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Review Article

Psychostimulant use disorder emphasizing methamphetamine and the opioid -dopamine connection: Digging out of a hypodopaminergic ditch

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ABSTRACT

Background: Approved food and drug administration (FDA) medications to treat Psychostimulant Use Disorder (PUD) are needed. Both acute and chronic neurological deficits related to the neurophysiological effects of these powerfully addictive drugs can cause stroke and alterations in mood and cognition.
Objective: This article presents a brief review of the psychiatric and neurobiological sequelae of methamphetamine use disorder, some known neurogenetic associations impacted by psychostimulants, and explores treatment modalities and outcomes.
Hypothesis: The authors propose that gentle D2 receptor stimulation accomplished via some treatment modalities can induce dopamine release, causing alteration of D2-directed mRNA and thus enhanced function of D2 receptors in the human. This proliferation of D2 receptors, in turn, will induce the attenuation of craving behavior, especially in genetically compromised high-risk populations.
Discussion: A better understanding of the involvement of molecular neurogenetic opioid, mesolimbic dopamine, and psychostimulant connections in "wanting" supports this hypothesis. While both scientific and, clinical professionals search for an FDA approved treatment for PUD the induction of dopamine homeostasis, via activation of the brain reward circuitry, offers treatment for underlying neurotransmitter functional deficits, potential prophylaxis, and support for recovery efforts.
Conclusion: Dopamine regulation may help people dig out of their hypodopaminergia ditch.

1. Introduction

Substance use disorders (SUD)s are serious public health problems that impact the lives of many individuals throughout the world. They are characterized by a compulsive drive to take drugs even in the presence of severe adverse events. [1–10]. Importantly, methamphetamine use disorder (MAUD) is prevalent in the US [11] and spreading throughout the world, including Australia [12,13], South-East and South-West Asia, and the US [14,15]. Despite very severe medicolegal consequences, more than 35 million people use methamphetamine and its analogs. The epidemiological profiles in the US have expanded from mainly white males who were bike riders or truck drivers [16] to include individuals of both sexes, adolescents of high school age, some being treated for attention-deficit/hyperactivity disorder (ADHD) [17], young professionals, and older adults [14]. Methamphetamine users often present to emergency rooms with varied neurological and psychiatric manifestations resulting in significant morbidity and mortality. Recently, Lappin & Sara [18] published a detailed review emphasizing that severe long-term impairment is a neuropsychiatric deficit associated with Psychostimulant Use Disorder (PUD). These authors explored psychostimulant neurochemistry; the moderators, mechanisms producing pathology, clinical responses, and the prognosis. They compared the effects of different psychostimulant types and reviewed the cerebral effects like stroke, neurocognitive impairment, Parkinson's disease, seizures, psychotic illness [18]. This present review further confirms the exhaustive literature and extends the current knowledge emphasizing the importance of connections between opioids, dopamine, and psychostimulants. It suggests and explains a novel treatment approach that moves beyond harm reduction to potential prophylaxis, especially in our youth.

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1.1. Pharmacodynamics

The delivery methods of amphetamine and methamphetamine, importantly effect, absorption, and potency, have clinical ramifications. Crystal methamphetamine is the most commonly used form and is predominately smoked or injected [19]. This crystalline form of methamphetamine induces modulating effects on microglial neuroimmune functions, elicits neuroinflammation and dopaminergic neurotoxicity [20]. Ropek et al. [21] found that long-term use of methamphetamine may cause DNA damage and adverse health effects like cancer and infertility. Oral methamphetamine is well-absorbed, with peak plasma concentrations achieved 3 to 6 h post-ingestion [22]. Methamphetamine acts on sympathetic nerve terminals stimulating the enhanced release of catecholamines, particularly dopamine in the mesolimbic, mesocortical, and nigrostriatal pathways. Due to the high lipophilicity, methamphetamine moves through the blood-brain barrier faster than other stimulants and resists degradation by monoamine oxidase enzyme [23]. Methamphetamine excretion rates are influenced by urinary pH, drug potency, and administration route; by injection, insufflation, or oral [24,25]. Methamphetamine is far more potent than amphetamine (purity generally >50%), and the half-life ranges from five to thirty hours [26]. The half-life of lower potency (<10%), street amphetamine is 7 h.

Cytochrome P450 2D6 (CYP2D6) is an enzyme mostly expressed in the liver and has a metabolic function that eliminates approximately 25% of clinically used drugs. Methamphetamine is a CYP2D6 inhibitor [27]. Other enzymes involved in the metabolism of methamphetamine or its metabolites in humans include glycine N-acyltransferase, butyrate-CoA ligase flavin-containing monooxygenase 3, and dopamine β-hydroxylase. The main metabolic pathways are aromatic para-hydroxylation, aliphatic alpha- and beta-hydroxylation, N-oxidation, N-dealkylation, and deamination [31].

2. Clinical features of methamphetamine use disorder

2.1. Acute psychiatric effects of methamphetamine

Users experience a sense of euphoria, increased productivity, hypersexuality, decreased anxiety, and increased energy immediately after taking the drug [28]. Methamphetamine users might experience agitation and aggression [29,30]. Impaired judgment, euphoric disinhibition, and psychomotor agitation are also associated with MAUD [31]. Behavioral and cognitive functions may also be altered [29,30,32,33]. These effects can last hours because the elimination half-life of methamphetamine varies, ranging from or 6 to 15 h for methamphetamine and 7 to 34 h for amphetamine. [34]. These half-life times represent metabolites and not active substances per se; they do not explain movement disorders like bonging effects or intoxication.

