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Mini Review

Theorizing The Dangers of Dopamine Antagonists and Dopamine Partial Agonists in Patients with a History of Alcohol Use Disorder

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Abstract

The utilization of dopamine antagonists and dopamine partial agonists in patients with a history of alcohol use disorder (AUD) presents notable risks. This article delves into the pharmacological effects of these agents on alcohol consumption and highlights the associated dangers through a brief review of existing literature. The article describes, as an example, a case where a female prescribed a partial agonist involuntarily and unusual for this person overconsumes alcohol and causes an almost fatal accident under the influence. We explore the mechanisms by which these medications influence dopamine pathways, their potential to exacerbate alcohol consumption, and the implications for clinical practice.

Keywords: Dopamine; Antagonists; Partial Agonists; Alcohol Use Disorder (AUD)

Introduction

Dopamine is a pivotal neurotransmitter involved in the brain's reward pathway, playing a crucial role in addiction and substance use disorders [1]. Dopamine antagonists and partial agonists are widely used to manage various psychiatric conditions, including schizophrenia and bipolar disorder [2,3]. However, their effects on individuals with a history of alcohol use disorder necessitate careful consideration due to their potential to increase alcohol consumption and interfere with recovery efforts [4]. This hypothesis aims to elucidate the complexities of these interactions and provide a framework for clinicians to navigate these challenges effectively.

Mechanisms of dopamine antagonists and partial agonists

Dopamine antagonists

Dopamine antagonists, such as antipsychotic medications, function by blocking dopamine receptors, thereby reducing dopamine activity in the brain [5-10]. Commonly prescribed antipsychotics include haloperidol, risperidone, and olanzapine. These medications are effective in managing psychiatric symptoms but may adversely affect individuals with AUD by altering dopaminergic signaling, which can lead to increased alcohol consumption as a compensatory mechanism [11-14]. The neurobiological basis for this involves the disruption of the mesolimbic dopamine system, a key component of the brain's

reward circuitry, which drives the individual to seek out substances that restore dopaminergic balance [15-17].

Dopamine partial agonists

Dopamine partial agonists, such as aripiprazole, have complex effects on the brain's reward pathways. These drugs partially activate dopamine receptors while also blocking excessive dopamine activity.

In some studies, dopamine partial agonists have been shown to reduce alcohol intake, particularly in individuals with alcohol use disorder by stabilizing dopamine levels and reducing cravings. However, other studies suggest that in certain conditions or at specific doses, these drugs can paradoxically increase alcohol intake. This effect may be due to the partial agonist activity not adequately compensating for the alcohol-induced dopamine release, thereby reinforcing alcohol-seeking behavior.

For example, studies on rats have shown mixed results, with some indicating increased alcohol consumption following treatment with dopamine partial agonists, while others show decreased intake. Similarly, clinical studies in humans have reported both reductions and increases in alcohol consumption, depending on various factors such as the individual's baseline drinking behavior, the specific dopamine receptor targeted, and the dose of the medication.

Dopamine partial agonists, such as aripiprazole and brexpiprazole (marketed as Abilify and Rexulti, respectively), possess both agonist and antagonist properties at dopamine receptors [18-20]. These agents stabilize dopamine levels rather than completely blocking them, offering therapeutic benefits for conditions like schizophrenia and bipolar disorder [21-24]. Nevertheless, their interaction with the dopaminergic system can lead to unintended consequences in patients with AUD, potentially exacerbating alcohol cravings and consumption. The pharmacodynamics of partial agonists involve complex receptor interactions that can unpredictably influence neurotransmitter dynamics in the context of AUD [25,26].

Overall, the effects of dopamine partial agonists on alcohol intake are complex and can vary based on numerous factors, making it crucial to consider individual differences and specific contexts when evaluating their impact on alcohol consumption.

Increased alcohol consumption in animal models

Utilizing the word term "dopamine blockers increase alcohol" entered into PUBMED on 7/13/24, resulted in 3,055 indexed articles. We provide herein a few biased selected examples to support our hypothesis requiring further confirmation, especially clinically.

Research utilizing animal models has demonstrated that dopamine antagonists can lead to increased alcohol consumption [27,28]. For instance, studies involving rats have shown that dopamine antagonists, such as haloperidol, significantly increase alcohol intake [29]. Additionally, in mice, others found that both dopamine D1 and D2 receptor mechanisms in alcohol-seeking behavior in mice showing that subsequent blockade induces an increased motivation to seek alcohol [30]. McBride and Li suggested that both the selectively bred rats and common-stock rats systemic administration of agents that (1) increase synaptic levels of serotonin or dopamine; (2) activate 5-HT1A, 5-HT2, D2, D3, or GABA(A) receptors; or (3) block of 5-HT3 receptors decrease ethanol intake in most animal models [31].

