



Review

## Future Newborns with Opioid-Induced Neonatal Abstinence Syndrome (NAS) Could Be Assessed with the Genetic Addiction Risk Severity (GARS) Test and Potentially Treated Using Precision Amino-Acid Enkephalinase Inhibition Therapy (KB220) as a Frontline Modality Instead of Potent Opioids

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**Abstract:** In this nonsystematic review and opinion, including articles primarily selected from PubMed, we examine the pharmacological and nonpharmacological treatments of neonatal abstinence syndrome (NAS) in order to craft a reasonable opinion to help forge a paradigm shift in the treatment and prevention of primarily opioid-induced NAS. Newborns of individuals who use illicit and licit substances during pregnancy are at risk for withdrawal, also known as NAS. In the US, the reported prevalence of NAS has increased from 4.0 per 1000 hospital births in 2010 to 7.3 per 1000 hospital births in 2017, which is an 82% increase. The management of NAS is varied and involves a combination of nonpharmacologic and pharmacologic therapy. The preferred first-line pharmacological treatment for NAS is opioid therapy, specifically morphine, and the goal is the short-term improvement in NAS symptomatology. Nonpharmacological therapies are individualized and typically focus on general

care measures, the newborn–parent/caregiver relationship, the environment, and feeding. When used appropriately, nonpharmacologic therapies can help newborns with NAS avoid or reduce the amount of pharmacologic therapy required and the length of hospitalization. In addition, genetic polymorphisms of the catechol-o-methyltransferase (COMT) and mu-opioid receptor (OPRM1) genes appear to affect the length of stay and the need for pharmacotherapy in newborns with prenatal opioid exposure. Therefore, based on this extensive literature and additional research, this team of coauthors suggests that, in the future, in addition to the current nonpharmacological therapies, patients with opioid-induced NAS should undergo genetic assessment (i.e., the genetic addiction risk severity (GARS) test), which can subsequently be used to guide DNA-directed precision amino-acid enkephalinase inhibition (KB220) therapy as a frontline modality instead of potent opioids.

**Keywords:** neonatal abstinence syndrome (NAS); reward deficiency syndrome (RDS); genetic addiction risk severity (GARS); hypodopaminergia; dopamine homeostasis; opioids and alcohol common mechanism

### 1. Introduction

In this nonsystematic review and opinion, we primarily selected articles from PubMed to craft a reasonable opinion to help forge a paradigm shift in the treatment and prevention of primarily opioid-induced neonatal abstinence syndrome (NAS). Unfortunately, NAS from exposure to opioids in utero has reached epidemic levels worldwide. In infants, it is well known that nonpharmacologic modalities are the standard of care. However, pharmacotherapy is often required for the treatment of NAS. This article examines the current standard-of-care nonpharmacological and pharmacological treatments and explores additional potential alternative nonpharmacological treatments that could improve NAS treatment outcomes.

## 1.1. Neonatal Abstinence Syndrome (NAS)

Newborns of individuals who use illicit and licit substances during pregnancy are at risk for withdrawal, also known as NAS. NAS is a spectrum of newborn neurobehavioral dysregulation symptoms that are complex, variable, and poorly understood. Although NAS is most frequently linked to opioid exposure, it can be related to other substances such as nicotine, methamphetamine, benzodiazepines, selective serotonin reuptake inhibitors (SSRIs), etc. [1,2]. The most common characteristic signs and symptoms of NAS indicate dysfunction in any of the following domains: motor and tone control, state control and attention, sensory integration, and autonomic functioning [3]. The onset of the signs and symptoms of NAS varies, depending on the history of substance exposure and the half-life of substance elimination. For opioids in particular, withdrawal can be delayed up to five days after birth or longer [4]. The presence and severity of these signs and symptoms provide the foundation for scoring systems (i.e., the Modified Finnegan Neonatal Abstinence Score, the Johns Hopkins Bayview Medical Center neonatal abstinence scoring sheet and initiation of treatment, etc.) that are used to make treatment decisions in newborns with NAS. The long-term consequences of NAS can include, but are not limited to, behavioral problems, neurodevelopmental delays, and when untreated, death [5].

## 1.2. Epidemiology and Economic Issues

Illicit drug use in the United States (US) has been steadily increasing and has reached unprecedented levels [6,7]. According to data from the National Survey on Drug Abuse and Health (NSDUH), in 2020 approximately 59.3 million individuals living in the US had used illicit drugs in the past year [6]. In addition, provisional data from the Centers for Disease Control and Prevention (CDC) revealed that there were approximately 107,622 drug overdose deaths in the US in 2021 [8]. This increase in illicit drug use in the US has resulted in an increase in NAS. In the US, the reported prevalence of NAS has increased from 4.0

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per 1000 hospital births in 2010 to 7.3 per 1000 hospital births in 2017, which is an 82% increase [9].

In a study by Patrick et al. [10], birth and economic data from 580 counties over 7 years were reviewed. These included 1803 metropolitan country-years, 1268 rural country-years, and 927 remote county-years. An assessment inclusive of these years found 6,302,497 births with 47,224 births diagnosed with NAS. Specifically, the median NAS range was 7.1 per 1000 hospital births. Notably, individuals diagnosed with NAS are associated with the 10-year unemployment rate. Victims of NAS in this global investigation presented in the lowest unemployment quartile.

