International Day Against

Drug Abuse

and Illicit Trafficking

Tech Pharma

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Theme 2024

The Evidence is clear:

Invest in Prevention

Dr. D.Y.Patil College of Pharmacy, Akurdi, Pune

VISION

To impart quality education to the Students and mould them into proactive multifaceted Pharmacists.

MISSION

To establish a centre of Academic excellence and research in Pharmacy Education and thereby produce professionally competent and ethically sound Pharmacist to cater to the needs of the global society.

PROGRAM EDUCATIONAL OBJECTIVES (PEOs)

After graduation students will

1. Reflect critical thinking and problem solving skills through their Pharmaceutical knowledge, expertise and competency in industry, higher studies and research.
2. Practice ethics and values in their profession.
3. Contribute effectively in various fields of social healthcare system.
4. Inculcate leadership and entrepreneurship capabilities through effective communications, appropriate time management and self-upgradation.
5. Foster interdisciplinary engagement in evolving healthcare sector through lifelong learning.

EDITOR'S DESK

Dr. Ramesh Katedeshmukh

Dr. Pavankumar Wankhade

Mrs. Kajal Bhagat

Drug abuse is one of the major challenges across the world as it continues to be a significant threat to global health and social well-being. The way drugs are impacting the youths and hampering their potential highlights the urgent need to find a solution to the drug problem. One such solution is International Day Against Drug Abuse and Illicit Trafficking, observed every year on June 26th. The annual campaign aims to raise awareness about the consequences of drug use which include physical and psychological harm, overdose deaths and societal problems.

Dr. Ramesh Katedeshmukh, Professor

The global drug problem presents a multifaceted challenge that touches the lives of millions worldwide. From individuals struggling with substance use disorders to communities grappling with the consequences of drug trafficking and organized crime, the impact of drugs is far-reaching and complex. Central to addressing this challenge is the imperative to adopt a scientific evidence-based approach that prioritizes prevention and treatment. The International Day against Drug Abuse and Illicit Trafficking, or World Drug Day, is marked on 26 June every year to strengthen action and cooperation in achieving a world free of drug abuse. This year's World Drug Day campaign recognizes that effective drug policies must be rooted in science, research, full respect for human rights, compassion, and a deep understanding of the social, economic, and health implications of drug use.

Dr. Pavankumar Wankhade, Assistant Professor

The International Day against Drug Abuse and Illicit Trafficking is observed every year on 26 June to bolster cooperation and action in achieving a world free of drug abuse. The theme of this year's World Drug Day is 'The evidence is clear: invest in prevention'. The current issue of the journal highlights on awareness of drug abuse. In this issue we published the articles author by students under the guidance of faculty. It contains detail information about drug abuse, its history, mechanism of drug addiction, overdose effects and its treatment. Thus, this particular issue will be helpful, for all pharmacist to understand their role better.

Mrs. Kajal Bhagat, Assistant Professor

"We would like to express our gratitude and heartfelt thanks to our beloved Principal Dr. Niraj Vyawahare for constant support and motivation. We are also grateful to our Vice Principal Dr. (Mrs). Shilpa Chaudhari, all the teaching, non-teaching staff and our students."

Our organization feels special and privileged in presenting this issue.

THANK YOU ONCE AGAIN TO ALL.

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INNOVATIVE STRATEGIES FOR ACHIEVING A DRUG-FREE WORLD: TACKLING OXYCODONE ABUSE

Ms. Pallavi Somthane
Department of Pharmaceutical Quality Assurance, Dr. D.Y. Patil College of Pharmacy, Akurdi Pune.

ABSTRACT:
Due of oxycodone's significant propensity for addiction, misuse poses a serious threat to public health. A multifaceted approach is necessary to address this. Virtual reality (VR) and smartphone apps complement. Prevention initiatives by providing interesting teaching resources that increase knowledge of the risks associated with opioids. Artificial intelligence (AI) and machine learning, which utilise predictive analytics to analyse medical information and identify patients who may be at-risk, are beneficial for early intervention. Treatment advances include telemedicine services that facilitate better access to care, personalised medicine, and non-addictive opioid substitutes. By reducing stress and cravings, complementary holistic therapies like yoga and meditation enhance conventional treatments. Policy and community involvement is essential, and public awareness initiatives, improved prescription monitoring.

INTRODUCTION:
Oxycodone, a powerful opioid prescribed for severe pain, has become a public health crisis due to its high potential for abuse and addiction. To tackle this issue, a comprehensive approach combining prevention, treatment, and policy is needed. Modern technology, such as mobile apps and virtual reality simulations, can be used to educate the public about the dangers of opioid misuse. Artificial intelligence and machine learning can be used to analyze electronic health records and identify patterns of potential misuse. AI-driven predictive analytics can also be integrated into prescription monitoring programs to detect and prevent doctor shopping and prescription fraud. Medication-assisted treatment (MAT) innovations, such as personalized medicine and telehealth services, can offer new solutions for opioid addiction. [1] Holistic and integrative approaches, such as yoga, meditation, and mindfulness, can complement traditional treatment methods by addressing stress and cravings while supporting overall well-being. Strengthening policy frameworks and community engagement is also crucial. Enhanced prescription drug monitoring programs, public awareness campaigns, and collaborative efforts between healthcare providers, policymakers, and community organizations are essential for creating a unified approach to combating oxycodone abuse.