Stimulants are detectable in hair one month after use. Any evidence that methamphetamine is present in the hair matrix provides marker information concerning use or abuse. Substances such as psychostimulants, and opioids, are detectable in hair analysis, are used clinically to measure use patterns across many months, and are not a measure of drug effects. [35]

Numerous articles related to the acute adverse effects of amphetamine and methamphetamine have emphasized their powerful impact on behavior in both animal models and humans [36–41]. It is noteworthy that brain astrocytes help neuronal metabolic processes and affect neuronal communication in various ways, including homeostatic glutamate regulation. It is interesting that following 2-h cocaine or methamphetamine self-administration and extinction, the nucleus accumbens (NAc) core of rodents displays reduced basal glutamate levels, transitioning to an elevated glutamate level during drug-seeking [42]. Siemsen et al. [42] reported that acute activation of Gq-coupled Designer Receptors Exclusively Activated By Designer Drugs (DREADDs) in this region inhibited cued methamphetamine seeking. Accordingly, these data indicate that low glutamate clearance in the NAc core does not mediate methamphetamine seeking following two-hour self-administration, yet engaging NAc core astrocytes can inhibit seeking.

Many drugs, including alcohol and stimulants, demonstrably increase sociability and verbal interaction and are recreationally consumed in social settings. One drug, 3,4-methylenedioxymethamphetamine (MDMA), ecstasy, seems to produce its prosocial effects by increasing plasma oxytocin levels, implicating the oxytocin system in responses to several other drugs of abuse [43]. However, recently, no evidence for this assumption was found; neither alcohol nor methamphetamine increased plasma oxytocin levels. Given these facts, the neurobiological mechanisms mediating the prosocial effects of drugs such as alcohol and methamphetamine remain to be identified [44].

2.2. The psychostimulant opioid -dopamine connection understanding the brain

The Reward Cascade enables us to comprehend the interrelatedness of the psychostimulant opioid -dopamine connection. There are several neurotransmitters involved in the standard processing of reward and punishment. They include pathways involving at least six major neurotransmitters and many second messengers. These neurotransmitter networks function within the mesolimbic system and the prefrontal cortex (PFC), where they regulate the final net pathway of “wanting,” causing neuronal dopamine release (see Fig. 1).

Fig. 1 illustrates the interaction of at least seven major neurotransmitter-pathways involved in the Brain Reward Cascade (BRC). In the hypothalamus, environmental stimulation results in the release of serotonin, which in turn via, for example, 5HT-2a receptors activate (green equal sign) the subsequent release of opioid peptides from opioid peptide neurons, also in the hypothalamus. In turn, the opioid peptides have two distinct effects, possibly via two different opioid receptors. One inhibits (red hash sign) through the mu-opioid receptor (possibly via enkephalin) and projects to the substantia nigra to GABAA neurons. Another stimulates (green equal sign) cannabinoid neurons (for example, the anandamide and 2-archydonoglcerol) through beta-endorphin linked delta receptors, which inhibit substantia nigra GABAA neurons. When activated, cannabinoids, primarily 2-archydonoglcerol, can indirectly disinhibit (red hash sign) GABAA neurons by activating G1/0 coupled to CB1 receptors in the Substantia Nigra. In the dorsal raphe nuclei (DRN), glutamate neurons can then indirectly disinhibit GABAA neurons in the substantia nigra through activation of GLU M3 receptors (red hash sign). GABAA neurons, when stimulated, will, in turn, powerfully (red hash signs) inhibit VTA glutaminergic drive via GABAB 3 neurons. It is also possible that the stimulation of ACH neurons that at the nucleus accumbens ACH can stimulate both muscarinic (red hash) or nicotinic (green hash). Finally, glutamate neurons in the VTA will project to dopamine neurons through NMDA receptors (green equal sign)to preferentially release dopamine at the nucleus accumbens (NAc), shown as a bullseye, indicates a euphoria, or “wanting” response [45].

One approach to treating cocaine use disorder, like current treatment for opioid use disorder, is replacement therapy using opioids like buprenorphine [46]. Castells et al. [47] showed that although psychostimulants improved cocaine abstinence compared to placebo, treatment retention did not improve in some analyses. Along these lines, Guo et al. [48] pointed out that there are no FDA approved medications for PUD. However, there is considerable interest in utilizing naltrexone (NTX), a non-selective opioid receptor antagonist, in preventing, for example, methamphetamine relapse. Guo et al. [48], utilizing a rodent model, found that acute NTX (40 mg/kg) intragastrically administered significantly reduced cue-induced drug-seeking behavior after extinction training. Similarly, intragastrical administration of NTX (30 mg/kg) significantly disrupted conditioned place preference (CPP) reactivated by intraperitoneal injection of methamphetamine (0.5 mg/kg).