## 2. Treatment of NAS

The management of NAS is varied and involves a combination of nonpharmacologic and pharmacologic therapy. The treatment goals for NAS include preventing NAS-associated complications and restoring normal newborn activities, such as nutrition intake, weight gain, sleep, and adjustment to the social environment [11]. As with all pharmacological treatments, the potential risks and benefits of treatment must be considered for each patient. For example, some disadvantages include prolonged hospitalizations and drug exposure, while some advantages include the relief of withdrawal symptoms and the prevention of potential complications.

## 2.1. Nonpharmacological Interventions

Nonpharmacologic care should be initiated at birth for all substance-exposed newborns, and the parent/caregiver should also be actively involved. It should continue throughout the newborn's hospitalization and after discharge, regardless of the need for pharmacologic treatment. When used appropriately, nonpharmacologic therapies can help newborns with NAS avoid or reduce the amount of pharmacologic therapy required. However, they do not serve as a substitute for pharmacotherapy when it is necessary. Nonpharmacologic therapies entail individualized assessments of the newborn and parent/caregiver's functioning; the environment, to determine specific newborn-parent/caregiver dyad triggers for dysregulation; and adaptative responses to the environment to reduce physiological and neurobehavioral symptoms and promote newborn-parent/caregiver dyadic regulation [3].

General care measures [3,12]:

General care measures in NAS include identifying the signs, symptoms, and triggers of physiological behavioral dysregulation and individualizing the care of the newborn based on these observations as well as promoting organization, competence, and physiological stability in newborns by identifying techniques that improve symptomatology that are specific to each newborn. For example, gentle vertical rocking can help reduce excessive irritability. Moreover, tremors and hypertonicity can be reduced by utilizing swaddling and positioning (i.e., the side-lying C position), which decrease motoric hyperactivity and allow newborns to organize their behaviors and become calm.

*Newborn–parent/caregiver relationship* [3]:

Nonpharmacologic interventions in this domain include assessing parental functioning and interaction with the newborn to help reduce dysregulation and promote dyadic synchronization [13]; educating the parent/caregiver on how to identify the signs of withdrawal; teaching the parent/caregiver about their newborn's sensitivities; helping the parent/caregiver develop strategies and respond to the newborn in a manner that reduces the newborn's dysregulation and expression of NAS; aiding the parent/caregiver in understanding their feelings surrounding their newborn's functioning so they can respond more appropriately; and managing maternal issues such as mental illness, limited health care access, intimate partner violence, etc., in order to maintain a healthy newborn-parent/caregiver relationship, which is vital for the newborn's development [5].

Environment [12]:

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Nonpharmacologic interventions in this domain include identifying potential sensory and environmental input sources of dysregulation for newborns and altering the environment to minimize their effects and dysregulation. For example, a newborn who becomes hypertonic or irritable with eye contact might need the parent/caregiver to avoid eye contact while feeding, handling, or performing other activities together. In addition, a newborn who becomes easily overstimulated by noise can be cared for in a quiet area. Finally, rooming-in (i.e., the colocation of the newborn and the parent/caregiver after delivery and beyond) has been found to reduce NAS severity [12,14,15] and is recommended in the inpatient setting.

Feeding:

For newborns with NAS, formula feeding should not necessarily be the default. In fact, breastfeeding has been shown to be successful in some individuals with opioid use disorder (OUD) [12,16–18]. Recommendations involving an individual's suitability for breastfeeding should be tailored for individuals with one or more of the following traits: the concurrent usage of other prescription medications; participation in prenatal care and/or substance use disorder (SUD) treatment during or after the second trimester; and relapse during the third trimester with abstinence maintained for 30 days prior to delivery.

Breastfeeding by methadone-maintained individuals seems to be safe and can lessen the severity of NAS and the necessity for pharmacological intervention [19–22]. The concentrations of methadone have been found to be low in human breast milk (range: 21–462 ng/mL) and do not appear to be associated with the parent's methadone dose [19]. The low concentrations of methadone found in human breast milk are unlikely to have a significant impact on the newborn's display of NAS, and other breastfeeding-related variables could be responsible for the decreased severity of NAS in breastfed infants of methadone-maintained individuals. In addition, buprenorphine is excreted in low concentrations into human breast milk and seems to be safe for newborns of buprenorphine-maintained individuals [23,24].

## 2.2. Pharmacological Interventions

Pharmacological management is initiated for newborns who display significant signs and symptoms of NAS despite adequate and personalized nonpharmacological care. The goal of pharmacological management is a short-term improvement in NAS symptomatology. Currently, opioid therapy is the preferred first-line treatment for NAS. This is based on limited data that show opioid therapy reduces the need for additional medications and shortens hospital stays [5,12,25–28]. Morphine and methadone are the preferred opioids, and the selection is based on the clinician/hospital. Morphine is typically the preferred agent of the two, while methadone is considered a reasonable alternative. However, there have been studies that indicate that methadone minimally reduces hospital stay and treatment duration when compared to morphine [29,30]. Buprenorphine is another agent that has been used and appears to be effective in the treatment of NAS [31,32]. However, its use in newborns is limited due to the high ethanol content (30%) and its challenging sublingual administration [12].