Using inbred strains of mice that differ widely in their innate preference for and consumption of ethanol, George., *et al*. [32]. demonstrate, in ethanol-preferring C57BL/6J (C57) mice, decreased dopamine content and turnover in the terminals of the mesolimbic and mesostriatal dopamine neurons, compared with ethanol-avoiding DBA/2J and BALBc mice. These data indicate that genetically determined hypodopaminergic function in these pathways plays a role in the predisposition to high voluntary intake of ethanol [33,34]. Importantly, [32] enhancing synaptic dopamine concentrations by augmenting the synthesis by L-3-4-dihydroxyphenylalanine with carbidopa, or by decreasing its degradation by monoamine oxidase-B blockade with selegiline, led to marked decreases in ethanol preference and in the high voluntary consumption of ethanol in C57 mice. Furthermore, the selegiline-mediated reduction in ethanol preference and drinking in C57 mice could be inhibited selectively by D1 and D2 DA receptor antagonists, indicating that dopamine activity at D1 and D2 receptors plays an important role in substance seeking. The high preference for ethanol in C57 animals could be attenuated by direct DA receptor activation by either D1 or D2 agonists.

Additionally, these studies have provided insights into the specific neural circuits and molecular pathways involved, offering

potential targets for future pharmacological interventions in humans.

Clinical reports and human studies

Clinical reports and studies in humans corroborate the findings from animal models, indicating that dopamine antagonists and partial agonists may contribute to increased alcohol consumption in individuals with AUD. In one study, European double-blind multicenter clinical trial, by Walter., *et al.* [35] comparing the D1, D2, D3 antagonist flupenthixol and placebo in 281 chronic alcohol-dependent patients (27.4% women) showed a significantly higher relapse rate and in the dopamine antagonist group compared to placebo.

A notable study found that patients with schizophrenia treated with dopamine antagonists exhibited higher alcohol consumption compared to those not on these medications [36]. In fact, Schizophrenia affects >3.2 million people in the USA. Lu., *et al.* [36] conducted an observational study using a cohort of 86 million patients in a nationwide health insurance dataset. Their results show that anxiety, posttraumatic stress disorder, and substance abuse commonly occur in adolescents and young adults prior to schizophrenia diagnoses. Furthermore, Green., *et al*. [37] pointed out that "*standard [D2 receptor blockers] , or typical, antipsychotic drugs do not limit such substance use and may even render it more likely".* In addition, they further suggest that *" ....the biological basis of substance use relates to a "reward-deficiency syndrome" secondary to dysfunctional dopamine-mediated mesocorticolimbic neurons in these individuals".*

Additionally, aripiprazole and brexpiprazole have been associated with mixed outcomes, with some patients reporting increased alcohol cravings and consumption. Specifically, brexpiprazole has been noted for its interactions with alcohol, potentially exacerbating the risks of increased consumption and adverse effects [38-45]. These findings underscore the necessity for individualized treatment plans and highlight the importance of understanding patient-specific factors that may influence these outcomes. In essence, although discussed in detail elsewhere [46], for early identification related to DNA polymorphic antecedents leading to RDS (e.g. alcohol seeking) behaviors.

Case Study: involuntary intoxication in a 46-year-old female psychotherapist

This case study explores the involuntary intoxication experienced by a 46-year-old female psychotherapist (LCSW) under psychiatric care for anxiety, depression, and PTSD. The patient's experience highlights the critical need for thorough patient education and screening for substance use disorders when prescribing psychotropic medications.

Patient background

The patient, a licensed clinical social worker, was undergoing treatment for anxiety, depression, and PTSD, primarily stemming from contentious Family Court issues and an investigation into the sexual abuse of her 7-year-old daughter. This investigation led to the arrest of her ex-husband.

Medication initiation

The patient's psychiatrist prescribed brexpiprazole (Rexulti) to manage her symptoms. It was the first time the patient had been prescribed this medication, and she was given sample packs without comprehensive warnings regarding alcohol consumption or potential side effects.

Adverse reaction and incident

On the first day of taking brexpiprazole, the patient consumed significantly more alcohol than usual, an occurrence that had never happened before. The following day, she experienced episodes of browning out and blacking out but continued taking the medication. Throughout that day, she continued drinking excessively, leading to near-complete memory loss of the day's events.

The day culminated in a multi-car accident around 5:00 PM. Details of whether she caused the accident, which resulted in injuries and a loss of life, remain unclear due to her impaired state. The patient only became aware of her actions when she was placed in a police car and subsequently arrested on eleven different driving violation charges.

Medical considerations

The patient's treatment team for Alcohol Use Disorder (AUD) believes that the antagonism and agonism of dopamine receptors in this patient, who has been genetically tested and found to have Reward Deficiency Disorder or hypodopaminergic conditions,

led to her binge drinking episode. Genetic testing revealed a high genetic burden for alcohol use disorder, including significant impairment of the dopamine reward system.

Legal considerations

Consultation with legal experts suggests that this case might meet the criteria for involuntary intoxication. Key points include:

- The psychiatrist did not screen the patient for alcohol use disorder before prescribing brexpiprazole.
- The patient was not warned about the potential for increased alcohol consumption as a side effect of the medication.
- The sample package lacked adequate warnings about the interaction between alcohol and brexpiprazole.