Both acute and long-term methamphetamine use is associated with

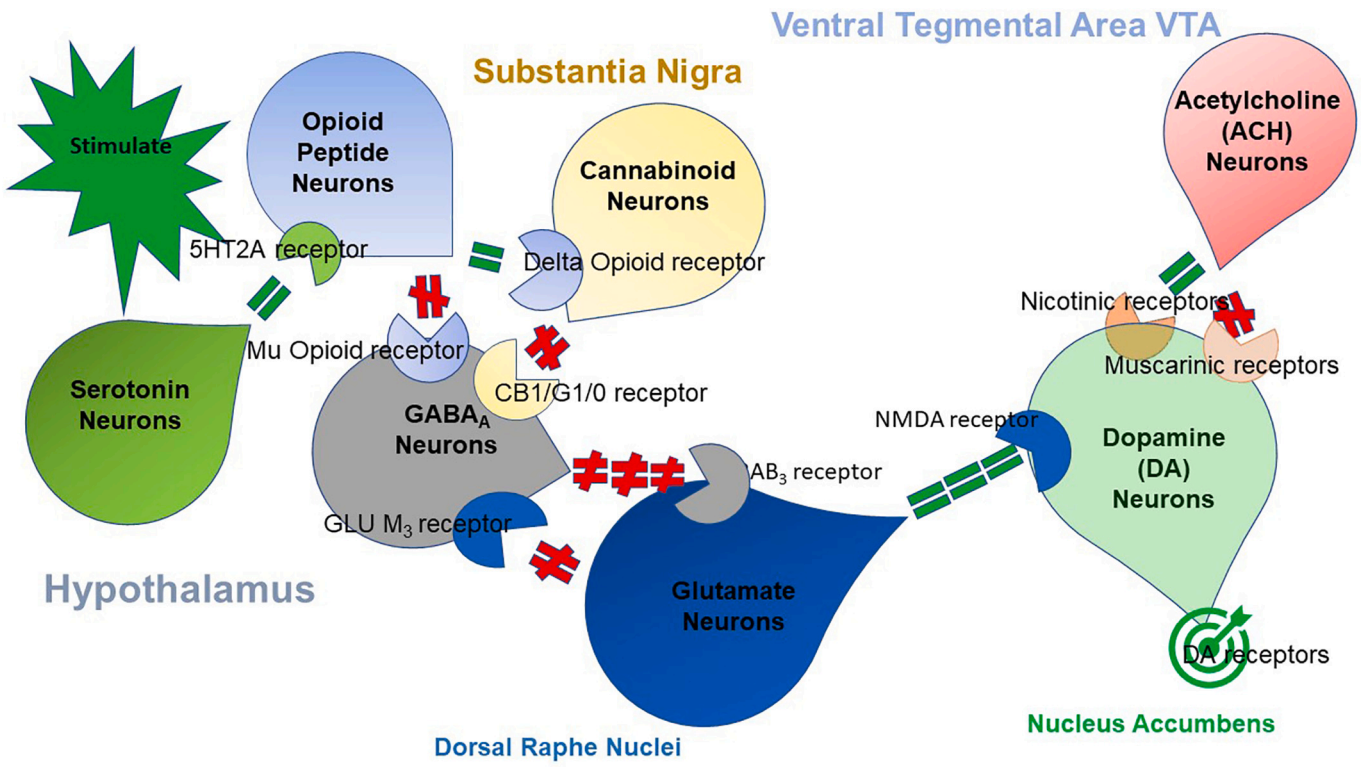

Fig. 1. The brain reward cascade.

cognitive dysfunction in several domains; however, there has been some argument against the acute impairment effects [49] despite dopamine depletion. For example, in animals, D3 receptor antagonists reverse the NMDA receptor blockade's behavioral manifestations and improve cognitive performances in various paradigms [50].

2.3. Chronic psychiatric effects of methamphetamine

Chronic abuse of methamphetamine contributes to anxiety, depression, aggressiveness, social isolation, psychosis, mood disturbances, and psychomotor dysfunction [28,33,51,52]. One interesting aspect of chronic methamphetamine psychosis is the complaint of ants or other bugs crawling in the chronic methamphetamine users' skin. Clinicians call this sign formication, delusions of parasitosis, or Ekbom syndrome [53,54].

Withdrawal from methamphetamine can produce anhedonia, irritability, fatigue, impaired social functioning, and intense craving for the drug [28,52]. There is compelling evidence that MAUD's negative neuropsychiatric consequences are, at least in part, due to drug-induced neuropathological changes in the exposed brains of these individuals [33,55]. The brain regions affected might account for the cognitive deficits include the frontostriatal and limbic circuits.

Methamphetamine has potent well-established psychostimulant effects and can induce psychosis with recreational and chronic use; some develop a persistent psychotic syndrome that shows similarities to schizophrenia [56]. However, Wearne et al. [56] provide an important clinical difference between acute induction of psychosis by methamphetamine and true schizophrenia as a mental condition. Specifically, they suggest the cognitive and behavioral symptoms are evidence that there are divergent aspects. Schizophrenia is associated with pronounced thought disorder and cognitive deficits mediated by the parietal cortex, such as difficulties with selective visual attention, while visual and tactile hallucinations appear to be more prevalent in acute methamphetamine-induced psychosis. Notably, the clinical significance based on this differential in symptoms provides a basis to distinguish between acute methamphetamine psychosis that represents a psychotic disorder distinct from schizophrenia [57].

Long non-coding RNAs (lncRNAs) play a crucial role in regulating neural diseases, including schizophrenia and SUD [58,59]. Miat and Neat2 PFC expression significantly decreased in the schizophrenia model mice, regardless of whether methamphetamine or MK801 induced the disease. Further, Li et al. [59] measured levels of these lncRNAs in the peripheral blood collected from treated and untreated patients with schizophrenia and healthy controls. They found significantly decreased levels of Neat1 and Neat2 in the peripheral blood of untreated patients with schizophrenia, but the trends in the expression of these lncRNAs nearly reached normal levels in treated patients with Schizophrenia.

Furthermore, crack users show a higher prevalence of psychiatric comorbidities - particularly antisocial personality disorders - compared to powder cocaine users [60]. Areal et al. [60] hypothesized that reduced PFC dopamine tone of patients mediates negative and cognitive symptoms of schizophrenia. They suggested that enhanced expression of D2R short isoform (D2S) in the PFC of such patients or hyperfunctioning NMDA receptors in this region might explain these symptoms. In fact, there is evidence for reduced dopamine tone in the PFC of mice exposed to crack smoke [61]. Areal et al. [60] found that upon crack inhalation, mice have shown decreased social interaction and working memory deficits analogous to schizophrenia's symptoms, along with increased D2S/D2L expression ratio and decreased expression of NR1, NR2A, and NR2B NMDA receptor subunits in the PFC.

2.4. Acute neurological effects of methamphetamine

Methamphetamine, similar to other psychostimulants such as cocaine, is a potent sympathomimetic that results in the release of norepinephrine and dopamine from synaptic nerve endings and causes an elevation of pulse rate and blood pressure [62]. Therefore, it is not surprising that the abuse of this drug is associated with neurological abnormalities, including ocular abnormalities [63] and increased risks

of strokes among users of this substance [64–72]. Strokes occur in many young patients and cause morbidity and mortality in methamphetamine using individuals. Kaku and Lowenstein [67] assessed the role of substance use disorders in presenting strokes in individuals aged 15 to 45. They reported that they were able to identify 21 cases of strokes associated with amphetamines. Hemorrhagic strokes appear to be the most common presentation of amphetamine-related strokes. In their report of drug-associated strokes, Perez et al. [70] reported that 2/4 were hemorrhagic. Urines were positive for amphetamines in all 4 cases. In another study, Darke et al. [64] reviewed cases of fatal strokes in Australia between 2009 and 2015. They found 38 cases, 37 of which were hemorrhagic. There appear to be poorer outcomes in patients who present with methamphetamine-induced hemorrhagic strokes than other stroke patients [68,73]. Hemorrhagic strokes are probably secondary to hypertensive crises elicited by high doses of the drug [65,70] and the presence of cerebral aneurysms in users' vessels [65,74]. Indeed, high blood pressures range around 190/120 to 250/160, and people with MAUD have presented with irregular beading of vessels and occlusive changes in their small arteries [75–77].