HISTORY OF OXYCODONE AND ITS COMMON NAMES:

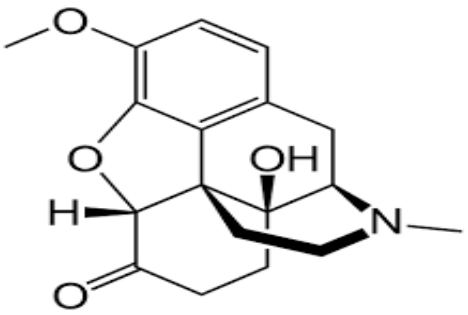


Fig. *Structure of Oxycodone*

In 2015 and beyond, increased regulatory scrutiny, legal actions against pharmaceutical companies, and opioid crisis awareness led to stricter prescribing guidelines and measures. [2]

Fig. *History of Oxycodone and Its Common Names*

COMMON NAMES AND BRAND VARIANTS: [3]

OxyContin:
The most well-known brand name for extended-release oxycodone. It is used for managing severe pain around the clock.

Percocet: A combination of oxycodone and acetaminophen (Tylenol), used for short-term relief of moderate to severe pain.

Percodan:

The U.S. discontinued a combination of oxycodone and aspirin in 2010 due to safety and efficacy concerns over the aspirin component.

Roxicodone:

An immediate-release form of oxycodone used for the management of severe pain that requires rapid relief.

Oxer:

Short for "Oxycodone Immediate Release," this formulation provides rapid pain relief for short-term

NEUROBIOLOGY OF OXYCODONE ADDICTION

Oxycodone, a potent opioid used for pain management, has a high addiction potential due to its impact on the brain's reward system. The primary mechanism of addiction involves oxycodone binding to mu-opioid receptors in the brain, leading to increased dopamine release in areas like the nucleus acumens and ventral tegmental area (VTA). This dopamine release reinforces the drug's pleasurable effects and promotes compulsive use. [3,4]

Key neurotransmitters involved include:

Dopamine: Elevated levels in the reward system contribute to the reinforcement of drug-seeking behavior.

Endogenous Opioids: Chronic use disrupts the balance of natural opioids, leading to tolerance and dependence.

Glutamate and GABA: Alterations in these neurotransmitters affect addiction and withdrawal symptoms.

Prolonged usage results in both functional and anatomical alterations, such as diminished decision-making ability and decreased grey matter in the prefrontal cortex. Developing efficient therapy, like as pharmaceutical interventions and behavioural therapies, to control and lessen oxycodone addiction is made easier with an understanding of these pathways.

Mechanism of Oxycodone Action and Abuse:

Oxycodone relieves pain by activating mu-opioid receptors, which reduces neurotransmitter release and enhances dopamine-driven euphoria. [5]

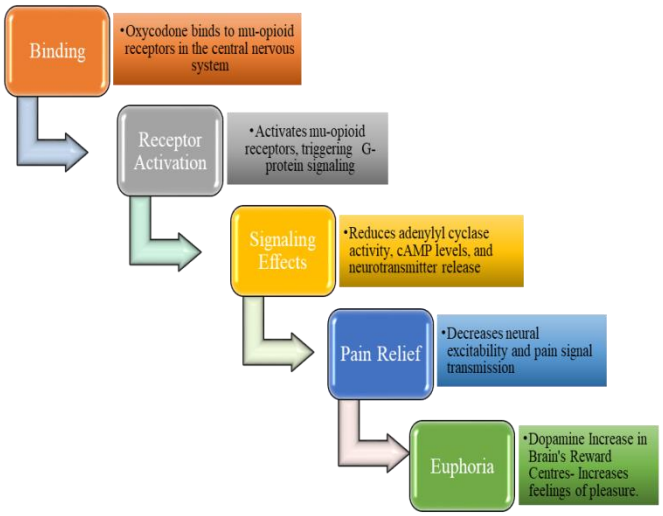


Fig. *Mechanism of Oxycodone Action and Abuse*

Detailed Overview of Oxycodone Overdose Effects and Clinical Manifestations: [6]

Primary issue: Respiratory depression due to drug depressing brainstem's respiratory centres.

Impact on central nervous system: Drowsiness, confusion, or coma.

Cardiovascular symptoms: Bradycardia and hypotension.

Gastrointestinal effects: Nausea, vomiting, constipation.

Pupillary constriction: Muscle flaccidity and diminished reflexes.

Seizures: Less common in severe cases.

Immediate treatment: Narcan, an opioid antagonist.

Supportive care: Maintain airway patency, provide oxygen, monitor vital signs.

Long-term management: Addiction counselling and follow-up care.

Treatment of Oxycodone Overdose: [7]

Emergency services should be called immediately for medical attention.

Naloxone, an opioid antagonist, can be administered via nasal spray or intramuscular injection. Supportive care includes airway management, oxygen therapy, and monitoring. Advanced interventions include intravenous fluids and cardiovascular support. Post-treatment, patients should be monitored for recurrence of overdose symptoms or complications. Prevention involves education on oxycodone risks, proper dosing, and

prescribed guidelines. Prescription monitoring programs can detect misuse or overprescribing.

Oxycodone Withdrawal Syndrome: [6,7]

Oxycodone withdrawal syndrome is a severe condition characterized by physical and psychological symptoms due to drug dependence. It can be acute, subacute, or post-acute. Effective management includes medical supervision, support, detoxification, medication-assisted treatment, supportive care, gradual tapering, and relapse prevention. Understanding symptoms and developing effective strategies are crucial for successful recovery.

Restlessness.

Watery eyes.

Runny nose.

Sweats/chills.

Irritability.

Anxiety.

Muscle aches and pains.

Gastrointestinal upset (nausea, vomiting, diarrhoea, abdominal cramps)

TREATMENT OF OXYCODONE DRUG ABUSE: [7,8]

The treatment of oxycodone abuse involves a comprehensive assessment, evaluation, and medical history. Medication-assisted treatment, including naloxone, buprenorphine, methadone, naltrexone, and clonidine, is used to manage withdrawal symptoms. Behavioral therapies, such as cognitive behavioural therapy, are used to help patients change negative thought patterns. Supportive care includes medical monitoring, nutritional and psychological support, and family therapy. Integrated treatment addresses co-occurring disorders and includes holistic approaches. Long-term recovery planning and harm reduction strategies are essential for successful recovery.