Given these factors, the patient's defense may argue that her actions were a result of involuntary intoxication induced by the medication, potentially mitigating her legal responsibility for the incident.

This case underscores the importance of

- Thorough screening for SUD before prescribing medications with known side effects related to alcohol consumption.
- Providing clear, comprehensive warnings about the potential interactions between psychotropic medications and alcohol.
- Ensuring patients are fully informed about the risks associated with new medications, particularly those affecting mental health and behavior.

The tragic outcome of this case highlights the need for improved communication and preventive measures in psychiatric care. Ensuring patients are adequately screened and informed can prevent similar incidents and improve overall patient safety.

Common drugs and lack of warnings

The following medications have been identified as posing a risk for increased alcohol consumption in patients with AUD

- Haloperidol
- Risperidone
- Olanzapine
- Aripiprazole (Abilify)
- Brexpiprazole (Rexulti)

Despite the evidence, there is a conspicuous absence of warnings on prescription labels regarding the potential for increased alcohol consumption associated with these medications. This lack of labeling can lead to unawareness among patients and healthcare providers, thereby increasing the risk of adverse outcomes. The absence of these warnings raises concerns about the adequacy of current pharmacovigilance practices and highlights the need for more rigorous post-marketing surveillance and patient education initiatives. Furthermore, liability may arise for healthcare providers who fail to advise patients about these risks, emphasizing the importance of informed consent and comprehensive patient counseling.

Implications for clinical practice

The potential for dopamine antagonists and partial agonists to increase alcohol consumption in individuals with a history of AUD presents significant challenges for clinicians. It is imperative to meticulously monitor patients on these medications and consider alternative treatments when managing co-occurring psychiatric conditions and AUD. Clinicians should also educate patients about the risks and work collaboratively to develop comprehensive treatment plans that address both psychiatric and substance use disorders. The integration of addiction medicine principles into psychiatric care is essential for optimizing outcomes and ensuring patient safety.

Recommendations for Clinicians

- **Patient Education**: Inform patients about the potential risks associated with dopamine antagonists and partial agonists, emphasizing the importance of monitoring alcohol consumption. Provide clear, accessible information about the signs of increased alcohol use and encourage open communication about any changes in drinking behavior.
- **Alternative Therapies**: Consider alternative pharmacological and non-pharmacological treatments for managing psychiatric symptoms in patients with AUD. Explore the use of medications with a lower risk of influencing alcohol consumption and incorporate behavioral interventions that support sobriety and mental health (e.g. cognitive behavioral therapy, awareness integration therapy, neuromodulation, acupuncture, brain spotting, nutraceuticals, diet etc.).
- **Regular Monitoring**: Implement regular monitoring of

alcohol consumption and psychiatric symptoms to identify and address any adverse effects promptly. Utilize tools such as urine drug screens, breathalyzers, and standardized questionnaires to systematically assess alcohol use and its impact on psychiatric treatment.

- **Integrated Care Plans**: Develop integrated care plans that encompass both psychiatric and substance use disorder treatments, ensuring a holistic approach to patient care. Collaborate with addiction specialists, primary care providers, and mental health professionals to coordinate care and address the multifaceted needs of patients with co-occurring disorders.
- **Screening for AUD**: Implement routine genetic screening for AUD in patients being considered for treatment with dopamine antagonists and partial agonists. Early identification of AUD can inform treatment decisions and help mitigate the risks associated with these medications.
- **Contraindications and Caution**: Recognize that dopamine antagonists and partial agonists should be contraindicated or used with extreme caution in patients with a history of AUD. Assess the risk-benefit ratio for each patient, considering alternative treatment options when appropriate.

Summary

Midbrain dopaminergic neurons (MDN) comprise approximately 0.0005% of the brain's neuronal population and play critical roles in mediating critical functions including cognition, food intake, and metabolism. MDN is also posited to underscore the pathophysiology of many neuropsychiatric disorders, characterized by multifactorial medical comorbidities, including metabolic disease, contributing to markedly increased morbidity and mortality [47]. The coexistence of multiple psychiatric conditions, known as psychiatric comorbidity [48], has garnered substantial attention due to its high prevalence and long-lasting impact [49].

It is known that lifetime psychiatric co-occurrence of substance use disorders (SUDs) is common and compared with individual SUDs is represented by augmented severity, and worse outcomes. According to Miller., *et al.* [49]. GWAS have documented similarly large genetic correlations between alcohol, cannabis, and opioid use disorders [50]. In fact, extending these findings, recent studies have identified multiple genomic loci that contribute to common risk for these SUDs and problematic tobacco use, implicating dopaminergic regulatory and neuronal development mechanisms in the pathophysiology of generalized SUD genetic liability, with certain signals demonstrating cross-species and translational validity [51-53]. It is indeed important that Polygenic scores (PGS) derived from the generalized genetic liability to SUDs outperform PGS for individual SUDs in prediction of serious mental health and medical comorbidities [49,53]. We now ask the logical question-Is generalized SUD genetic liability RDS and pre-addiction a clinical presentation across one's lifespan? If we could assume this to be true, then logically, In terms of preventing substance abuse, one goal would be to induce a proliferation of DA D2 receptors or strengthening dopamine physiology in genetically prone individuals instead of blocking dopamine function with powerful D2 antagonists or even partial agonists [54]. It is noteworthy, while *in vivo* experiments employing a typical D2 receptor agonist induce down regulation, experiments have shown that repetitive more gentle stimulation of the dopamine receptor system via a known D2 agonist results in significant proliferation of D2 receptors in spite of genetic antecedents. Potentially, D2 receptor stimulation signals negative feedback mechanisms in the mesolimbic system to promote mRNA expression causing proliferation of D2 receptors [55].