In addition to strokes, methamphetamine users can also present acutely with seizures [66,78]. Isoardi et al. [66] reviewed the clinical presentations courses of 329 patients who presented to an emergency department. They found that two patients presented with seizures, and 21 had rhabdomyolysis. Rhabdomyolysis can be a lethal complication of methamphetamine [79] because it can lead to kidney failure and its associated medical and neurological consequences [80]. Rhabdomyolysis is often a complication of methamphetamine-induced hyperpyrexia, which is almost always a sign of amphetamine intoxication [81]. Matsusue et al. [82] examined susceptibility genes from autopsy samples of 18 methamphetamine abusers. Examination of mutations in the ryanodine receptor 1 (RYR 1), carnitine palmitoyltransferase II (CPT II), a very-long-chain acyl-CoA dehydrogenase (VLCAD), and cytochrome P450 (CYP) 2D6 genes were performed. In two cases, different identified RYR1 mutations that caused amino acid substitutions (612)Ala>Thr and (4295)Ala>Val. A new mutation (54Glu) > Ala was found in the CPT II gene in one case, while in 17 cases, there were mutations that did not change activity. Also, mutations that did not change the VLCAD gene activity occurred in six cases. Homozygosity in the CYP2D6 gene for CYP2D6*10, associated with a significant reduction of metabolic activity in three cases, while two cases carried a different previously unreported missense mutation (344)Arg > Gln and (48)His>Tyr. The new CPT II mutation RYR1 identified in the study was not observed in a control group [81]. However, despite all of this work, the authors found no significant mutations that reduced enzyme activity in the suspected cases of rhabdomyolysis and no direct genetic link to rhabdomyolysis.

2.5. Chronic neurological effects of methamphetamine

Studies in animals have found significant methamphetamine-induced neurodegenerative changes in brain dopaminergic areas (see [62] for a comprehensive review). Therefore, it was necessary to document if similar changes with clinical ramifications occurred in humans. These ideas were tested by Callaghan et al. [36,83], who reported that the risk of developing Parkinson's disease was 75% higher among methamphetamine abusers compared to a control group. They also observed higher risk in MAUD users compared to cocaine users, suggesting that methamphetamine might have been a specific culprit due to known damage to the dopaminergic system that methamphetamine does not share with cocaine. Moreover, the administration of toxic doses of methamphetamine to rodents is associated with reactive astrocytosis and microglial activation [62] in various brain regions. Sekine et al. [37,84] tested the possibility that human methamphetamine users might also exhibit microgliosis in their brains and found increased markers of activated microglia in the midbrain, striatum, thalamus, orbitofrontal cortex, and insular cortex of methamphetamine abusers. Because reactive microglial cells can produce reactive, toxic compounds [38], and methamphetamine-induced Parkinsonism might be related to the chronic toxic effects of these cells on neurons [39].

Other movement abnormalities observed in methamphetamine users include motor stereotypies and choreoathetoid movements [40,85,86]. Motor stereotypies may include bizarre, aimless, and repetitive movements such as drawing or writing [86] defined as punding [41]. There seem to be some differences between men and women in the manifestation of these stereotypic movements. Men appear to repetitively manipulate such items as clocks, watches, or radio sets, whereas women would brush their hair, polish their nails, or re-arrange items in their purses [41,86]. Patients with Parkinson's disease receiving levodopa treatment have similar movement abnormalities [87]. Choreoathetoid movements include repetitive writhing movements of the face, including abnormal movements of the mouth and tongue, head, arms, and lower extremities with a dance-like quality [40,85,88]. Rhee et al. [88] described one patient who had a rolling motion of his arms and writhing motion of his trunk. Urine toxicology screens are almost always positive for methamphetamine or amphetamine, the major metabolite of methamphetamine. Similar to choreoathetosis observed in other neurological disorders, the movement abnormalities disappear during sleep. Clinicians need to note that some of these movement abnormalities can last a very long time even after the patients abstain from taking the offending agent [85]. Management of these cases has included benzodiazepines and dopamine D2 antagonists, with variable degrees of success [40,88]. However, given the complications associated with these drugs, it would be preferable to observe patients who present with abnormal movements associated with methamphetamine. In severe cases, activated charcoal is also more advisable than using psychiatric drugs with addictive potentials or with side effects that also include abnormal movements.

3. Neurobiological aspects of psychostimulant abuse and interventions

The FDA has not yet approved any agent to treat psychostimulant dependence. Dopaminergic signaling is a widely accepted key factor in the initiation and continued motivation to use the stimulant class of substances. Psychostimulants like cocaine release large amounts of neuronal dopamine at the NAc and have potent inhibitory effects on the dopamine transporter system, further increasing synaptic dopamine.

Trace-amine-associated receptor 1 (TAAR1) gene, thought to be intronless, is a G -protein-coupled receptor activated by trace amines including beta-phenylethylamine, p-tyramine, octopamine, and tryptamine. The encoded protein responds little or not to dopamine, serotonin, epinephrine, or histamine but responds well to the trace amines. TAAR1 agonists trace amines reduce the neurochemical effects of cocaine and amphetamines and attenuate SUD associated with these two psychostimulants [89]. The mechanism involves blocking dopamine's firing rate in the limbic system, conserving dopamine, and decreasing the hyperdopaminergic state caused by psychostimulant induced excessive dopamine release. The opposite is true for TAAR1 antagonists [89–96].