Yoga aids in stress management, physical health, mindfulness, self-awareness, and sleep improvement by reducing triggers for drug use, improving strength, flexibility, and detoxification.

Fig. *Treatment of Oxycodone Drug Abuse with help of Yoga & Meditation*

NON-PHARMACOLOGICAL TREATMENT OF OXYCODONE ADDICTION: [9]

Behavioural Therapy: Cognitive Behavioural Therapy (CBT) alters negative thought patterns and Contingency Management rewards positive behaviour.

Counselling and Support Groups: Individual and group therapy offer personal guidance and peer support.

Lifestyle Interventions: Yoga and meditation reduce stress and enhance emotional regulation, while exercise improves physical health and mood.

Educational and Vocational Support: Job training and education provide stability and personal growth.

Family Therapy: Involves family in recovery, addressing dynamics and offering support. These approaches address the psychological and social aspects of addiction, supporting comprehensive recovery.

Legal Status of Oxycodone in India: [9,10]

In India, oxycodone is classified as a **Schedule H1 drug** under the Drugs and Cosmetics Act, 1940. This classification means:

Prescription-Only: Oxycodone can only be dispensed with a prescription from a licensed medical practitioner. **Controlled Substance**: Its use is highly regulated due to its potential for abuse and addiction. **Regulatory Oversight**: The production, distribution, and sale of oxycodone are monitored by the Drug Controller General of India (DCGI) and state regulatory authorities to prevent misuse and illegal trafficking. The stringent controls reflect the need to balance its therapeutic benefits for severe pain management with the risks associated with its misuse and dependence.

CONCLUSION:

Combating oxycodone abuse requires public education, holistic treatments like yoga, and expanded addiction support. Strengthening prescription monitoring, enforcing regulations, and developing abuse-deterrent formulations are key. Investing in non-addictive pain management alternatives will further reduce reliance on opioids. A unified effort from healthcare, policy, and communities is essential.

REFERENCE:

1. Lipari, R.N. and Van Horn, S.L. Trends in substance use disorders among adults aged 18 or older. The CBHSQ Report: June 29, 2017. Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration, Rockville, MD. https://www.samhsa.gov/data/sites/default/files/report_2790/ShortReport-2790.html
2. John A. Gale, Anush Y. Hansen, and Martha Elbaum Williamson, “Rural Opioid Prevention and Treatment Strategies: The Experience in Four States,” Maine Rural Health Research Center (2017), https://muskie.usm.maine.edu/Publications/rural/WP62-Rural-Opioid-PreventionTreatment-Strategies.pdf.
3. The Associated Press-NORC Center for Public Affairs Research (2018). Americans Recognize the Growing Problem of Opioid Addiction http://www.apnorc.org/PDFs/Opioids%202018/APNORC_ Opioids_Report_2018.pdf.
4. https://medlineplus.gov/druginfo/meds/a682132.html
5. Theodore J. Cicero, James A. Inciardi, Alvaro Muñoz,Trends in Abuse of OxyContin® and Other Opioid Analgesics in the United States: 2002-2004,The Journal of Pain,Volume 6, Issue 10,2005,Pages 662-672, https://doi.org/10.1016/j.jpain.2005.05.004.
6. Barth L. Wilsey M.D., Scott M. Fishman M.D., in Essentials of Pain Medicine and Regional Anesthesia (Second Edition), 2005 **Minor and Short-Acting Opioids**
7. James E. Barrett, Aryan Shekarabi and Saadet Inan Pharmacological Reviews June 15, 2023, PHARMREV-AR-2021-000506; DOI:
8. https://doi.org/10.1124/pharmrev.121.00050
9. https://www.nejm.org/doi/full/10.1056/NEJMc1204141
10. Zwisler ST, Enggaard TP, Mikkelsen S, Verstuyft C, Becquemont L, Sindrup SH, Brosen K (2012) Lack of association of OPRM1 and ABCB! Single-nucleotide polymorphisms to oxycodone response in postoperative pain. J Clin Pharmacol 52: 234-242.
11. OxyContin (oxycodone hydrochloride) Extended-Release Tablets. Full prescribing information. Purdue Pharma L.P; [accessed 2022 Aug 2]. Available from: http://app.purduepharma.com/xmlpublishing/pi.aspx?id=o Google Scholar

HEMP: MARIJUANA

Mrs. Kajal Bhagat
Department of Pharmacognosy, Dr. D Y Patil College of Pharmacy Akurdi Pune.

ABSTRACT

Hemp (cannabis sativa) is the same species of plant as cannabis. Unlike cannabis, hemp contains very low level of delta-9-tetrahydrocannabinol (THC). Both hemp and cannabis also contain cannabinoids such as cannabidiol (CBD) cannabidivarin (CBDV), cannabigerol (CBG), and others. The 2018 Fram Bill established the specific definition of hemp versus cannbis by limiting the THC content of hemp to no more than 0.3%. Hemp seeds contain fats, protein and other chemicals. People use hemp for constipation, high cholesterol, eczema, arthritis and many other conditions, but there is no good scientific evidence to support these uses. Don't confuse hemp with Canadian hemp, hemp agrimony, cannabis or CBD. These are not the same. Unlike cannabis, it is legal to sell hemp and hemp products under federal law in the US

INTRODUCTION

Hemp**,** (*Cannabis sativa*), plant of the family Cannabaceae cultivated for its bast fibre or its edible seeds. Hemp is sometimes confused with the cannabis plants that serve as sources of the drug marijuana and the drug preparation hashish. Although all three products hemp, marijuana, and hashish contain tetrahydrocannabinol (THC) a compound that produces psychoactive effects in humans, the variety of cannabis cultivated for hemp has only small amounts of THC relative to that grown for the production of marijuana or hashish.

