on methadone and buprenorphine to naltrexone. MAT discontinuation is an important overdose risk factor, and clinicians often recommend naltrexone after long-term agonist maintenance for OUDs. Clonidine may have additional roles in reducing withdrawal distress from other drug cravings during MAT maintenance and in neonates.

An intriguing concept is that receptor tolerance entails the enhancement of receptor regulation mechanisms, such as desensitization and internalization. Furthermore, as suggested by Christie,[150] the adaptations leading to cellular tolerance are multifaceted, involving several significant processes, including upregulation of cAMP/PKA and cAMP response element-binding signaling, as well as mitogen-activated protein kinase cascades in opioid-sensitive neurons. These mechanisms have implications not only for tolerance and withdrawal but also for synaptic plasticity during cycles of intoxication and withdrawal. Such adaptations could potentially impact the likelihood of relapse.

It is also important to point out that some early experiments suggested that the LC might not be a primary site for opioid-induced withdrawal. However, a complete lesion of catecholaminergic nerve cell bodies in the LC, achieved by intracerebroventricular injection of 6-hydroxydopamine, resulted in the total abolition of SS14-specific binding in the structure. Specifically bound [^{125}I][Tyr^{0},D-Trp^{8}]SS14 and TH+ cell density overlapped with SS14. Furthermore, it is known that tyrosine hydroxylase is the rate-limiting enzyme involved in the synthesis of catecholamines, especially dopamine. Gagne *et al.*[151] revealed that somatostatin binding sites are uniformly localized on all noradrenergic neurons of the LC. There is abundant evidence supporting the role of catecholamines, especially in opioid-induced withdrawal and LC.[152]

The shift to long-term or perpetual use of powerful and addictive opioids such as buprenorphine and methadone is a logical response to an OUD crisis and opioid overdose epidemic. Detoxification and abstinence are associated with more deaths, overdoses, and medical problems. It is of interest that the combination of clonidine and long-acting naltrexone maybe as effective and comparable in some cases to just using buprenorphine alone, to detoxify patients for opioid treatment (X: BOT). However, work be Lee *et al.* in an attempt to determine the potential effectiveness of naltrexone versus buprenorphine did not provide definitive results. As suggested by Lee *et al.*[153] except for health and other professionals, successful outcomes are not generally the case. This prompts the question: What are the logical short- and longer-term outcomes to be achieved for OUD patients? Typically, a positive OUD outcome is defined by not dying, attending clinics to receive opioid maintenance medication, or avoiding overdoses and emergency room visits. In physicians, outcomes are distinctly different, focusing on returning to full premorbid function. These include negative urine tests, attending Caduceus meetings, following a detailed psychosocial post-evaluation treatment plan, and achieving positive social, job return-performance, and spouse-partner ratings.

While extensive research is required, it is necessary to revisit the issues of depression, suicide, and despair associated with chronic iatrogenic opioid administration using MATs. Treatment without a focus on recovery and without addressing "dopamine homeostasis" may contribute to a revolving door, where many patients with OUD relapse and overdose, repeatedly receiving the same treatment without long-term success.[70,154]

5. Locus coeruleus therapeutics: Applications to other areas – behavioral addictions

As discussed in the current article, dysfunction of the LC-NA system affects many neuropsychiatric and neurological diseases, including opioid and other drug withdrawal symptomatology, Parkinson's disease, depression, anxiety, post-traumatic stress disorder, ADHD, and Alzheimer's disease. It has become evident that even in cases where the LC is not directly involved in the disorder, manipulating LC activity could improve health outcomes. Disruption of the feedback loop supporting the dysfunction could re-establish a healthy physiological response, moving the patient toward normal daily activity.[141] There are selective NA reuptake inhibitors, such as atomoxetine, used for opioid withdrawal.[155] NA agonistic agents are used for ADHD,[156] and for Parkinson's disease, the alpha-2 adrenergic receptor antagonist lofexidine[157] is used for cognitive dysfunction[158,159] and reboxetine for depression.[160]

Emerging evidence suggests the possibility of minimally invasive procedures for manipulating the LC, such as regulating the circuit from the suprachiasmatic nucleus to the LC through a relay in the dorsomedial hypothalamus.[161] Another potential method is transcutaneous vagus nerve stimulation, a non-invasive procedure reported to possess positive effects on psychiatric and neurological disorders, such as depression.[162]

Despite the potential benefits, noradrenergic compounds are not frequently administered as a frontline therapeutic modality. NA dysfunction contributes to many aspects of brain disorders, but many human clinical trials have not distinguished specific NA effects from dopamine effects. Indeed, more is known about the specific effects of dopamine and associated neuron degeneration and other physiological and psychiatric effects.[163]