Based on many studies, weakened tonic and improved phasic dopamine discharge lead to a hypodopaminergic/glutamatergic trait are salient features of reward deficiency syndrome (RDS). One treatment that may help is the pro-dopamine mixture KB220. In many clinical trials and neuroimaging studies, KB220 variants have been shown to enhance resting-state functional connectivity in humans (abstinent heroin addicts), naïve rodent models, and to regulate extensive theta action in the cingulate gyrus of abstinent psychostimulant abusers [97,98].

3.1. Neurogenetic impact: a brief snapshot of hypodopaminergia

3.1.1. Serotonin

Improved prevention and treatment of drug addiction will require a

deeper understanding of genetic factors contributing to susceptibility to excessive drug use [97,98]. Selective breeding of a mouse model can aggregate 'addiction alleles' and be used to identify the coordinated effects of multiple genes. Wheeler et al. [99] were the first to utilize selective breeding for self-administration of any psychostimulant drug mouse lines that could orally self-administer high (MAHDR) or low (MALDR) amounts of methamphetamine. The results of conditioned place preference and taste aversion indicate that compared to MALDR mice, MAHDR mice are less sensitive to the aversive effects and relatively more sensitive to the rewarding effects of methamphetamine. Moreover, genes differentially expressed in the drug-naïve state, including Slc6a4 (serotonin transporter), Htr3a (serotonin receptor 3A), Rela [nuclear factor kappaB (NFkappaB)], and Fos (cFos). These genes represent candidates whose expression levels may predict methamphetamine consumption, susceptibility to methamphetamine, and reward and aversion.

3.1.2. Cannabinoid

Sensitization to cocaine and amphetamine was augmented after early life ethanol exposure might partly explain an elevation in the rewarding properties of psychostimulants. Gene expression analysis revealed that the expression of many genes, including CB1 receptor type genes, were altered in the neurological regions involved in the reinforcing effects of psychostimulant abuse [100].

3.1.3. Glutamine

In the central nervous system, glutamate is the primary excitatory neurotransmitter related to the behavioral effects of psychostimulant drugs. Notably, imbalances in glutamate homeostasis, a key feature of the glutamatergic hypothesis of addiction, may be assisted by the presynaptic synthesis of glutamate by brain glutaminases [101]. Glutaminases are the main glutamate-producing enzymes in the brain, and dysregulation of their function associated with neurodegenerative diseases and neurological disorders. Despite a lack of clarity about the molecular mechanisms that regulate drug-induced neuronal sensitization and behavioral plasticity, recent findings from mouse models have shown that drugs induce changes in the expression profiles of key glutamatergic transmission genes. Blanco et al. [102] found that animals following chronic cocaine-sensitization exhibited decreased total glutaminase activity in both the dorsal striatum and the PFC associated with an increase in kidney glutaminase (KGA) mRNA expression in these brain areas. They suggested that chronic cocaine administration modulates glutamate production through the regulation of glutaminase expression and activity. These actions were observed mainly in the PFC-dorsal striatum circuit, the neuroanatomical target for the psychostimulant sensitization properties of cocaine.

3.1.4. GABA

Inhibitory gamma-aminobutyric acid (GABA)-mediated neurotransmission plays an essential role in regulating the PFC. Increasing evidence suggests that dysfunctional GABAergic processing of the PFC may underlie certain deficits reported across psychotic disorders. Wearne et al. [103] found that a methamphetamine challenge resulted in a significant sensitized behavioral (locomotor) response in methamphetamine pretreated animals compared with saline pretreated controls. The metabotropic GABAB1 receptor, and mRNAs of transporters (GAT1 and GAT3), ionotropic GABAA receptor subunits (α3 and β1), were upregulated in the PFC of sensitized rats compared with saline controls. These findings indicate that after sensitization to methamphetamine, GABAergic mRNA expression alters at pre and postsynaptic levels; the result is transcriptional upregulation of several inhibitory genes. The consequences of these GABA-mediated neurotransmission changes are important in the PFC and may underlie some symptoms of executive dysfunction and psychotic disorders.

3.1.5. Dopamine

La Foll et al. [104] reviewed the literature implicating the receptors of the D1 family (DRD1 and DRD5) and of the D2 family (DRD2, DRD3, and DRD4) in drug addiction, including psychostimulants. This meta-analysis of the studies evaluating DRD2 and drug and alcohol dependence indicates a significant association. Overall, this review in-part indicates that dopaminergic function is affected by the interrelatedness of a myriad of chemical messengers in the brain reward circuitry and their associated genetic polymorphisms. These polymorphisms, in turn, may influence many of the pharmacological properties and addictiveness of psychostimulants. Chronic cocaine exposure results in long-lasting neuroadaptations that involve gene expression mediated by dopamine and alterations in cellular signaling in different brain regions, such as the striatum. Solís et al. [105] found that cocaine- and amphetamine-induced behavioral sensitization is deficient in D2−/− knockout mice. In naïve- and in cocaine- or amphetamine-treated D2−/− mice, the expression of dynorphin and a marker of direct-pathway striatal neurons, primarily regulated by D1R, is reduced.

Moreover, c-Fos expression observed in D2−/− mice was reduced in acutely but not in chronically treated animals. Inactivation of D2R increased c-Fos expression in neurons of the striatopallidal pathway. The elimination of D2R blunted the locomotor and striatal c-Fos response to the full D1 agonist, SKF81297. In conclusion, D2R is critical for developing behavioral sensitization and the associated gene expression after cocaine administration.

3.1.6. Catechol-O-methyltransferase (COMT)

The function of catechol-*O*-methyltransferase (COMT) is the degradation of catecholamines, and a functional polymorphism (Val158Met) may influence enzyme activity. A study of African descent individuals found that the (Val158Met) variation in COMT increases cocaine dependence risk. The low enzyme activity 158Met allele or haplotypes containing this variant might have functional effects on dopamine-derived reward processes and cortical functions, resulting in increased susceptibility for cocaine dependence [106].