Individuals with comorbid psychiatric diagnoses often experience poorer outcomes and severe deficits in various cognitive and behavioral domains [56]. Many psychiatric disorders have their approximate peak onset in adolescence, coinciding with the emergence of comorbidity [57]. For example, a population-based study on the well-being of adolescents found that 27.9% of participants aged 14–17 reached multiple diagnostic criteria [58].

Finally, the high prevalence of comorbid mental disorders suggests shared neurobiological origins among different psychopathologies. There is mounting evidence to support our hypothesis that many mental disorders can be understood as extreme deviations from a continuous spectrum in the population and different mental disorders may demonstrate similar deficits in multiple cognitive functions, as envisaged by Research Domain Criteria (ROC) [59,60].

We propose a "reward deficiency solution system" that integrates early genetic risk diagnosis, medical monitoring, and nutrigenomic

dopamine agonist modalities to address the significant global issue hindering our youth from leading productive and fulfilling lives daily. The neuroscience community is conducting excellent research employing cutting-edge molecular-genetic technologies and neuroimaging to enhance our understanding of the complex functions of brain reward circuits, which play a significant role in addiction symptomatology. Despite this progress, there is still debate over how to clinically manipulate neurotransmitters such as dopamine to treat and prevent different forms of addictive diseases, even though it is widely acknowledged that dopamine is a significant neurotransmitter implicated in behavioral and substance addictions [61-63]. (Figure 1).

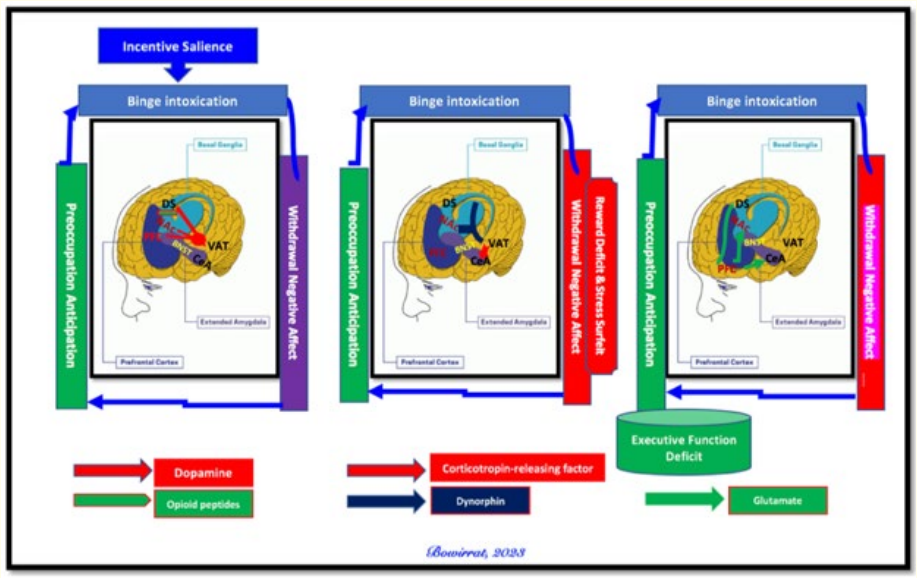

Figure 1: The three stages of addictive mechanisms: Binge/Intoxication, the stage at which a person imbibes an intoxicating psychoactive substance and experiences its rewarding or pleasurable effects, involves basal ganglia structures; Withdrawal/Negative Affect, the stage at which a person experiences a negative emotional state in the absence of the psychoactive substance, involves many stress hormone responses and the extended amygdala and locus coeruleus; and Preoccupation/Anticipation, the stage at which one seeks psychoactive agents again after a period of abstinence, involving interactions of the prefrontal cortex, the extended amygdala, and the basal ganglia. Not shown is the neurotransmitter norepinephrine, which is also activated in the extended amygdala during withdrawal. PFC- prefrontal cortex, DS - dorsal striatum, NAc - BNST - bed nucleus of the stria terminalis, CeA - central nucleus of the amygdala, VTA (Modified from U.S. Department of Health and Human Services (HHS), Of- fice of the Surgeon General, Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health. Washington, DC: HHS, 2016.) with permission Blum., *et al*. [61].