A 2020 systematic review by Zankl et al. identified 16 trials including 1110 infants [5]. In one of the trials (N=80 infants), morphine was compared to supportive care alone, and the results showed that morphine increased the length of treatment and hospitalization but shortened the time needed to regain birthweight. In trials that compared morphine to methadone (two trials, N=147 infants), it was found that they both had comparable rates of breastfeeding success, length of hospitalization, and treatment failure. In trials that compared morphine to buprenorphine (three trials, N=113 infants), it was found that they both had comparable rates of treatment failure, but the length of hospitalization was shorter in the buprenorphine group. In a separate network meta-analysis utilizing both indirect and direct comparisons (18 trials, N=1072 infants), six medications were evaluated, including morphine, methadone, buprenorphine, clonidine, phenobarbital, and DTO. Morphine and methadone were associated with the lowest rates of treatment failure,

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but the differences were not statistically significant [33]. Additionally, buprenorphine was found to have the shortest length of hospitalization.

In addition, according to a meta-analysis by Cleary et al., there were no statistically significant differences in the incidence of NAS in newborns of women on higher doses of opioids when compared to lower doses in studies that used an objective NAS scoring system and prospective studies [34]. Similarly, Bakstad et al. reported that the maternal methadone or buprenorphine dose was not predictive of the occurrence or need for NAS treatment in newborns [35].

A second medication is sometimes required in newborns who have severe NAS that is not sufficiently controlled with a single agent [5,33,36,37]. The two most commonly used second-line medications are clonidine and phenobarbital. Typically, clonidine is the preferred second-line medication due to concerns regarding phenobarbital's adverse effects, including oversedation, a high alcohol content, challenges with weaning substance-exposed newborns from phenobarbital, and phenobarbital's potential long-term impacts on neurodevelopment based on animal studies [12,38–41]. In addition, the concurrent use of phenobarbital and clonidine appears to reduce the consequences of opioid-induced negative neuronal development in newborns with NAS [36,42].

Agthe et al. found that, in a clinical trial (N = 80) with newborns who had intrauterine exposure to heroin or methadone, the addition of clonidine to standard opioid therapy was found to decrease pharmacological treatment (11 vs. 15 days) when compared to placebo [43]. The placebo group also required higher dosages of opioid therapy. No significant short-term complications, such as bradycardia, hypotension, hypertension, or oxygen desaturations, were observed in either group. However, the clonidine group had three deaths (sudden infant death syndrome (SIDS), myocarditis, and homicide). Johnson et al. compared the use of phenobarbital and opioid therapy together to opioid therapy alone and found that the combined therapy decreased the length of hospitalization and the duration of symptoms when compared to opioid therapy alone [44]. However, despite the use of phenobarbital in the treatment of NAS, no safety profile has been established, and the alcohol content remains a concern [45]. Finally, in a retrospective multicenter study (N = 563) by Merhar et al., it was found that the length of hospitalization and morphine treatment was shorter for newborns who were treated with a combined therapy of morphine and phenobarbital compared to those who were treated with a combined therapy of clonidine and morphine [37]. However, more newborns were discharged on phenobarbital than clonidine (78% vs. 29%).

## 2.3. Neurodevelopmental Issues with Opioid Treatment

Czynski et al. [46] reported that the prevalence of NAS has increased by 333% over the last two decades, which translates to approximately one infant born every 15 min in the United States [47]. This unfortunate statistic reveals that 50-80% of newborn infants exposed to opioids in utero develop NAS. Along these lines, Boardman et al. [48] suggested that a literature summary of 40 years necessitated a reassessment of ways to treat NAS without opioids, even during withdrawal periods. These investigators identified knowledge gaps and urged the scientific community to re-evaluate childhood clinical outcomes such as infant brain development and visual and long-term neurocognitive function. Van den Hoogen et al. [49], assessing the behavioral and cFos responses, known to be a marker for neuronal activation in neonatal animals withdrawing from opioids, found increased cFos expression in spinally projecting neurons within the periaqueductal grey (PAG), locus coeruleus, and rostral ventromedial medulla (RVM). They also observed that the narcotic antagonist naloxone precipitated profound withdrawal symptoms across all developmental levels and stages within several key brainstem regions. Another example of neurodevelopmental issues linked to opioids was investigated by others [46], involving mothers maintained on methadone or buprenorphine but randomized to morphine vs. methadone. Czynski et al. [46] reported that adding phenobarbital to the treatment routine resulted in several medical problems, suggesting that sedative hypnotics may not be an appropriate

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modality in these NAS cases. Finally, Witt et al. [50] evaluated long-term childhood and infant mortality involving 1900 individuals diagnosed with NAS and 12,283 controls. The results indicated that NAS-diagnosed children were readmitted to the hospital within five years of life more frequently when compared to non-NAS controls. Most perplexing was the finding that in NAS patients there was an unadjusted significant increased mortality risk ratio of 1.94 (95% CI 0.99–3.80). Witt and associates [50] concluded that childhood readmission due to NAS "argues" for innovative (possibly nonpharmacological) early interventions to prevent morbidity and possibly mortality.