A BRIEF HISTORY OF HEMP

Hemp is a variety of the Cannabis sativa plant that is grown for its fiber and seeds. It is different from marijuana, which is another variety of Cannabis sativa that is grown for its psychoactive effects. It has very low levels of THC, the compound that causes the high in marijuana. The origin of hemp cultivation is not clear, but some evidence suggests that it may have originated in Central Asia or China. The earliest archaeological evidence of hemp cultivation dates back to 8000 BC in China, where hemp was used to make rope, cloth, and paper. Hemp was also used as food and medicine in ancient China. have originated in Central Asia or China. The earliest archaeological evidence of hemp cultivation dates back to 8000 BC in China, where hemp was used to make rope, cloth, and paper. Hemp was also used as food and medicine in ancient China. Hemp cultivation spread to other parts of the world over time. It was introduced to India around 2800 BC, where it was used for religious and medicinal purposes. It was also cultivated in ancient Greece and Rome, where it was used to make clothing and sails. It reached North America in the 1500s, where it was grown by European settlers and Native Americans. Hemp cultivation reached its peak in the 18th and 19th centuries, when it was a major crop in many countries around the world. It was used to make a variety of products, including paper, textiles, canvas, rope, oil, soap, paint, and fuel. It was also a valuable source of protein and oil for human and animal consumption.

However, in the early 20th century, hemp cultivation began to decline due to a number of factors. One of them was the rise of synthetic fibers, such as nylon and rayon, which replaced hemp in many applications. Another factor was the passage of laws that made it illegal to grow hemp in many countries. These laws were influenced by the anti-marijuana movement, which associated hemp with marijuana and claimed that both were harmful and addictive substances. As a result of these factors, hemp cultivation became almost extinct in many parts of the world by the mid-20th century. Only a few countries continued to grow hemp legally or illegally for industrial or medicinal purposes.

PHYSICAL DESCRIPTION

The hemp plant is a stout, aromatic, erect annual herb. The slender cane like stalks are hollow except at the tip and base. The leaves are compound with palmate shape, and the flowers are small and greenish yellow. Seed-producing flowers form elongate spike like clusters growing on the pistillate, or female, plants. Pollen-producing flowers form many-branched clusters on staminate, or male, plants.

CULTIVATION AND PROCESSING

Hemp originated in Central Asia. Hemp cultivation for fibre was recorded in China as early as 2800 BCE and was practiced in the Mediterranean countries of Europe early in the Christian era, spreading throughout the rest of Europe during the Middle Ages. It was planted in Chile in the 1500s and a century later in North America.

Fig. 1 Cultivation of Hemp

Hemp is grown in temperate zones as an annual cultivated from seed and can reach a height of up to 5 metres (16 feet). Crops grow best in sandy loam with good drainage and require average monthly rainfall of at least 65 mm (2.5 inches) throughout the growing season. Crops cultivated for fibre are densely sowed and produce plants averaging 2–3 metres (6–10 feet) tall with almost no branching. Plants grown for oilseed are planted farther apart and are shorter and many-branched. In fibre production, maximum yield and quality are obtained by harvesting soon after the plants reach maturity, indicated by the full blossoms and freely shedding pollen of the male plants. Although sometimes pulled up by hand, plants are more often cut off about 2.5 cm (1 inch) above the ground.

Fig. 2 Whole seeds of Hemp

Fig. 3 Hulled hemp seeds

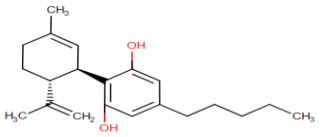
Fibres are obtained by subjecting the stalks to a series of operations including retting, drying, and crushing and a shaking process that completes separation from the woody portion, releasing the long, fairly straight fibre, or line. The fibre strands, usually longer than 1.8 metres (5.8 feet), are made of individual cylindrical cells with an irregular surface.

ACTIVE INGREDIENT IN MARIJUANA

Tetrahydrocannabinol (THC) is the active ingredient present in all parts of both the male and female marijuana plants, but it is most concentrated in the resin (cannabin) in the flowering tops of the female plant. It was first isolated from the Indian hemp plant (*Cannabis sativa*) and synthesized in 1965.

EFFECTS OF CONSUMING OR SMOKING MARIJUANA

Marijuana's effects vary, depending on the strength and amount consumed. Psychological effects can include mild euphoria, visual hallucinations, anxiety, depression, extreme variability of mood, paranoia, and psychoses. Physical effects can include reddening of the eyes, dryness of the mouth and throat, an increase in the heartbeat, chest tightness, drowsiness, unsteadiness, and lack of coordination.

Type	Small Molecule
Structure	
Generic Name	Cannabidiol
Brand Names	*Epidiolex, Sativex*
Groups	Approved, Investigational
Weight	Average: 314.469 Monoisotopic: 314.224580206
Chemical Formula	$C_{21}H_{30}O_2$
DrugBank Accession Number	DB09061

MECHANISM OF ACTION

Mechanism of pharmacological action for CBD

Cannabis sativa has long been used for neurological and psychological healing. Recently, cannabidiol (CBD) extracted from cannabis sativa has gained prominence in the medical field due to its

non-psychotropic therapeutic effects on the central and peripheral nervous systems. CBD, also acting as a potent antioxidant, displays diverse clinical properties such as anticancer, antiinflammatory, antidepressant, antioxidant, antiemetic, anxiolytic, antiepileptic, and antipsychotic effects. In this review, we summarized the structural activity relationship of CBD with different receptors by both experimental and computational techniques and investigated the mechanism of interaction between related receptors and CBD. The discovery of structural activity relationship between CBD and target receptors would provide a direction to optimize the scaffold of CBD and its derivatives, which would give potential medical applications on CBD-based therapies in various illnesses.