To investigate the involvement of the noradrenergic system in pathological gambling (PG), Pallanti *et al.*[164] measured the neuroendocrine growth hormone (GH) response to the alpha-2 adrenergic receptor agonist clonidine and placebo in PG individuals and controls. One hypothesized mechanism, as proposed by these authors, is that clonidine's net effects entail reducing neurotransmission by suppressing LC activity and stimulating GH secretion through activation of post-synaptic alpha-2 adrenergic receptors in the hypothalamus. The area under the curve for GH response to clonidine was found to be significantly lower in the PG group compared to controls. Notably, individuals with PG exhibited significantly blunted GH responses relative to controls at 120 and 150 min post-clonidine administration. These findings support the notion that the diminished sensitivity of post-synaptic alpha-2 receptors may be linked to elevated noradrenergic secretion in PG. This peripheral noradrenergic dysfunction aligns with attenuated corticofrontal noradrenergic function observed in positron emission tomography (PET) studies of PG.[17]

In an interesting study, Saddichha *et al.*[165] demonstrated that clonidine was effective in reducing compulsive soap eating, known as sapophagia, but not feeding behavior, suggesting an effect on compulsive behavior rather than on eating disorders. Another study by Cazala[166] demonstrated that clonidine specifically stimulates alpha-noradrenergic receptors and has two distinct effects on intracranial self-stimulation (ICSS) behavior: it acutely depresses ventral hypothalamic ICSS at low doses, while it causes a discrete increase in dorsal ICSS. In addition, evidence indicates that chronic clonidine administration affects conflict behavior in rats, increasing punished responding in the conflict test. The authors suggest that clonidine may have some potential as an anti-panic drug.[167] Experiments in Blum's laboratory clearly pointed out that a reduction in serotonin levels in the brains of rodents resulted in an enhanced fear reaction, potentially implicating clonidine in serotonergic transmission.[168]

Some researchers consider smoking behavior, not just nicotine dependence, to be related to oral fixation and potentially a behavioral addiction.[169] Moreover, combined data from nine double-blind placebo-controlled trials (N = 813) revealed that the smoking quit rate with clonidine was significantly greater than with placebo. Moreover, the in-depth analysis suggested that clonidine potentiates the effect of individual behavior therapy and may be more beneficial for female smokers compared to male smokers.[170] Current standards of care for medically supervised withdrawal include treatments with mu-opioid receptor agonists such as methadone, partial agonists like buprenorphine, and alpha-2 adrenergic receptor agonists such as clonidine and lofexidine. Newer agents also utilize these pharmacological mechanisms, including tramadol for mu-opioid receptor agonism and tizanidine for alpha-2 agonism.[5] To explore the initiation of detoxification in individuals addicted to opioids/opioids, Blum's laboratory developed a protocol for use in treatment centers, particularly for heavily dependent opioid/opioid subjects.[171,172] Moreover, future research endeavors encompass managing withdrawal while stabilizing patients with OUD on extended-release naltrexone, transitioning patients from methadone to buprenorphine for OUD treatment, and tapering opioids in patients with chronic, non-cancer pain. However, compliance remains a challenge that could potentially be addressed through the addition of a pro-dopamine regulator.[173]

6. Limitations

While this article takes a narrative approach rather than a systematic review, we acknowledge the potential for bias in our overall perspective on this topic. It is important to recognize that some studies present alternative views, suggesting that regions proximal to the LC, such as the periaqueductal gray, as well as other brain structures independent of the LC noradrenergic system, may play a more significant role in the manifestation of opioid withdrawal syndrome.[174]

In a study by Christie,[174] intracellular recordings of membrane potassium current were conducted from rat LC *in vitro*. The researchers observed tolerance to the opioid-induced increase in potassium conductance, with a more pronounced effect observed for normorphine compared to [Met^5]enkephalin and [D-Ala^2,MePhe^4,Gly^5-ol]enkephalin. Experiments using the irreversible receptor blocker beta-chlornaltrexamine indicated that normorphine exhibited

lower intrinsic efficacy than [Met[5]]enkephalin and [D-Ala[2], MePhe[4], Gly[5]-ol]enkephalin. This adaptation was not attributed to any changes in the properties of the potassium conductance mediated by mu-receptors, as both full and partial agonists at alpha-2 adrenergic receptors, which are linked to the same potassium conductance, remained unchanged in their effectiveness. In addition, no association was found between this adaptation and any alterations in the affinity of mu-receptors for the antagonist naloxone.