## 2.4. A Case in Favor of Non-Opioid Treatment in NAS

Opioid pharmacokinetics are influenced in neonates by a higher body water content that can alter drug distribution and metabolic processes that are not mature and can lead to low plasma protein and liver enzyme activity. For example, these factors could affect cleared metabolites, resulting in a prolonged half-life of opioids. This is further complicated by reduced renal excretion, which might be due to immature tubular secretion, glomerular filtration, and reabsorption [51]. In addition, animal experiments have shown that an immature blood–brain barrier in neonates may result in an augmented sensitivity to opioids [52].

An argument against the utilization of opioids to treat NAS has been espoused by some investigators globally [53–56], and a word search for "acupuncture and NAS" revealed 102 PubMed listings (26 January 2022). Following an extensive review of the literature, including the Cochrane Databases, Jackson et al. [53] reported that acupuncture is a safe and effective nonpharmacological alternative to potent opioids for the treatment of NAS.

Similarly, while not in neonates but in adults, our laboratory observed a significant attenuation of opioid withdrawal symptoms with a well-researched nutraceutical complex prodopaminergic regulator (KB220Z) as an aqua-power liquid variant [57]. Out of 17 heavily opioid-dependent patients during detoxification, only three received buprenorphine/naloxone (Bup/Nx) along with KB220Z. We first used a dose of KB220Z of two ounces (oz) twice daily before meals, along with other detoxifying agents, including clonidine, benzodiazepines, and gabapentin. The dose of KB220Z was maintained for six days in five patients. Then, in a second scenario, we employed a higher dose of four oz every six hours over six days. The higher dose was utilized in another 12 patients. Only three people relapsed with these two protocols during the first two weeks of the experiment. Importantly, the remaining 82% were maintained on KB220Z. Specifically, these subjects were maintained without any additional Bup/Nx for a minimum of 120 days and, in one subject, 214 days. One limitation is the inability to interpret these results or make any conclusions regarding specific KB220Z effects.

If further confirmed in more extensive studies, using KB220Z for opiate/opioid detoxification may provide a novel way to eliminate the need for addictive opioids during withdrawal and detoxification. This paradigm shift, which requires extensive research, may translate to a reduction in universally employing powerful and addictive opioids to treat OUD and NAS [58].

## 2.5. Snapshot of Dopaminergic Mechanisms in Addiction

Undoubtedly, substance and nonsubstance behavioral addiction is a complex genetic and epigenetic disease that afflicts millions worldwide. Clinically, a major issue biologically is a breakdown in the function of the brain's reward circuitry in many cases, even in newborns, especially as a function of specific known genetic risk variants as antecedents compounded by the epigenetic effects of in utero opioids that impact behavior. It is of interest that much of our knowledge of the neurobiological underpinnings of human behavior regarding "reward dysfunction" has been derived from animal research. Poisson et al. [59] recently reviewed the evidence related to the critical role of striatal dopamine (DA) in all addictive behaviors. While our laboratory has been at the forefront of DA genetics and its association with not only severe alcoholism but also general reward defi-

ciency [60,61], Poisson and associates [59] contributed to the identification of specific and distinct mesostriatal and nigrostriatal DA circuit functions in substance use disorder (SUD). Although at least seven major neurotransmitter systems (serotoninergic, endorphinergic, GABAergic, glutamatergic, opioidergic, acetylcholinergic, and dopaminergic) are involved, striatal dopamine is essential for controlling one's craving behaviors, impairments in decision making that underlie several risk-taking behaviors, anti-socialization, and overall compulsive and impulsive behaviors (Figure 1).

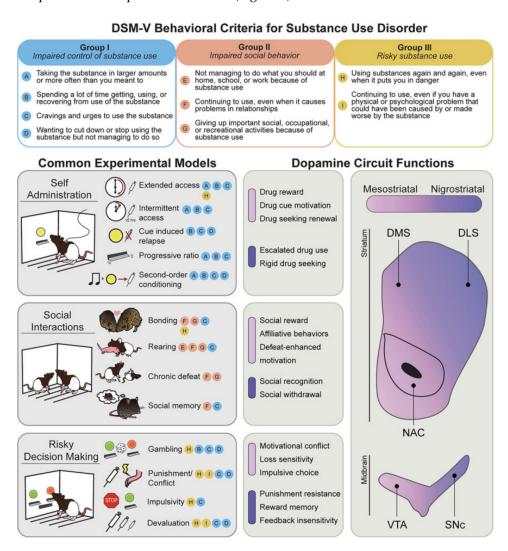


Figure 1. Behavioral models are used to classify the phenotypes of substance use disorder (SUD). (Top) The behavioral criteria of SUDs (circled letters) can be sorted into three main categories: impaired control of substance use (Group II), impaired social behavior (Group II), and risky substance use (Group III). (Left) Common rodent experimental models and the SUD criteria that are thought to best approximate them. Note that most models capture multiple SUD features. (Right) Mesostriatal circuits (light purple), including dopamine projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc), and nigrostriatal circuits (dark purple), including dopamine projections to the dorsomedial (DMS) and dorsolateral striatum (DLS), generally have dissociable roles in different components of major SUD models. The middle panels list the most clearly defined roles for these two systems in each SUD category.