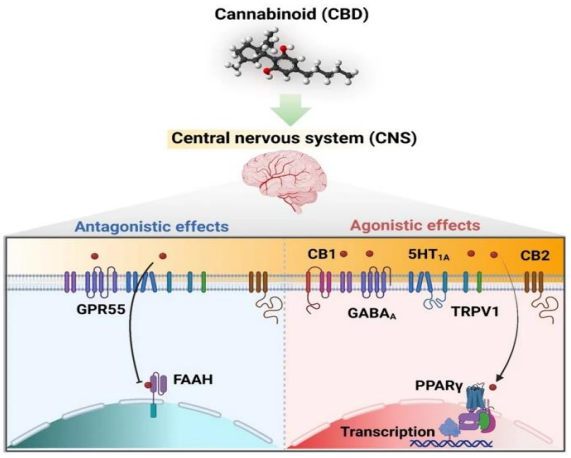


Fig. 4 Pharmacological action of CBD

Mechanism of action of cannabinoids

Cannabinoids function by stimulating two receptors, cannabinoid receptor type 1 (CB1) and type 2 (CB2), within the endocannabinoid system. This system is a complex network of organs throughout the body, expressing the cannabinoid receptors and playing a homeostatic role. Functions of the endocannabinoid system include pain, memory, movement, appetite, metabolism, lacrimation/ salivation, immunity, and even cardiopulmonary function. It bears mentioning that the vast majority of end-effects from cannabinoids, including psychotropics, are from activation of CB1, with CB2 serving more important roles in immune and inflammatory functions.

Endogenously, endocannabinoids serve as neuro-regulatory modulators responsible for retrograde neurotransmission. Here, a post-synaptic neuron releases endocannabinoids that bind to predominantly CB1 receptors on the presynaptic neuron. This binding results in inhibited presynaptic calcium channel activation and subsequent presynaptic neurotransmitter release. If the presynaptic neurotransmitters are predominantly inhibitory such as GABA, the net effect is excitatory and vice versa.

Binding to the different parts of the central nervous system mediates different psychotropic properties of cannabinoids, particularly THC These areas and end-effects include:

- Hippocampus: impairment of short-term memory
- Neocortex: impairment of judgment and sensation
- Basal ganglia: altered reaction time and movement
- Hypothalamus: increased appetite
- Nucleus accumbens: euphoria
- Amygdala: panic and paranoia
- Cerebellum: ataxia
- Brainstem: anti-emesis
- Spinal cord: analgesia

Other end-effects of CB1 activation peripherally include dry mouth, conjunctivitis, tachycardia, hypotension, and bradypnea.

Mechanism of action of CBD anxiety Multiple mechanisms may account for the anti-depressive and anxiolytic activities of CBD. The proposed anti-anxiety activity may result from CBD inhibiting the inactivation of AEA, a neurotransmitter[59, 60] and CBD interacting with 5-HT_{1A} receptors.

Unique mechanism of action includes CBD CBD is a weak agonist of human TRPV1 and lowers their sensitivity to capsaicin, thus leading to the possibility that this cannabinoid exerts anti-inflammatory action in part by desensitization of sensory nociceptors [45]. Another relevant mechanism of CBD is enhancing endocannabinoid actions.

Mechanism of action of CBD in the body CBD can either enhance or inhibit activation of its binding site targets. CBD blocks activation of the equilibrative nucleoside transporter (GPR55) and the TRP cation channel subfamily (glycine receptors, TRPM8), among others, and enhances activity of the serotonin 1A receptor, glycine receptors α1 and α3, and TRPA1.

Mechanism of action for CBD sleep

One proposed mechanism for CBD-induced sedative effects, and in turn better sleep quality, is the central downregulation of the corticotropin-releasing hormone (CRH) gene and a resultant decrease in systemic cortisol, mediated directly through CB_1 receptor expression on CRH neurons in the paraventricular nucleus

Mechanism of action of CBD in epilepsy

The authors propose that CBD blocks a "positive feedback loop" in which seizures increase LPI-GPR55 signaling, which likely encourages more seizures, which in turn increases levels of both LPI and GPR55.

Mechanism of action of topical CBD

CBD contributes to various anti-inflammatory mechanisms and stimulates immune cell functions, including the suppression of proinflammatory cytokines, such as TNF-α, growth factors, IL-1 beta (IL-1β), and chemokines, as well as the inhibition of immune cell activation, migration, proliferation, maturation, and antigens.

Mechanism of CBD in the brain

CBD inhibit the enzymatic activity of fatty acid amide hydrolase which is responsible for the degradation of AEA. Since AEA also acts as an agonist of the cannabinoid receptors, CBD and its related increase in AEA abundance might therefore indirectly stimulate CB1 and CB2 signaling.

Mechanism of action of cannabinoids pain

There are a number of potential mechanisms by which cannabinoids may produce antinociception in the spinal cord. Cannabinoids can act at spinal CB_1 receptors to inhibit capsaicin-sensitive fibers in lumbar dorsal horn slices and to decrease noxious stimulus-evoked firing of wide dynamic range (WDR) neurons.

Mechanism of action of CBD anticonvulsant
Preclinical evidence suggests CBD reduces neuronal hyperexcitability through multiple mechanisms, including modulation of intracellular calcium via G protein-coupled receptor 55 (GPR55), extracellular calcium influx via transient receptor potential vanilloid type 1 (TRPV1) channels, and adenosine-mediated signaling

PRODUCTS AND USES

The fibre, longer and less flexible than flax, is usually yellowish, greenish, or a dark brown or gray and, because it is not easily bleached to sufficiently light shades, is rarely dyed. It is strong and durable and is used for cordage—e.g., twine, yarn, rope, cable, and string—and for artificial sponges and such coarse fabrics as sacking (burlap) and canvas. Some specially processed hemp has a whitish colour and attractive lustre and is used to make fabric similar to linen for clothing. Hemp textiles can be used to make shoes. Hemp fibre is used to make bioplastics that are recyclable and biodegradable, depending on the formulation. The novel "hempcrete," a composite material made of hemp and a lime binder, can be used similarly to traditional concrete in non-load-bearing applications. Hemp can also be used as an alternative to wood pulp in some instances; it is frequently used in papermaking and is a sustainable alternative to fibreglass insulation in buildings. The edible seeds contain about 30 percent oil and are a source of protein, fibre, and magnesium. Shelled hemp seeds, sometimes called hemp hearts, are sold as a health food and may be eaten raw; they are commonly sprinkled on salads or blended with fruit smoothies. Hemp seed milk is used as an alternative to dairy milk in drinks and recipes. The oil obtained from hemp seed can be used to make paints, varnishes, soaps, and edible oil with a low smoke point. Historically, the seed's chief commercial use has been for caged-bird feed.