One study from Noble et al. [107] found that the prevalence of the A1 allele in cocaine-dependent (CD) subjects ($n = 53$) was 50.9%. It was significantly higher than either the 16.0% prevalence ($P < 10(-4)$) in non-substance abusing controls ($n = 100$) or the 30.9% prevalence ($P < 10(-2)$) in population controls ($n = 265$) wherein substance abusers were not excluded. Moreover, a significantly higher prevalence ($P < 10(-2)$) of the B1 allele was found in CD subjects ($n = 52$) compared with non-substance abusing controls ($n = 53$); 38.5% vs. 13.2%. Logistic regression analysis of CD subjects identified potent routes of cocaine use and the interaction of early deviant behaviors and parental alcoholism as significant risk factors associated with the A1 allele. The cumulative number of these three risk factors in CD subjects was positively and significantly ($P < 10(-3)$) related to A1 allelic prevalence. The data shows a strong association of the minor alleles (A1 and B1) of the DRD2 with cocaine dependence.

3.1.7. Opioid

The identification of genes influencing sensitivity to opioids [108] and stimulants [109] may provide fundamental insights into the genetics of drug abuse and are important for determining their mechanism of action. To identify and quantify trait loci (QTL) for both open field activity and sensitivity to the locomotor stimulant response to methamphetamine, Bryant et al. [109] used a panel of C57BL/6 J (B6; recipient)x A/J (donor) chromosome substitution strains (CSS). They used association mapping of cis expression QTLs and bioinformatic resources to parse genes within the confidence interval 95% of the chromosome 11 QTL. Both psychostimulants and opioids increase dopamine release associated with locomotor stimulation and the subjectively rewarding effects of these drugs in humans [110]. Dopamine- and cyclic AMP-regulated phosphoprotein-32 (DARPP-32) is a potent phosphatase inhibitor expressed highly in dopamine-receiving neurons in the NAc

[111] that modulates both psychostimulant-induced locomotor activity [112] and opioid-induced locomotor activity [113].

Although there is a substantial overlap between divergent substance and non -substance use disorders, different classes of abused drugs, including opioids (heroin, morphine, and oxycodone, other opioids) and psychostimulants (cocaine and amphetamines) tend to cause different neuroadaptations in various brain regions dependent in the distribution and concentration of their biochemical sites of actions [114]. Cadet's group reviewed the literature and provided evidence for the effects of psychostimulants and opioids on immediate-early genes (IEG) expression in the brain [115]. While the review identified some contrasting effects of these classes of drugs on gene expression, the end result following chronic abuse of these seemingly different drugs is indeed hypodopaminergia.

The μ-opioid receptor is involved in the rewarding effects of not only opioids like morphine but also psychostimulants like amphetamine. Dlugos et al. [116] reported that oprm1 gene variants modulate amphetamine-induced euphoria in humans, especially rs1799971 and rs510769, and a three-SNP haplotype formed with rs1918760, rs2281617, and rs1998220.

4. Methamphetamine, neurological deficits, and potential treatment outcomes

Despite these caveats, the nature and magnitude of cognitive deficits associated with chronic MAUD increase the risk for poorer health outcomes, unemployment, high-risk behaviors, treatment non-adherence, and relapse [117]. For example, patients with a history of MAUD complain of cognitive problems and difficulties of every-day functioning [118], and poor cognition appears to be a factor in poor treatment outcomes [117]. Patients who have deficits in executive function and memory maintain elevated drug-seeking behaviors [119].

Neurologists need to become familiar with the presentations of patients who suffer from methamphetamine use disorders because of the complex neuropsychiatric signs and symptoms they present to emergency rooms. The many neurochemical effects of methamphetamine on the brain significantly impact their neurological care. These issues are relevant because of the increased prevalence of some of these neurological problems in young methamphetamine users.

4.1. An overview of current treatment options related to a psychostimulant use disorder

Substance use disorders are a severe and chronic health problem. Relapse rates are 60 to 80% —after the first year of medication-assisted treatment. The immense complexity of brain functions and dysfunctions has kept neuroscience in almost a perpetual state of infancy, lacking "out the box" thinking. Addiction to cocaine or methamphetamine is indeed most perplexing, and PUD may be the SUD most in need of a better solution. While there are many clinical trials underway looking at using existing medications in an off-label fashion, there are currently no medications approved explicitly for either stimulant.

One important caveat in terms of treating cocaine and or amphetamine-type drugs is that unlike, for example, opioids having specific type opioid receptors, these psychostimulant drugs do not have a discrete target for pharmaceutical intervention. Instead, these drugs use multiple brain pathways to produce their effects, and a single compound is unlikely to exert sufficient control over the entire mechanism. With this in mind, the proposal is to find ways to target the multiple neurotransmitter deficits caused by PUD utilizing the BRC as a blueprint seems prudent (see Fig. 1).

There are two types of treatment modalities to consider; pharmacodynamic and pharmacokinetic. Pharmacodynamic drugs work in the brain at the site where the substance acts; agonism or antagonism helps stimulate or block, for example, opioid receptors. Pharmacokinetic drugs included vaccines and monoclonal antibodies, and even gene therapy that break-down the substance while it is still in the bloodstream, are immune-based therapies that work before the substance crosses the blood-brain barrier [120,121]. For potential treatment outcomes using both pharmacodynamic and pharmacokinetic modalities, see Table 1.

4.2. Dopamine agonist therapy: D2 or not D2?

Researchers have known for decades that the neurotransmitter dopamine plays a significant role in the addiction process, and treatment and scientists have focused on it, but unfortunately, this approach has not generated a 'magic bullet." Dackis & Gold [122] pioneered the seminal dopamine depletion concept of cocaine abuse and suggested dopamine D2 agonism utilizing the powerful D2 agonist bromocriptine. The result, chronic downregulation of D2 receptors, is one example of how a singular treatment may not work [122,123].