As Poisson et al. [59] pointed out, most of the brain's dopamine neurons are in two midbrain regions (Figure 1): the ventral tegmental area (VTA) and the substantia nigra pars compacta (SNc). Others revealed that DA neurons in the VTA mainly project to the ventral striatum, specifically the nucleus accumbens (NAc) core and shell. The

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NAc shell comprises the mesostriatal pathway and links to certain frontal regions in the prefrontal cortex, pallidum, and amygdala [62,63]. The work of Nestler's group [64] and others [65,66] has shown that DA neurons in the VTA intermingle with GABAergic and glutamatergic neurons. In contrast, the SNc DA neurons project to the dorsomedial (DMS) and dorsolateral (DLS) striatum almost exclusively and comprise a well-known nigrostriatal system [67–69]. Importantly, in the striatum, Gerfen [70] showed that DA neurons contact GABAergic medium spiny neurons (MSNs) that contain excitatory type 1 (D1-MSNs) or inhibitory type 2 (D2-MSNs) DA receptors. Kupchik et al. [71] have further confirmed this work. The primary role of DA's modulatory effect on striatal activity due to these outputs involves the control of specific behaviors (such as motivation and reward learning). It is indeed well known that most highly addictive psychoactive drugs (such as cocaine, alcohol, and morphine) cause the release of DA in the NAc and other striatal regions. According to Collins and Saunders [72], based on terminal mechanisms, DA release may play an essential role in many infractions related to aberrant drug use and cravings and even drug reinstatement or relapse, the cornerstone of unwanted SUD [73-77]. A review of the literature revealed that DA neurons across the VTA and SNc circuitry impact a wide array of behavioral functions, showing significant overlap or co-occurrence across many reward-related behaviors [78-81]. Mesostriatal DA neurons contribute to the execution of goal-directed behaviors and learning. However, nigrostriatal DA, specifically in the DLS, impacts movement control and even the execution of rigid habitual actions that translate to addiction heterogeneity [82–87]. It is important to recognize that DA has a powerful effect on many behaviors that, when impaired, induce in the reward circuitry maladapted dysfunctional behaviors and addiction, including poor decision making, a prominent underpinning of compulsive behaviors [88–119].

## 2.6. Evidence-Based Prodopaminergic Regulation (KB220)

Genetic polymorphisms of the catechol-o-methyltransferase (COMT) and mu-opioid receptor (OPRM1) genes appear to affect the length of stay and the need for pharmacotherapy in newborns with prenatal opioid exposure [120]. These findings are consistent with data from adult studies that demonstrated that variations in these genes are associated with adult opioid dependence variability [121]. Epigenetic modifications to the OPRM1 gene have also been linked to the severity of NAS [122]. Thus, it appears prudent to incorporate genetic testing in order to reveal reward circuitry gene polymorphisms, especially those associated with dopaminergic pathways and opioid receptors, as a means of improving NAS treatment outcomes [123].

Therefore, after a decade of attempting to reduce severe NAS symptomatology with nonpharmacological approaches, including acupuncture and transcranial stimulation [124,125], we propose adding the complex prodopaminergic regulator (KB220Z) based on genetic assessment (i.e., the genetic addiction risk severity (GARS) test), along with other non-opioid modalities. KB220Z is a formulation of enkephalin, enkephalinase inhibitors, and dopamine-releasing neuronutrients that is utilized to induce dopamine homeostasis for the detoxification and treatment of individuals genetically predisposed to developing addictive and compulsive behaviors known as reward deficiency syndrome (RDS) (Table 1) [61]. The formulations are based on the results of the GARS test, which evaluates the presence of reward genes and risk alleles and can successfully stratify the potential for developing OUD-related risks (Table 1) [61]. In addition, second-line non-opioid pharmacological agents such as clonidine [126] could also be used in the short term, followed by longer-term dopamine regulation with KB220 variants.

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GARS Listed Nutrient	Neuroadaptagen Target
D-Phenylalanine	Opioid peptides
L-Phenylalanine	Dopamine
L-tryptophan	Serotonin
L-Tyrosine	Dopamine
L-Glutamine (low dose)	GABA
Chromium	Serotonin
Rhodiola Rosea	COMT/MOA
Passionflower (low dose)	Benzodiazepine = GABA complex
Pyridoxine	Enzyme Catalyst

**Table 1.** Neuroadaptagen amino-acid therapy (NAAT) \*.

In the most recent reiteration, additional nutrients have been added to the formula, such as  $\beta$ -nicotinamide adenine dinucleotide ( $\beta$ -NAD) to function as a catalyst for dopamine synthesis [127] and N-acetyl-cysteine [128] to help promote glutaminergic drive in the VTA to release DA in the NAc.

It is noteworthy that globally we are facing a significant challenge in the increased utilization of opioids to reduce ongoing stress. In 2021, the USA had over 100,000 narcotic-overdose-induced fatalities [129]. Certainly, NIAAA and NIDA continue to struggle with innovation to help reduce or eliminate this catastrophic epidemic. However, we are concerned with the current FDA-approved medication assistance treatments (MAT). The concern is that MAT works by blocking dopamine function and release at the preneuron in the NAc. While we understand short-term use to reduce harm [130], we oppose long-term use for tertiary treatment [131].

The research-based neuronutrient KB220, which has been intensely investigated in at least 38 studies, has demonstrated clinical benefit [45]. The effects include, but are not limited to, reduced against medical advice (AMA) rates; reward system activation, including blood oxygen level dependent (BOLD) dopamine signaling; a reduction in craving behavior; relapse prevention; and the attenuation of stress, anger, and aggressive behaviors. It is noteworthy that our group has recently published an additional twelve studies utilizing KB220 variants [132]. Based on animal research and clinical trials, the prodopamine regulator KB220 shows promise in treating addiction and pain as well as opioid-induced withdrawal symptomatology [133].