STORAGE

Hemp oil oxidizes and turns rancid within a short period of time if not stored properly;[18] its shelf life is extended when it is stored in a dark airtight container and refrigerated. Both light and heat can degrade hemp oil.

OTHER HEMPS

Although only the hemp plant yields true hemp, a number of other plant fibres are called "hemp." These include Indian hemp (*Apocynum cannabinum*), Mauritius hemp (*Furcraea foetida*), and sunn hemp (*Crotalaria juncea*).

DIFFERENCE BETWEEN CANNABIS AND SYNTHETIC CANNABINOIDS

Cannabis is the plants that contains compounds called cannabinoids. Some cannabinoids are Psychoactive, meaning they act on the brain to modify mood or consciousness. Cannabis is usually smoked or vaporized and inhaled. It can also be consumed via tea, baked goods, candies or other edible means.

Like the naturally occurring cannabinoids present in the cannabis plant, there are a number of synthetic

cannabinoids that are made in a laboratory. Two synthetic cannabinoids are approved for use by the USFDA to treat nausea and vomiting induced by chemotherapy, both available in capsule form.
Other Synthetic cannabinoids that are not legal have gained popularity in recent years. Those synthetics are often sprayed on dried plant material for smoking and sold under the names “Spice” and “K2”. The synthetic cannabinoids generally have much stronger effects than cannabis.

CONCLUSION

Cannabis dependence causes disability across the globe. It is a disorder primarily experienced by young adults, and our estimates suggest that burden is higher in high income countries. It has not been shown to increase mortality as opioid and other forms of illicit drug dependence do. Nonetheless, in some countries, cannabis dependence produces more years lived with disability than drugs like amphetamines and cocaine, largely because rates of cannabis use are higher than for the stimulant drugs. Our estimates suggest that, although cannabis use is a risk factor for schizophrenia, it is not a major contributor to population level disease burden for that disorder.

REFERENCES:

1. Ibeas Bih C, Chen T, Nunn AV, Bazelot M, Dallas M, Whalley BJ: Molecular Targets of Cannabidiol in Neurological Disorders. Neurotherapeutics. 2015 Oct;12(4):699-730. doi: 10.1007/s13311-015-0377-3.
2. Zhornitsky S, Potvin S: Cannabidiol in humans-the quest for therapeutic targets. Pharmaceuticals (Basel). 2012 May 21;5(5):529-52. doi: 10.3390/ph5050529.
3. Ujvary I, Hanus L: Human Metabolites of Cannabidiol: A Review on Their Formation, Biological Activity, and Relevance in Therapy. Cannabis Cannabinoid Res. 2016 Mar 1;1(1):90-101. doi: 10.1089/can.2015.0012. eCollection 2016.
4. Ruggiero RN, Rossignoli MT, De Ross JB, Hallak JEC, Leite JP, Bueno-Junior LS: Cannabinoids and Vanilloids in Schizophrenia: Neurophysiological Evidence and Directions for Basic Research. Front Pharmacol. 2017 Jun 21;8:399. doi: 10.3389/fphar.2017.00399. eCollection 2017.
5. Laprairie RB, Bagher AM, Kelly ME, Denovan-Wright EM: Cannabidiol is a negative allosteric modulator of the cannabinoid CB1 receptor. Br J Pharmacol. 2015 Oct;172(20):4790-805. doi: 10.1111/bph.13250. Epub 2015 Oct
6. Pertwee RG: The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. Br J Pharmacol. 2008 Jan;153(2):199-215. doi: 10.1038/sj.bjp.0707442. Epub 2007 Sep 10.
7. MacCallum CA, Russo EB: Practical considerations in medical cannabis administration and dosing. Eur J Intern Med. 2018 Mar;49:12-19. doi: 10.1016/j.ejim.2018.01.004. Epub 2018 Jan 4.
8. Baron EP: Comprehensive Review of Medicinal Marijuana, Cannabinoids, and Therapeutic Implications in Medicine and Headache: What a Long Strange Trip It's Been .... Headache. 2015 Jun;55(6):885-916. doi: 10.1111/head.12570. Epub 2015 May 25.
9. Kaur R, Ambwani SR, Singh S: Endocannabinoid System: A Multi-Facet Therapeutic Target. Curr Clin Pharmacol. 2016;11(2):110-7.
10. Elsohly MA, Slade D: Chemical constituents of marijuana: the complex mixture of natural cannabinoids. Life Sci. 2005 Dec 22;78(5):539-48. doi: 10.1016/j.lfs.2005.09.011. Epub 2005 Sep 30.
11. Qian Y, Gurley BJ, Markowitz JS: The Potential for Pharmacokinetic Interactions Between Cannabis Products and Conventional Medications. J Clin Psychopharmacol. 2019 Sep/Oct;39(5):462-471. doi: 10.1097/JCP.0000000000001089.
12. Health Canada Product Label [Link]
13. New York Times: F.D.A. Panel Recommends Approval of Cannabis-Based Drug for Epilepsy (April 2018) [Link]
14. GW Pharmaceuticals Announces Positive Phase 3 Pivotal Study Results for Epidiolex (cannabidiol) [Link]
15. FDA Briefing Document - Peripheral and Central Nervous System Drugs Advisory Committee Meeting (April 19, 2018) [Link]
16. FDA Approved Drug Products: EPIDIOLEX (cannabidiol) oral solution [Link]