Reward Deficiency Syndrome (RDS) is a key concept in understanding the neurobiological underpinnings of various addictive, compulsive, and impulsive behaviors, including alcohol use disorder. One of the most notable papers on RDS, *"Reward Deficiency Syndrome (RDS): A Cytoarchitectural Common Neurobiological Trait of All Addictions,"* published in the International Journal of Environmental Research and Public Health, provides a comprehensive overview of the genetic and neurochemical foundations of RDS. This paper emphasizes RDS as a common factor in multiple addictive behaviors, highlighting its significance in addiction treatment and management (MDPI) [64].

Another significant publication, *"Introducing Precision Addiction Management of Reward Deficiency Syndrome, the Construct That*

Underpins All Addictive Behaviors," in Frontiers in Psychiatry, introduces the concept of Precision Addiction Management (PAM). This approach utilizes genetic predisposition assessments and personalized interventions to treat RDS. The article underscores the potential of genetic testing, such as the Genetic Addiction Risk Score (GARS), to tailor treatments for individuals suffering from addiction [65].

Additionally, the article *"Should Reward Deficiency Syndrome (RDS) Be Considered an Umbrella Disorder for Mental Illness and Associated Genetic and Epigenetic Induced Dysregulation of Brain Reward Circuitry?"* published in the Journal of Personalized Medicine, explores the hypothesis that RDS could serve as an umbrella term for various mental health disorders. It discusses the genetic and epigenetic influences on brain reward circuitry and the potential for integrating RDS into future diagnostic manuals like the DSM-VI (MDPI) [66].

Understanding RDS is crucial for clinicians when managing patients with AUD, particularly when considering the effects of dopamine antagonists and partial agonists. These medications can impact the dopamine pathways significantly, which is already compromised in individuals with RDS, leading to potential exacerbation of alcohol consumption and interference with recovery efforts.

In terms of treating AUD, instead of powerful drugs and in conjunction with induction of "dopamine homeostasis" such as KB220 [67], we are also proposing Awareness Integration Therapy (AI) [67]. (AIT) represents a multi-modality psychotherapeutic paradigm designed to augment self-awareness, alleviate past traumas and psychological barriers, and foster clarity and positive attitudes. Constructed by amalgamation of insights and techniques drawn from diverse therapeutic models such as Cognitive Behavioral Therapy (CBT), Existential Therapy, Person-Centered Therapy, Emotion-Focused Therapy (EFT), Mind-Body Therapy (MBT), Eye Movement Desensitization and Reprocessing (EMDR), Hypnosis, and Mindfulness, AIT offers a comprehensive approach. By integrating various elements from these methodologies, AIT establishes an inclusive and adaptable framework to address the entire human experience. This ensures the optimization of therapeutic efficacy, enabling the generation of lasting and transformative outcomes for individuals undergoing treatment.

In order to enhance readership comprehension, we provide a schematic summary as represented in figure 2.

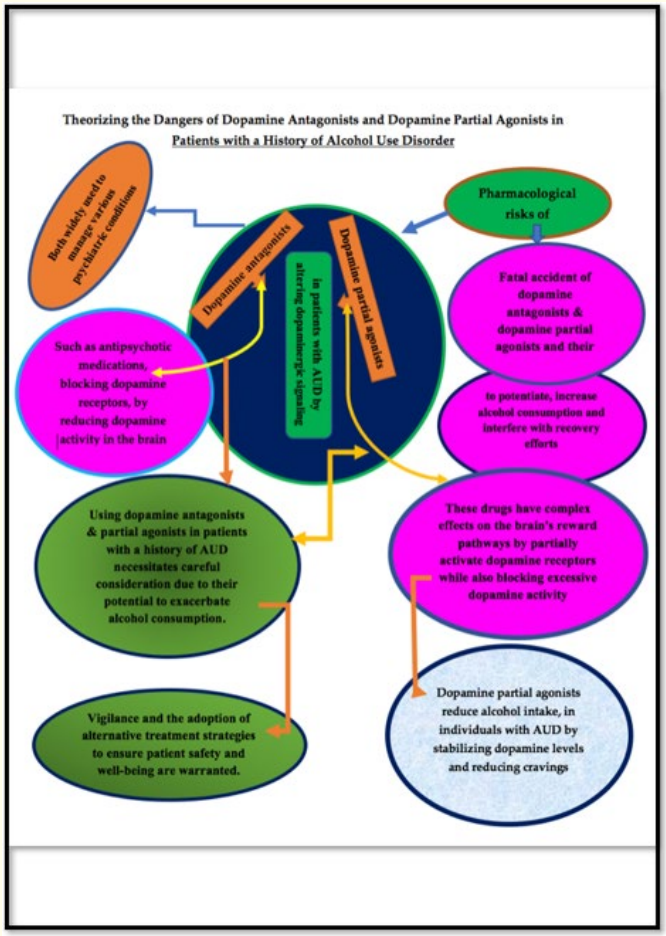

Figure 2

Conclusion

The use of dopamine antagonists and partial agonists in patients with a history of alcohol use disorder necessitates careful consideration due to their potential to exacerbate alcohol consumption. Both animal and human studies underscore the need for vigilance and the adoption of alternative treatment strategies to ensure patient safety and well-being. Further research is essential to elucidate the underlying mechanisms and to establish guidelines for the safe and effective management of co-occurring disorders. Enhanced understanding of these interactions will inform

clinical practice and improve outcomes for patients with complex psychiatric and substance use profiles. Additionally, healthcare providers must be aware of the legal and ethical implications of failing to inform patients about these risks, underscoring the importance of thorough patient education and informed consent.