While additional neurobiological and genetic studies are required to help understand the mechanism of action of this neuronutrient, possible studies related to NAS seem prudent. However, the evidence advocates for the induction of "dopamine homeostasis" [105]. We believe that the utilization of this nonpharmacological approach could enable an approach free from side effects that induces the "normalization" of brain neurotransmitter signaling epigenetically. Moreover, it is reasonable to predict that the utilization of this neuronutrient (KB220) could lead to improved function and the attenuation of NAS.

It is vital that addiction researchers realize that providing opioids to treat opioid abuse is counterproductive and lacks ways to induce real potential prophylaxis. Instead, we propose long-term prophylaxis utilizing our concept of coupling GARS to help determine precision prodopaminergic regulation via KB220.

With that said, we are encouraged by these results, as published over the last 50 years. We look forward to continued advancements in appropriate nutrigenomic solutions for the millions of victims of all addictions, including reward surfeit syndrome (RSS) in adolescents and RDS in adulthood [105] as well as addictions to substances such as drugs and food and to behaviors such as smoking, gambling, and gaming, especially in our next

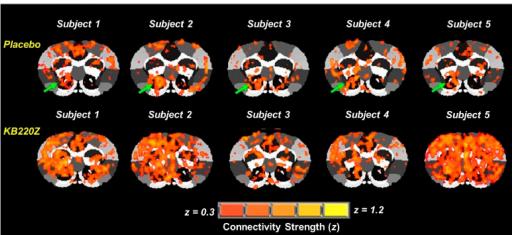
<sup>\*</sup> Table 1 describes the ingredients and proposed neurotransmitter targets of KB220.

generation. Understanding these simple precepts may engender novel ways to treat NAS with nonpowerful opioids.

The neurological effects of KB220 in naïve rodents, uncovered in studies conducted by Marcelo Febo [134], showed BOLD activation using KB220 in regions of interest related to the brain reward circuitry. Specifically, there was a significant increase in the functional connectivity of the NAc with the medial and lateral anterior thalamic nucleus and the surrounding somatosensory cortex (Figure 2). Another important finding revealed that KB220Z augmented the connectivity between corticothalamic areas and this region of the reward system.

Additionally, with KB220Z vs. placebo, when the anterior thalamic nucleus was the selected seed RIO, there was minimal evidence of connectivity observed outside this area. Febo et al. [134] found a significant enhancement in connectivity with surrounding sensory cortical areas and the regions mentioned above, including the NAc (both left and right). A more substantial effect on the resting state functional connectivity (rsFC) in the dorsal hippocampus was of real interest. Furthermore, connectivity was increased between the left and right dorsal hippocampi, the upper limb somatosensory regions, the NAc and limbic cortical areas, and the anterior cingulate (Figure 2).





**Figure 2.** Representative cross-correlation maps show five subjects: placebo-controlled and KB220Z-treated rats. The maps correspond to the resting-state connectivity for the NAc (highlighted in green in the atlas map above the figure; only the left seed is shown). Note the distributed but significant connectivity between various brain regions and the NAc in the placebo subjects. KB220Z increased connectivity, especially between the left and right accumbens, dorsal striatum, and limbic cortical areas, such as the anterior cingulate, prelimbic, and infralimbic regions. Correlation maps for the representative subjects are presented at a threshold of  $0.3 \le z \ge 1.2$  [135] (with permission).

A follow-up study utilizing KB220Z was also administered to abstinent Chinese heroin abusers to help map the brain reward circuitry interaction potential in humans. Along these lines, it is noteworthy that Willuhn et al. [136] reported that cocaine use and even non-substance-related addictive behavior surge as dopaminergic function is decreased. Understanding that reduced or deficient levels of brain DA enhance heroin-seeking behavior. Treatment strategies, including a DA agonist therapy that conserves dopamine function, could prevent relapse to opioids.

The effect of KB220Z on the reward circuitry of ten heroin addicts undergoing protracted abstinence for an average of 16.9 months was investigated [135]. Specifically, in a randomized, placebo-controlled crossover study of KB220Z, five subjects completed

the triple-blinded experiment. Additionally, nine patients were genotyped utilizing the GARS test.

KB220Z induced an enhanced BOLD activation in caudate–accumbens–dopaminergic pathways compared to placebo following a one-hour acute administration. Moreover, KB220Z also attenuated the resting state activity in the putamen of abstinent heroin-dependent subjects. In the second phase of this preliminary investigation of all ten abstinent heroin-dependent patients, three brain regions of interest were significantly activated from the resting state by KB220Z compared to placebo.

Interestingly, augmented functional connectivity was observed in a putative network that included the cerebellum, medial frontal gyrus, dorsal anterior cingulate, NAc, occipital cortical area, and posterior cingulate. These results and other qEEG studies [137,138] support the notion of a putative anticraving/anti-relapse role for KB220Z in opioid dependence by direct or indirect dopaminergic interaction.