A REVIEW ARTICLE: FENFLURAMINE

Dr. Sonali Mahaparale, Ms. Chaitali Rohit, Ms Sunanda Valvi

Department of Pharmaceutical Quality Assurance, Dr. D Y Patil College of Pharmacy, Akurdi

ABSTRACT

Fenfluramine is a drug that was once used as an appetite suppressant in the treatment of obesity. It was marketed under names such as Pondimin. It works by affecting neurotransmitters in the brain, including serotonin, which can influence appetite and mood. However, fenfluramine was withdrawn from the market in the late 1990s due to its association with serious side effects. It waslinked to heart valve problems and a condition called pulmonary hypertension. As a result, its use became restricted, and it was largely replaced by other weight loss treatments with better safety profiles. The antiseizure activity of fenfluramine in Dravet syndrome is thought to be mediated by both its serotonergic activity and its interactions with sigma-1 receptors. Interestingly, recent research has explored fenfluramine's potential in other areas, including the treatment of certain neurological and psychiatric conditions, but its use remains limited and highly controlled due to its history of adverse effects. Fenfluramine hydrochloride has classically been described as acting Fenfluramine hydrochloride has classically been described as acting pharmacologically through a serotonergic mechanism. Therefore, it was initially used as an anorectic drug, given that impaired serotonin homeostasis may be associated with increased food intake. Although positive results were documented, cardiovascular concerns resulted in its temporary withdrawal. Nevertheless, a novel role in patients with epilepsy was later suggested by isolated clinical observations. The

wide application of genetic testing allowed the classification (predominantly as Dravet syndrome) of patients in whom benefit was seen, while with the development of zebrafish models, its antiepileptic properties were confirmed at a molecular level. Data from randomized clinical trials have shown a beneficial effect of fenfluramine, as an adjunct therapy, on seizure control for children with Dravet syndrome, though

there is still uncertainty about the impact on neurodevelopment in these patients. No signs of heart valve disease have been documented to date. Long-term and appropriately designed clinical studies will verify whether fenfluramine is a therapeutic agent of high importance, living up to the promise shown so far pharmacologically through a serotonergic mechanism. A racemic combination of two enantiomers is fenfluramine, also known as pondimin. (+)-Fenfluramine was sold under the brand name Redux. It is also known as dexfenfluramine. (1) The byproducts of fenfluramine metabolism are (±)-norfenfluramine and (+)-norfenfluramine, respectively, from dexfenfluramine. The release of neuronal serotonin (5-HT) through a carrier-mediated exchange mechanism is one of the main effects of fenfluramine and its metabolites. (2) Furthermore, specific 5-HT receptors, specifically those belonging to the 5-HT2 receptor family, are directly agonistically activated by fenfluramine and nor fenfluramine.(3) On the other hand, phentermine selectively releases dopamine.(2)

HISTORY OF DRUG WITH COMMON NAMES OF DRUG

In September 1997, fenfluramine and dexfenfluramine were taken

off the market due to the link between the use of phentermine and fenfluramine (phen/fen) and dexfenfluramine and valvular heart disease (VHD). Controlled prevalence of echocardiography. Extensive in vivo microdialysis research in rat brains demonstrates that phentermine raises extracellular dopamine (DA), fenfluramine raises extracellular serotonin (5-HT), and the combination of phen/fen enhances both transmitters. (5) The therapeutic potential of the phen/fen medication combination is believed to be based on the dual stimulation of central DA and 5-HT transmission. (4,5) Assessing the risk-benefit ratio of such drugs is made more difficult by the observed links

between fenfluramine and its active d-isomer (d-fenfluramine) and cardiac valvulopathy and primary pulmonary hypertension (PPH). (6) Identification of the mechanism or mechanisms of drug-induced PPH may facilitate the creation of novel medications that elicit phen/fen-like neurochemical responses without the unintended side effects. Thorough epidemiological data indicate that the risk of PPH is increased by fenfluramine, d-fenfluramine, and aminorex, but not by other anorexic drugs. (7,8) The mechanism by which aminorex, fenfluramine, and perhaps chlorphentermine increase the risk of PPH is not known.

NEUROBIOLOGY AND MECHANISM OF DRUG ABUSE OR ADDICTION

Phentermine and fenfluramine, also known as phen/fen, are amphetamine analogues that have been used to treat obesity (4) and substance misuse issues (5). Several investigators independently reported in the mid-to-late 1970s that rats given oral or intraperitoneal single doses of fenfluramine (range: 15–27 mg/kg) experienced long-lasting, dose-related reductions in cerebral serotonin (approximately 30%–70%, depending on the dose, brain region, and post drug survival).(9-15) These long-term declines in brain levels of 5-hydroxyindoleacetic acid, the primary metabolite of serotonin, the activity of tryptophan hydroxylase, the rate-limiting enzyme in serotonin synthesis, and the density of serotonin uptake sites, which are structural proteins on serotonin nerve endings, were linked to these serotonin depletions in the brain. Although the exact mechanism underlying fenfluramine's long-lasting decreases in serotonin axonal markers was not immediately apparent, the authors of these and later reports (16) hypothesized that fenfluramine's actions were similar, if not identical to, those of drugs with known toxic potential for brain serotonin neurons, such as p-chloroamphetamine, 5,6-dihydroxytryptamine, and 5,7-dihydroxy tryptamine (17-18). Numerous labs have since verified the long-term effects of fenfluramine on serotonin neurons in the rat brain. (19-20). D-fenfluramine differs from fluoxetine in that it causes serotonin to be depleted and increases the 5HIAA-serotonin ratio, indicating that it primarily functions by releasing serotonin rather than inhibiting its uptake. D-fenfluramine, on the other hand, de-decreases 5HIAA concentration, with the exception of a brief and slight increase that occurs immediately after medication administration. This means that it is not just a serotonin-releasing agent like Ro 4-1284. Previous studies have demonstrated that fenfluramine reduces brain serotonin turnover [21, 22], while Ro 4-1284 promotes brain serotonin turnover [23]. Tryptophan hydroxylase is rapidly and persistently decreased by fenfluramine [24, 25].