However, other work provides evidence for possible augmented dopamine function to treat and prevent relapse in PUD [124–127]. This polypharmacy platform seminal work could provide important information that may significantly improve the recovery of individuals with psychostimulant and polydrug abuse problems, specifically those with genetically induced dopamine deficiency [128]. This finding is in agreement with the work of Volkow et al. et al. [129] and others [130] in terms of brain electrical activity and short circuit activity in addiction.

Other alternatives involve dopamine transport blockers (DTBs), dopamine receptor antagonists (DRAs), and dopamine enzyme inhibitors (DEIs). Each targets a different aspect of dopamine.

4.3. Dopamine transport blockers

Dopamine transport blockers (DTB) increase dopamine in the receptor by blocking the transport or "reuptake" of dopamine. They were initially developed to treat depression, reuptake inhibitors that target serotonin (rather than dopamine). The development of DTB to treat addiction has been without success. The compound NS-2359 is a case in point, a triple reuptake inhibitor that works on dopamine, serotonin, and norepinephrine to keep levels of all three of these neurotransmitters high. After failing in Phase II trials for depression, it was explored in alcohol and cocaine addiction for more than a decade. A trial with cocaine-experienced individuals, however, failed (personal communication). A host of D3-specific compounds for nicotine, cocaine, alcohol, methamphetamine, or heroin, including SB-277011A, SB-414796, compound 35, and NGB 2904, are in early-stage development, which could take 20 years and cost billions [131].

4.4. Dopamine enzyme inhibitor

The most promising dopamine enzyme inhibitor targets the enzyme beta-hydroxylase is nepicastat, aka SY sN117. Disulfiram, approved to treat alcoholism, uses the same mechanism of action. In several controlled clinical trials for cocaine, Disulfiram was modestly successful. Blocking dopamine beta-hydroxylase will increase dopamine and potentially reduce cocaine cravings [132]. Currently, there are no published data on SYN117, but it is in clinical trials.

Interestingly, treatment targets now include specific neurotransmitters like glutamate, endocannabinoids, and GABA. These include glutamate-enhancers like *N*-acetylcysteine and modafinil, and GABAergic medications, like topiramate, which target endocannabinoids, and transcranial magnetic stimulation (TMS) [133–135].

4.5. Vaccines and monoclonal antibodies

The experimental addiction treatments with the highest-profile of all are vaccines. Vaccines are pharmacokinetic therapies that trigger the immune system to produce antibodies to target the substance while still in the bloodstream, blocking or reducing its passage into the brain.

Table 1
Potential treatment outcomes: pharmacodynamic and pharmacokinetic modalities.

Proposed treatment	Comments	Reference (s)
rTMS	rTMS was found to be effective in five studies at 86/128 (67%) subjects	Makani R, Pradhan B, Shah U, Parikh T. Role of Repetitive Transcranial Magnetic Stimulation (rTMS) in Treatment of Addiction and Related Disorders: A Systematic Review. Curr Drug Abuse Rev. 2017;10(1):31–43.
Pro-dopamine regulation	Neuro-nutrient called KB220 was found to be effective in at least 38 studies: AMA rate, attenuation of craving behavior, reward system activation including BOLD dopamine signaling, relapse prevention, as well as a reduction in stress, anger, and aggressive behaviors.	Blum K, Modestino EJ, Gondre -Lewis et al. Pro-Dopamine Regulator (KB220) A Fifty-Year Sojourn to Combat Reward Deficiency Syndrome (RDS): Evidence-Based Bibliography (Annotated). CPQ NeurolPsyc2018; 1(2) 2018
Dopamine transport blockers (DTB)	The compound NS-2359 is a case in point, a triple reuptake inhibitor that works on dopamine, serotonin, and norepinephrine to keep levels of all three of these neurotransmitters high (see personal communication comments in the text).	A search in PUBMED revealed zero publications
Dopamine D3 and D4 antagonists	Buspirone is an antagonist of both D3 and D4 receptors and produced a marked downward shift in the dose-effect function for cocaine-maintained behavior, reflecting substantial decreases in self-administration of one or more unit doses of IV cocaine in each subject.	Bergman J, Roof RA, Furman CA, Conroy JL, Mello NK, Sibley DR, Skolnick P. Modification of cocaine self-administration by buspirone: potential involvement of D3 and D4 dopamine receptors. Int J Neuropsychopharmacol. 2013 Mar;16(2):445–58.
Dopamine enzyme inhibitor targets the enzyme beta-hydroxylase is nepicastat, aka SY sN117	While to date, there are no published studies on SY sN117 per se with repeated measures analysis of variance, corrected for population structure, disulfiram pharmacotherapy reduced cocaine-positive urines from 80% to 62% ($p = .0001$), and this disulfiram efficacy differed by DBH genotype group. Patients with the normal DβH level genotype dropped from 84% to 56% on disulfiram ($p = .0001$), whereas those with the low DBH level genotype showed no disulfiram effect.	Kosten TR, Wu G, Huang W, Harding MJ, Hamon SC, Lappalainen J, Nielsen DA. Pharmacogenetic randomized trial for cocaine abuse: disulfiram and dopamine β-hydroxylase. Biol Psychiatry. 2013 Feb 1;73(3):219–24.
Vaccines	Cocaine vaccines have been in clinical trials but have not been as effective as hoped mainly because of difficulty in evoking a sufficiently large antibody response	Orson FM, Wang R, Brimijoin S, Kinsey BM, Singh RA, Ramakrishnan M, Wang HY, Kosten TR. The future potential for cocaine vaccines. Expert Opin Biol Ther. 2014 Sep;14 (9):1271–83.
Monoclonal antibodies	The human (gamma1 heavy chain)/murine (lambda light chain) chimeric mAb 2E2 has excellent affinity and specificity for cocaine, and recent animal studies have demonstrated 2E2's ability in vivo to reduce cocaine levels in the brain as well as alter cocaine self-administration behavior in rats.	Lape M, Paula S, Ball WJ Jr. A molecular model for cocaine binding by the immunotherapeutic human/mouse chimeric monoclonal antibody 2E2. Eur J Med Chem. 2010 Jun;45(6):2291-8.