Preclinical experiments and human trials associated with KB220 variants have been published and reviewed [45]. Early formulations of KB220 increased brain enkephalin levels in rodents [136], reduced alcohol-seeking behavior in C57/BL mice [135], and converted ethanol-preferring C57/BL mice via pharmacogenetics to the same level of nonpreference as alcohol-averse DBA mice [136]. Thus, based on these and other animal and human studies [137–169], using KB220Z might be an ideal treatment for NAS, particularly to counteract underlying brain hypodopaminergia.

# 2.7. Common Neurochemical Mechanisms Related to Alcohol and Opiate/Opioid-Induced Withdrawal Symptomatology

Wallace et al. [170] reported that as many as 47% of pregnant women misuse/abuse alcohol, and at least 6% misuse or abuse illegal drugs such as opioids. The European Monitoring Centre for Drugs and Drug Addiction has noted that approximately 500 thousand opioid-dependent Europeans are, unfortunately, on opioid maintenance substitution therapy (OMST) [171]. It is indeed a fact that about 30,000 opioid-dependent women have become pregnant [172]. The treatment of women involved with a combination of alcohol and opioid dependence is very complex and is a challenge that must be faced to attenuate the onslaught of unwanted NAS [173,174].

Since the early 1970s, Blum's group has investigated the common neurochemical and genetic underpinnings of all addictive behaviors. One area of investigation by this group was a common mechanism among opiates, alcohol, and neurotransmitter involvement in withdrawal symptomology—the commonality concept related to condensation products derived from the identification of in vivo isoquinoline formation. There is enough evidence to suggest that these condensation amines "link" to opiates. The message here is that when one imbibes alcohol, opiate-like isoquinolines are formed [175]. These isoquinolines induce a robust enhancement of ethanol-induced withdrawal symptoms (EIW) [176]. For example, a series of experiments revealed that the inhibition of catecholamine synthesis results in the potentiation of EIW [177]; haloperidol, a D2 dopamine receptor (DRD2), potentiates EIW [178]; serotonergic blockers potentiate EIW [179]; dopamine suppresses EIW [180]; morphine suppresses EIW [181,182]; naloxone inhibits alcohol dependence [183]; and clonidine enhances EIW [184–186].

Of interest is the finding that by employing quantitative electroencephalography (qEEG) as an imaging tool, Miller et al. [153] showed the impact of one formulation of KB220 as a putative activator of the mesolimbic system. These investigators [153] found that intravenous administration reduces or "normalizes" aberrant electrophysiological parameters of the brain reward circuitry region. Specifically, KB220 significantly normalized widespread theta and alpha activity in alcoholics and heroin abusers, showing several neurotransmitter-linked polymorphic genes measured by the GARS test. The authors [153] suggested that the chronic activation of dopaminergic receptors, such as DRD2, will increase upregulation, induce an augmented "dopamine sensitivity," and ultimately "enhance the sense of happiness," specifically, for example, in carriers of the DRD2 A1 allele.

2.8. Genetic Addiction Risk Severity (GARS): Promoting the Early Identification of Polymorphic Risk Alleles in RDS

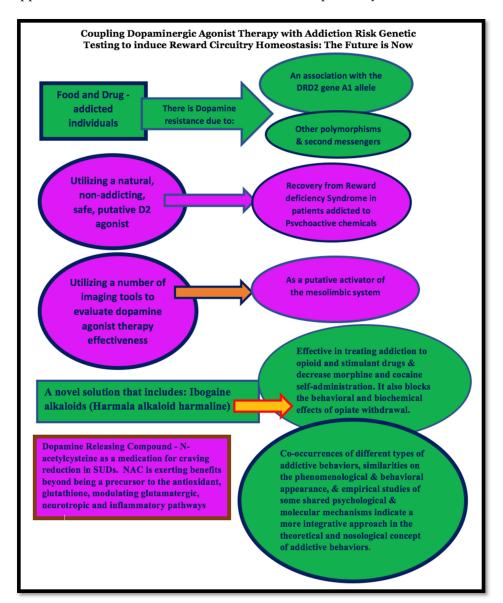
Since 1990, when our laboratory published the DRD2 Taq A1 allele and severe alcoholism association in JAMA, there has been an explosion of genetic candidate association studies, including genome-wide association studies (GWAS). To develop an accurate test to help identify those at risk for at least alcohol use disorder (AUD), Blum's group developed the GARS test, consisting of ten genes and eleven associated risk alleles. To statistically validate the selection of the risk alleles measured by GARS for alcohol, we applied a strict analysis to studies that investigated the association of each polymorphism with AUD or AUD-related conditions published from 1990 until 2021. This analysis calculated the Hardy-Weinberg equilibrium of each polymorphism in cases and controls. Pearson's χ2 test or Fisher's exact test were applied to compare the gender, genotype, and allele distribution, if available. The statistical analyses found the 95% CI for the odds ratio (OR) and the post hoc risk for alcoholism prevalence to be an estimated 8% of the population, revealing a significant detection. The likelihood ratio (LR) results also showed significance for DRD2, DRD3, DRD4, dopamine transporter gene (DAT1), catechol-o-methyltransferase (COMT), mu opioid receptor gene (OPRM1), and serotonin transporter gene (5-HTT) at 5%. The United States and European patents on a ten-gene panel and eleven risk alleles had been issued prior to this statistical analysis.