Bibliography

1. Blum K., *et al*. "Offering a putative neurobiological "dopamine homeostatic" solution to overcome the perils of the reward deficiency syndrome pandemic: emergence of "precision behavioral management". *Annals of Translational Medicine* 23 (2022): 1291.

2. Drake RE., *et al*. "Schizophrenia and Co-Occurring Substance Use Disorder: A Review of the Literature". *Schizophrenia Bulletin* 30.4 (2004): 507-523.

3. De Fruyt J., *et al*. "Clinical Use of Aripiprazole in the Treatment of Schizophrenia and Schizoaffective Disorder". *The International Journal of Neuropsychopharmacology* 5.1 (2002): 1-19.

4. Engleman EA., *et al*. "Haloperidol Increases Alcohol Consumption in Rats". *Neuropsychopharmacology* 33.4 (2008): 900-910.

5. Tomkins DM., *et al*. "Dopamine D2 Antagonists Increase Alcohol Consumption in Rats". *Psychopharmacology* 133.1 (1997): 53-57.

6. Wang SM., *et al*. "Investigational dopamine antagonists for the treatment of schizophrenia". *Expert Opinion on Investigational Drugs* 26.6 (2017): 687-698.

7. Pidathala S., *et al*. "Mechanisms of neurotransmitter transport and drug inhibition in human VMAT2". *Nature* 623.7989 (2023): 1086-1092.

8. Yun S., *et al*. "Antipsychotic drug efficacy correlates with the modulation of D1 rather than D2 receptor-expressing striatal projection neurons". *Nature Neuroscience* 26.8 (2023): 1417-1428.

9. Tyler J., *et al*. "High intensity interval training exercise increases dopamine D2 levels and modulates brain dopamine signaling". *Frontiers in Public Health* 11 (2023): 1257629.

10. Bach P., *et al*. "Molecular Imaging Studies of Alcohol Use Disorder". *Current Topics in Behavioral Neurosciences* (2023).

11. Walter H., *et al*. "Dopamine and alcohol relapse: D1 and D2 antagonists increase relapse rates in animal studies and in clinical trials". *Journal of Biomedical Science* 8.1 (2001): 83-88.

12. Jangard S., *et al*. "Striatal dopamine D2 receptor availability as a predictor of subsequent alcohol use in social drinkers". *Addiction* 118.6 (2023): 1053-1061.

13. Bulwa ZB., *et al*. "Increased consumption of ethanol and sugar water in mice lacking the dopamine D2 long receptor". *Alcohol* 45.7 (2011): 631-639.

14. Caine SB., *et al*. "Role of dopamine D2-like receptors in cocaine self-administration: studies with D2 receptor mutant mice and novel D2 receptor antagonists". *Journal of Neuroscience* 22.7 (2002): 2977-2988.

15. Xiao T., *et al*. "A role for circuitry of the cortical amygdala in excessive alcohol drinking, withdrawal, and alcohol use disorder". *Alcohol* 4 (2024): 151-159.

16. Agoglia AE and Herman MA. "The center of the emotional universe: Alcohol, stress, and CRF1 amygdala circuitry". *Alcohol* 72 (2018): 61-73.

17. Blum K., *et al*. "Should Reward Deficiency Syndrome (RDS) Be Considered an Umbrella Disorder for Mental Illness and Associated Genetic and Epigenetic Induced Dysregulation of Brain Reward Circuitry?" *Journal of Personalized Medicine* 12.10 (2022): 1719.

18. Mohr P., *et al*. "Dopamine Receptor Partial Agonists: Do They Differ in Their Clinical Efficacy?" *Frontiers in Psychiatry* 12 (2022): 781946.

19. Ferraiolo M., *et al*. "Receptor density influences the recruitment bias of aripiprazole and brexpiprazole at the dopamine D_{2L} receptor". *Fundamental and Clinical Pharmacology* 36.6 (2022): 976-984.

20. Williams BD., *et al*. "Aripiprazole and Other Third-Generation Antipsychotics as a Risk Factor for Impulse Control Disorders: A Systematic Review and Meta-Analysis". *Journal of Clinical Psychopharmacology* 44.1 (2024): 39-48.

21. Frankel JS and Schwartz TL. "Brexpiprazole and cariprazine: distinguishing two new atypical antipsychotics from the original dopamine stabilizer aripiprazole". *Therapeutic Advances in Psychopharmacology* 7.1 (2017): 29-41.