Nicotine and cocaine vaccines have been in clinical trials but have not been as effective as hoped mainly because of difficulty in evoking a sufficiently large antibody response [136]. Monoclonal antibodies (mAbs), another type of pharmacokinetic, are produced in the lab and then injected into a patient [137]. Developed and effective in animals against cocaine, amphetamine, PCP, and heroin, they are but not yet tested in people.

Notably, while possibly an exciting academic experiment, the use of vaccines may not have great clinical acceptance. The very specific drug by drug nature of vaccines impairs their widespread usefulness and may make it problematic since users could develop a dependence on a different drug of choice and have no effect from these vaccines, even if mAbs endure. Even if specific mAbs like Ch-mAb7F9 [138] show some promise and may reduce the drug effect, the problem is that multiple methamphetamine effects on the brain provide no single target site.

4.6. rTMS and Psychostimulants

There is some evidence to consider repetitive transcranial magnetic stimulation (rTMS) to have heuristic value in treating chronic cocaine abuse. Pettorruso et al. [139] reported on the positive benefits of utilizing rTMS on cocaine craving intake and comorbid psychiatric symptoms. They found that after four weeks of rTMS treatment, 9 out of 16 subjects (56.25%) had a negative urinalysis test. Moreover, craving scores significantly improved, and global psychopathological issues such as depressive symptoms, anhedonia, and anxiety also significantly improved with rTMS treatment. Interestingly, they found that those patients with lower baseline scores on the SCL-90 Global Severity Index (GSI) were more likely to have benefited from this type of treatment. Ma et al. [140] accomplished a meta-analysis involving 16 units of analysis in 12 eligible studies, coded and forwarded to a random-effect analysis. In doing so, Ma et al. [140] found a highly positive main effect of stimulation (Hedge's $g = 1.116$, CI = [0.597, 1.634]). Further subgroup analysis found that only high-frequency repetitive transcranial magnetic stimulation (rTMS) could elicit a significant decrease in craving, while the outcome of low-frequency stimulation was relatively inconclusive.

4.7. Pro-dopamine regulation (KB220)

The central nervous system rewarding properties of cocaine may activate a common catecholaminergic reward system in the mesolimbic circuitry of the brain. Brown et al. studied driving-under-the-influence (DUI) offenders with cocaine-related problems by [141]. The neuro-nutrient pro-dopamine regulator Tropamine (KB220) consisting of amino-acid precursors and other nutritional substances designed to restore catecholaminergic, serotonergic, opioidergic, and GABAergic deficits in cocaine abusers, significantly attenuated relapse rates and enhanced recovery in these DUI outpatient offenders over ten weeks. Follow-up on the Tropamine group over a ten-month post-period showed a 53% overall recovery rate. Also, Blum et al. [142] in abstinent psychostimulant abusers using quantitative electroencephalographic

(qEEG) imaging in a randomized, triple-blind, placebo-controlled, crossover study involving oral KB220Z revealed an increase of alpha waves and low beta wave activity in the parietal brain region. These results indicate a phase change from low amplitude or low power in the brain to a more regulated state by increasing an average of 6.169 mV across the prefrontal cortical region. In their cohort of 14 subjects, 72% had the DRD2 Taq A1 genotype suggestive of genetic risk for psychostimulant seeking behavior. The authors concluded, "This seminal work will provide important information that may ultimately lead to significant improvement in the recovery of individuals with psychostimulant and polydrug abuse problems, specifically those with genetically induced dopamine deficiency." Other work from Blum's group [143] showed that Tropamine in cocaine abusers significantly reduced both the withdrawal against medical advice (AMA) rate and drug hunger of in-patients at a 30-day chemical dependence program. Specifically, the AMA control (no KB2220) rate was 37.5%, and for the Tropamine (KB220) group was only 1.2%, indicative of an approximate nine-fold improvement. Compared to the control group, the KB220 group showed a significant improvement of a drug hunger index (consisting of various behavioral observations and requests for benzodiazepines) measured throughout the 30-day program stay. Finally, Cold [144] provided evidence that the pro dopamine regulator KB220 significantly reduced cocaine in induced withdrawal symptoms in humans attending an in-patient residential program.

5. Summary

FDA medications to treat PUD are greatly needed to curtail dependence on these powerful drugs that cause acute and chronic neurological deficits and neurophysiological effects, including craving, alterations in mood, cognition, stroke movement, and other disorders. This article briefly reviewed these known effects and outlined some known neurogenetic associations impacted by cocaine, methamphetamine, and other stimulants utilizing articles primarily listed in PUBMED. The authors reviewed some experimental treatments and proposed that gentle D2 receptor stimulation might be accomplished via several alternative modalities outlined herein. This gentle induction of dopamine release potentially causes alteration of D2-directed mRNA and enhanced human D2 receptors' function. This proliferation of D2 receptors, in turn, will induce the attenuation of craving behavior, especially in genetically compromised high-risk populations. The comprehensive understanding of dopamine's role in the NAc as a "wanting" messenger in the mesolimbic dopamine system further supports a treatment goal of enhanced D2 receptor function. While both the scientific and, more importantly, the clinical professionals must await an approved FDA treatment for PUD, the potential induction of dopamine homeostasis, via activation of the brain reward circuitry such as repetitive transcranial magnetic stimulation (rTMS) and neuro nutrient therapy to provide dopamine may augment regulation [145,146] and help people dig out of their hypodopaminergia ditch [97].

Declaration of Competing Interest

Dr. Kenneth Blum through his company owns issued and pending patents on pro-dopamine regulation (KB220) that has been licensed to Ivitalize Inc. as a worldwide exclusive agreement. Dr. Blum owns a minor interest in Ivitalize Inc. Dr. Blum is Chairman of "The Kenneth Blum Behavioral & Neurogenetic Institute" a division of Ivitalize Inc. There are no other conflicts.

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