One possible etiological root cause of addiction involves the identified neurotransmitter network function within the mesolimbic and prefrontal cortex (PFC) brain regions. It is essential that the scientific community recognizes that the subsequent regulation of the final reward and motivational pathway of "wanting" translates to the physiological induction of "normal" neuronal dopamine release. The typical neuromodulating aspects of neurotransmission and its disruption from chronic exposure to drugs and behavioral addictions necessitate an approach that involves achieving "dopamine homeostasis," especially for AUD and other unwanted RDS behaviors [187–190]. Interestingly, Bidwell et al. [191], utilizing functional MRI imaging, found that during alcohol cueing DRD2 promoter methylation was strongly associated with responses to alcohol cues in many brain circuitry regions related to reward. In addition, the clinical metrics of AUD severity were positively associated with methylation of the promotor region of the DRD2 gene. This finding details early work from our laboratory [60], whereby we suggested that the DRD2 A1 allele residing outside of the promotor region in the 3' region of the genome, now known to be involved in the transcription process related to mRNA expression, is the root cause of severe alcoholism.

Figure 3 displays this article's primary tenant. It provides a schematic showing the interactive events related to coupling gentle dopaminergic agonists (not potent D2 agonists such as bromocriptine) with genetic risk testing as one way to induce homeostasis of the brain reward circuitry.

Blum's laboratory has worked to successfully develop the GARS test, an accurate genetic test to predict risk liability for RDS behaviors, including AUD. The association to determine risk using a clinical outcome, the addiction severity index media version (ASI-MV), was accomplished with the Institute of Behavioral Genetics, University of Colorado, Boulder. Ten reward candidate genes were selected to develop this patented GARS test. They included the dopamine receptors (DRD1, 2, 3, and 4); DAT1; 5-HTT, COMT, monoamine oxidase (MAO), gamma-aminobutyric acid (GABA), OPRM1, and some single nucleotide polymorphisms (SNPs) and point mutations, all chosen to reflect a hypodopaminergic trait. The functions of the chosen alleles of the ten genes were determined to negatively influence the net release of dopamine at the brain reward site. Thousands of association studies have provided conclusive evidence of RDS-specific risks. Unfortunately, our laboratory is the only group investigating this potentially important DNA-directed test that could be used early in life to identify specific polymorphic risk alleles. With that in mind, several studies and reviews have been published. A sampling

of these peer-reviewed articles provides the fundamental rationale to enable the futuristic applications of the GARS in all RDS behaviors to help identify risk [60,61,192–212].



**Figure 3.** Schematic of our proposed model to treat and identify genetic antecedents and to provide a way of inducing "dopamine homeostasis."

In our opinion, subsequent large-scale genomics studies have had limited success in identifying alleles implicated in addiction and RDS. Although GWAS and next-generation sequencing are valuable genetic tools, the primary reason for this known limited success is resolvable. For example, GWAS identifies novel clusters of genes that may relate to an etiological root as a genetic antecedent to RDS behaviors such as AUD. However, we believe the next critical step following GWAS clusters is the subsequent convergence to individual candidate genes, despite their small contributions to the overall variance [213].

This precision addiction management technology (Figure 4) was developed to accurately identify genetic addiction risk severity using the GARS test and was awarded the first USA and foreign patents. As previously mentioned, Blum, Noble, and associates [60,187,189] published the first confirmed association of the DRD2 gene A1 allele with severe alcoholism and other RDS behaviors. Following this work, Blum et al. developed the GARS test and the prodopamine regulator, a precision DNA-guided nutraceutical neuronutrient (research ID code: KB220) (Figure 4).

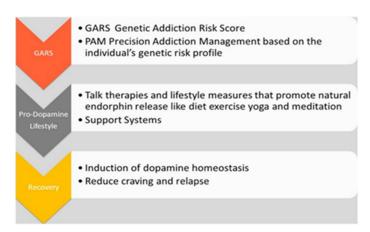
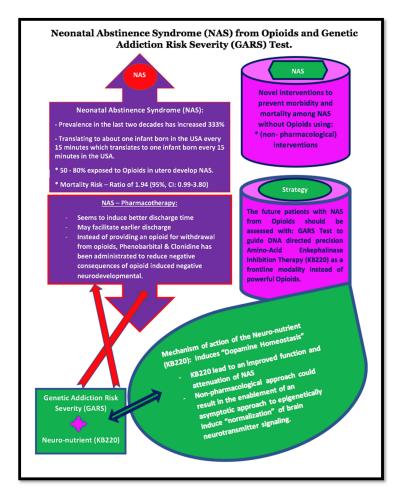


Figure 4. Precision addiction management platform [210] (with permission).

### 3. Conclusions

Based on this extensive literature and additional research, we suggest that in the future, in addition to the current standard-of-care nonpharmacological therapies, patients with opioid-induced NAS should be assessed with the GARS test to guide DNA-directed precision amino-acid enkephalinase inhibition (KB220) therapy as a frontline modality instead of potent opioids (Figure 5).



**Figure 5.** This schematic represents the paradigm shift required to circumvent the use of powerful opioids to treat opioid-induced NAS. We propose to couple the GARS test with DNA-directed precision KB220 therapy to detoxify and maintain patients with NAS using a non-opioid nutraceutical neuronutrient alternative.

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