22. Kikuchi T., *et al*. "Discovery research and development history of the dopamine D_2 receptor partial agonists, aripiprazole and brexpiprazole". *Neuropsychopharmacology Reports* 41.2 (2021): 134-143.

23. Frampton JE. "Brexpiprazole: A Review in Schizophrenia". *Drugs* 79.2 (2019): 189-200.

24. Azorin JM and Simon N. "Dopamine Receptor Partial Agonists for the Treatment of Bipolar Disorder". *Drugs* 79.15 (2019): 1657-1677.

25. Fusaroli M., *et al*. "Impulse Control Disorders by Dopamine Partial Agonists: A Pharmacovigilance-Pharmacodynamic Assessment Through the FDA Adverse Event Reporting System". *International Journal of Neuropsychopharmacology* 25.9 (2022): 727-736.

26. Huang M., *et al*. "The Role of Dopamine D_3 Receptor Partial Agonism in Cariprazine-Induced Neurotransmitter Efflux in Rat Hippocampus and Nucleus Accumbens". *Journal of Pharmacology and Experimental Therapeutics* 371.2 (2019): 517-525.

27. George SR., *et al*. "Low endogenous dopamine function in brain predisposes to high alcohol preference and consumption: reversal by increasing synaptic dopamine". *Journal of Pharmacology and Experimental Therapeutics* 273.1 (1995): 373-379.

28. Hodge CW., *et al*. "Alcohol self-administration: further examination of the role of dopamine receptors in the nucleus accumbens". *Alcohol, Clinical and Experimental Research* 21.6 (1997): 1083-1091.

29. Sciascia JM., *et al*. "Blocking dopamine d1-like receptors attenuates context-induced renewal of pavlovian-conditioned alcohol-seeking in rats". *Alcohol, Clinical and Experimental Research* 38.2 (2014): 418-427.

30. El-Ghundi M., *et al*. "Disruption of dopamine D1 receptor gene expression attenuates alcohol-seeking behavior". *European Journal of Pharmacology* 353.2-3 (1998): 149-158.

31. McBride WJ and Li TK. "Animal models of alcoholism: neurobiology of high alcohol-drinking behavior in rodents". *Critical Reviews in Neurobiology* 12.4 (1998): 339-369.

32. George SR., *et al*. "Low endogenous dopamine function in brain predisposes to high alcohol preference and consumption: reversal by increasing synaptic dopamine". *Journal of Pharmacology and Experimental Therapeutics* 273.1 (1995): 373-379.

33. Dennen CA., *et al*. "Genetic Addiction Risk Severity Assessment Identifies Polymorphic Reward Genes as Antecedents to Reward Deficiency Syndrome (RDS) Hypodopaminergia's Effect on Addictive and Non-Addictive Behaviors in a Nuclear Family". *Journal of Personalized Medicine* 12.11 (2022): 1864.

34. Blum K., *et al*. "Should We Embrace the Incorporation of Genetically Guided "Dopamine Homeostasis" in the Treatment of Reward Deficiency Syndrome (RSD) as a Frontline Therapeutic Modality?" *Acta Scientific Neurology* 4.2 (2021): 17-24.

35. Blum K., *et al*. "Enhancement of alcohol withdrawal convulsions in mice by haloperidol". *Clinical Toxicology* 9.3 (1976): 427-434.

36. Lu C., *et al*. "Large-scale real-world data analysis identifies comorbidity patterns in schizophrenia". *Translational Psychiatry* 12.1 (2022): 154.

37. Green AI., *et al*. "Clozapine for comorbid substance use disorder and schizophrenia: do patients with schizophrenia have reward-deficiency syndrome that can be ameliorated by clozapine?" *Harvard Review of Psychiatry* 6.6 (1999): 287-296.

38. Anton RF., *et al*. "Efficacy of Aripiprazole for Alcohol Dependence: A Randomized Controlled Trial". *Alcoholism: Clinical and Experimental Research* 32.5 (2008): 1017-1025.

39. Cervenka S and Farde L. "Dopamine D (2) receptor occupancy by aripiprazole in schizophrenia patients and in healthy subjects". *International Journal of Neuropsychopharmacology* 11.2 (2008): 207-216.

40. Bergman J., *et al*. "Modification of cocaine and alcohol self-administration by aripiprazole: Comparison with typical and atypical antipsychotics in rats". *Neuropsychopharmacology* 33.11 (2008): 2824-2836.

41. Vassoler FM., *et al*. "The effects of aripiprazole on alcohol intake in female rats". *Behavioural Brain Research* 261 (2014): 31-37.

42. Salling MC and Martinez D. "Brain Stimulation in Addiction: Mechanisms and Targets". Current *Opinion in Neurobiology* 40 (2016): 1-8.

43. Rodd ZA., *et al*. "Effects of aripiprazole on ethanol self-administration in alcohol-preferring (P) rats". *Alcoholism: Clinical and Experimental Research* 27.10 (2003): 1582-1589.