We believe that other sites besides the LC are certainly involved in opioid-induced withdrawal. However, the preponderance of available literature supports the role of the LC, as evidenced by a plethora of clinical data, with at least 80 articles suggestive of the LC's role in opioid withdrawal.[175]

7. Conclusion

To assist the readership's comprehension, a summary schematic is provided (Figure 1). Clonidine operates through agonism at the alpha-2A receptor, a subtype of the alpha-2 adrenergic receptor predominantly located within the PFC. In the PFC, it inhibits the release of NE, which is implicated in withdrawal symptoms. Consequently, clonidine is effective in alleviating withdrawal-related anxiety, hypertension, and tachycardia. Gold *et al.* demonstrated the ability of clonidine to reverse the effects of LC stimulation, thereby propelling the noradrenergic hypothesis for opioid withdrawal into the forefront of research. In the 1980s, the efficacy of clonidine in facilitating the transition to long-acting injectable naltrexone was confirmed for physicians, executives,

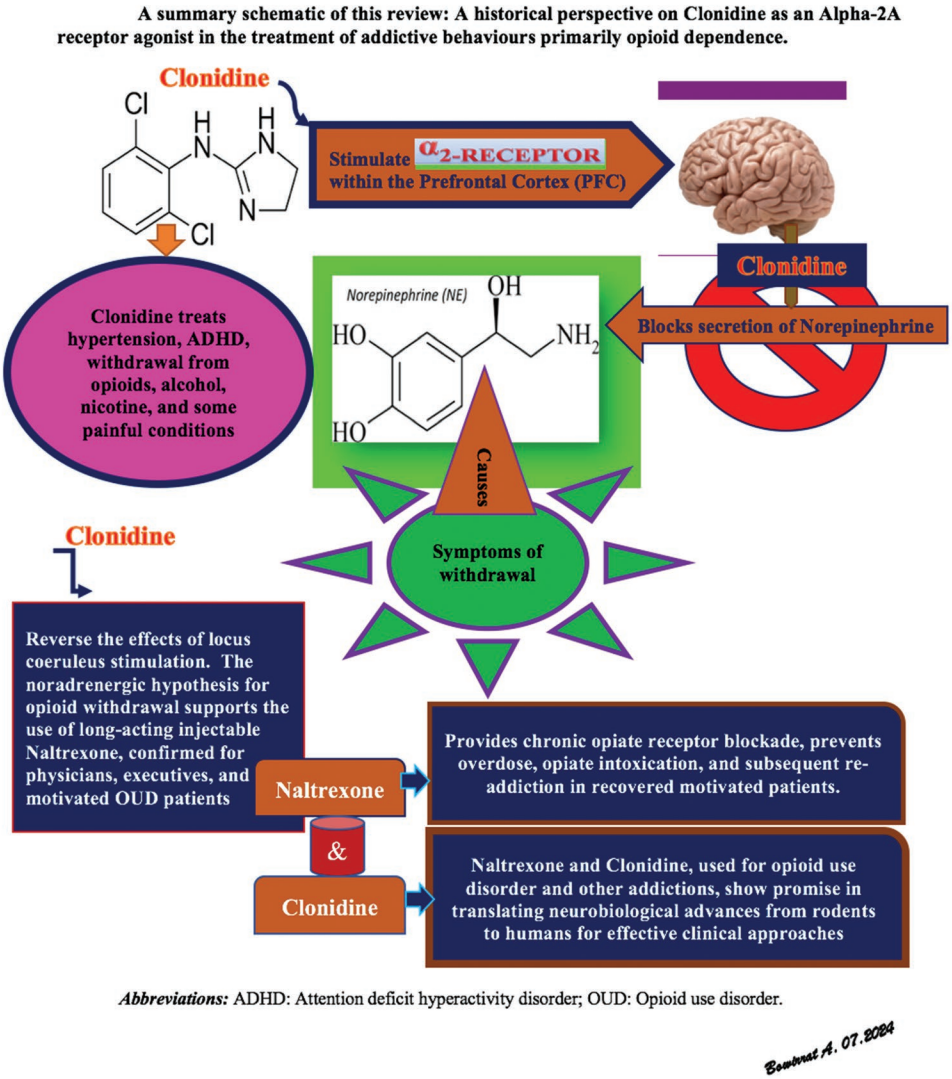


Figure 1. A summary schematic of this review
Abbreviations: ADHD: Attention deficit hyperactivity disorder; OUD: Opioid use disorder.

and other motivated individuals with OUDs. Despite its challenges with compliance, naltrexone offers sustained blockade of opioid receptors, mitigating the risk of overdose, intoxication, and subsequent re-addiction in motivated patients. The development of clonidine and naltrexone as treatment modalities for OUDs, as well as other addictions, underscores the potential for translating neurobiological advancements from rodent models (bench) to non-human primates and ultimately to humans (bedside), leading to novel and efficacious clinical interventions (Table 1).

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Conflict of interest

Dr. Blum is the inventor of GARS® and Pro-dopamine Regulation (KB220Z™). There are no other conflicts of interest.

Author contributions

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Writing – original draft: All authors
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