44. Haney M., *et al*. "Aripiprazole maintenance decreases alcohol self-administration in humans". *Drug and Alcohol Dependence* 56.2 (1999): 181-190.

45. Wiers CE., *et al*. "Effects of aripiprazole on neural alcohol cue-reactivity in alcohol-dependent patients". *Psychopharmacology (Berl)* 231.8 (2014): 1541-1550.

46. Blum K., *et al*. "Summary Document Research on RDS Anti-addiction Modeling: Annotated Bibliography". *Journal of Addiction Psychiatry* 8.1 (2024): 1-33.

47. Espeso-Gil S., *et al*. "A chromosomal connectome for psychiatric and metabolic risk variants in adult dopaminergic neurons". *Genome Medicine* 12 (2020): 19.

48. Szoke A., *et al*. "Multimorbidity and the Etiology of Schizophrenia". *Current Psychiatry Reports* 26.5 (2024): 253-263.

49. Miller AP., *et al*. "Generalized genetic liability to substance use disorders". *Journal of Clinical Investigation* 134.11 (2024): e172881.

50. Blum K., *et al*. "TO BE OR NOT TO BE" GWAS Ends the Controversy about the DRD2 Gene as a Determinant of Reward Deficiency Syndrome (RDS)". *Psychology Research and Behavior Management* 16 (2023): 4287-4291.

51. Levey DF., *et al*. "Bi-ancestral depression GWAS in the million veteran program and meta-analysis in >1.2 million individuals highlight new therapeutic directions". *Nature Neuroscience* 24 (2021): 954-963.

52. Kimbrel NA., *et al*. "A genome-wide association study of suicide attempts in the million veterans program identifies evidence of pan-ancestry and ancestry-specific risk loci". *Molecular Psychiatry* 27 (2022): 2264-2272.

53. Hatoum AS., *et al*. "Multivariate genome-wide association meta-analysis of over 1 million subjects identifies loci underlying multiple substance use disorders". *Nature Mental Health* 1 (2023): 210-223.

54. Blum K., *et al*. "Activation instead of blocking mesolimbic dopaminergic reward circuitry is a preferred modality in the long term treatment of reward deficiency syndrome (RDS): a commentary". *Theoretical Biology and Medical Modelling* 5 (2008): 24.

55. Boundy VA., *et al*. "Differential coupling of rat D2 dopamine receptor isoforms expressed in Spodoptera frugiperda insect cells". *Journal of Pharmacology and Experimental Therapeutics* 276.2 (1996): 784-794.

56. Braverman ER and Blum K. "Substance use disorder exacerbates brain electrophysiological abnormalities in a psychiatrically ill population". *Clinical Electroencephalography* 27.4 (1996): 5-27.

57. Paus T., *et al*. "Why do many psychiatric disorders emerge during adolescence?" *Nature Reviews Neuroscience* 9.12 (2008): 947-957.

58. Solmi M., *et al*. "Age at onset of mental disorders worldwide: large-scale meta-analysis of 192 epidemiological studies". *Molecular Psychiatry* 27.1 (2022): 281-295.

59. Casey BJ., *et al*. "DSM-5 and RDoC: progress in psychiatry research?" *Nature Reviews Neuroscience* 14.11 (2013): 810-814.

60. Williams LM., *et al*. "Precision psychiatry and Research Domain Criteria: Implications for clinical trials and future practice". *CNS Spectrums* 29.1 (2024): 26-39.

61. Gold MS., *et al*. "Molecular role of dopamine in anhedonia linked to reward deficiency syndrome (RDS) and anti- reward systems". *Frontiers in Bioscience (Schol Edition)* 10.2 (2018): 309-325.

62. Zeine F., *et al*. "Solving the Global Opioid Crisis: Incorporating Genetic Addiction Risk Assessment with Personalized Dopaminergic Homeostatic Therapy and Awareness Integration Therapy". Journal of Addiction Psychiatry 8.1 (2024): 50-95.

63. Cronje F., *et al*. "Hypothesizing Enhanced Brain Activity as A Function of Dopamine Homeostasis as Observed with KB220 in A Male with Delayed Cognitive Performance". *Acta Scientific Neurology* 7.7 (2024): 49-56.

64. Blum K., *et al*. "Reward Deficiency Syndrome (RDS): A Cytoarchitectural Common Neurobiological Trait of All Addictions". *International Journal of Environmental Research and Public Health* 18.21 (2001): 11529.

65. Blum K., *et al*. "Introducing Precision Addiction Management of Reward Deficiency Syndrome, the Construct That Underpins All Addictive Behaviors". *Frontiers in Psychiatry* 9 (2018): 548.

66. Blum K., *et al*. "Should Reward Deficiency Syndrome (RDS) Be Considered an Umbrella Disorder for Mental Illness and Associated Genetic and Epigenetic Induced Dysregulation of Brain Reward Circuitry?" *Journal of Personalized Medicine* 12.10 (2022): 1719.

67. Zeine F. "Awareness integration: a new therapeutic model". *International Journal of Emergency Mental Health* 16.2 (2018): 278-283.