OVERDOSE EFFECT WITH CLINICAL MANIFESTATION AND ITS TREATMENT

The data from case reports and short case series (up to three patients) demonstrating a significant reduction in seizure frequency when fenfluramine was added to the current treatment plan were first presented by Gastaut et al., Aicardi et al., and Clemens. The self-induced syncope and self-induced photosensitive epilepsy were the underlying diagnoses, and the maximum daily dose of fenfluramine was 60 mg. The fenfluramine dosage ranged from 0.5 to 1.5 mg/kg. (26-29) Fenfluramine's possible application as an antiepileptic treatment was based on the theory that 5-HT receptors, which are extensively expressed in various regions of the central nervous system, interact with various ion channel types to modify their function and neuronal excitability. An overdose of fenfluramine can lead to severe clinical manifestations affecting multiple body systems. Patients may initially experience agitation, confusion, and hallucinations due to its impact on the central nervous system. In more severe cases, seizures can occur. Cardiovascular effects include tachycardia, hypertension, and potentially dangerous arrhythmias, reflecting its stimulant properties. Additionally, an overdose may cause hyperthermia, which can exacerbate the risk of seizures and other complications. If not promptly treated, these effects can lead to life-threatening conditions, including cardiovascular collapse, respiratory distress, and multi-organ failure. Immediate medical intervention is critical in managing these symptoms and preventing fatal outcomes. Treatment involves

immediate supportive care, including stabilization of airway, breathing, and circulation, along with the administration of benzodiazepines to control agitation and seizures. In cases of severe hypertension or arrhythmias, intravenous antihypertensives or antiarrhythmics may be required. Activated charcoal can be administered if the patient presents early to limit absorption, and continuous monitoring in an intensive care setting is often necessary to manage the evolving clinical picture. After long-term usage as an appetite suppressant, fenfluramine consumption might cause withdrawal symptoms. As the body gets used to not having the medicine, these symptoms could include mood swings including anger, depression, or anxiety. People may also feel drained, eat more, and have irregular sleep patterns, including insomnia. Drug cravings might also happen, which makes the withdrawal process difficult. It is usually necessary to manage these symptoms under medical supervision, and it is advised to gradually reduce the dosage in order to lessen its effects. In order to handle any physical or emotional difficulties that may emerge at this time, supportive care is essential. When fenfluramine is used as an appetite suppressant for an extended period of time, withdrawal symptoms may occur. Anger, sadness, or anxiety are examples of these feelings that may occur as the body adjusts to not taking the medication. In addition, people may eat more, feel exhausted, and experience inconsistent sleep patterns, including insomnia. Additionally, drug cravings may occur, which complicates the withdrawal process. Usually, medical care is required to manage these symptoms, and it is recommended to gradually lower the dosage to minimize its effects. Supportive treatment is necessary to address any physical or emotional issues that may arise at this time.

NON-PHARMACOLOGICAL TREATMENT OF FENFLURAMINE

The focus of non-pharmacological treatment for fenfluramine abuse is on lifestyle, behavioral, and psychological therapies as a means of promoting recovery and averting relapse. Important strategies include counseling or psychotherapy, where patients can examine the emotional and psychological elements influencing their substance abuse, and cognitive-behavioral therapy (CBT), which assists people in recognizing and altering harmful thought patterns and behaviors connected to drug use. Motivational Interviewing (MI) fortifies the patient's resolve to alter, while Narcotics Anonymous (NA) support groups offer continuous motivation and a feeling of belonging. Making lifestyle changes like consistent exercise, eating a healthy diet, and getting enough sleep is essential to regaining physical and mental health. Furthermore, mindfulness exercises and stress-reduction methods like yoga and meditation assist people in controlling their stress levels and lower their chance of relapsing.

LEGAL STATUS IN INDIA

In the 1980s, modest case series and other observational studies of children with photosensitive or self-induced epilepsy revealed fenfluramine's antiseizure effect. The medication fenfluramine, which has been used to treat obesity and, more recently, specific forms of epilepsy, has a complicated legal history in India. Fenfluramine was first used as an appetite suppressor. However, in several nations, including India, it was taken off the market in the late 1990s due to worries about major cardiovascular adverse effects, such as pulmonary hypertension and damage to the heart valves. Fenfluramine was reapproved in several countries in recent years, but only under very rigorous rules, to treat the severe form of epilepsy known as Dravet syndrome. As of right now, fenfluramine's regulatory position in India is cautious; it is not easily accessible and requires stringent approval procedures for any new uses. s use is restricted and closely monitored, particularly due to its historical association with severe side effects. For specific cases, such as Dravet syndrome, fenfluramine might be available under special circumstances, but this would require approval from regulatory authorities like the Central Drugs Standard Control Organization (CDSCO).

CONCLUSION

The shift in fenfluramine's use from obesity to epilepsy influences the present developments in the

creation of novel antiseizure drugs and compels us to carefully consider how epilepsy clinical trials will be designed in the future. A biologics-based era of therapies appears to be taking the place of symptom-centered approaches. Fenfluramine was also quite successful in lowering GTC seizures, indicating that patients with this particular seizure subtype may find fenfluramine to be an especially beneficial option. Furthermore, fenfluramine was found to be generally well-tolerated, and its safety profiles for both short- and long-term treatment of DS were similar to those documented in earlier RCTs and OLE studies. Notably, no signs of pulmonary arterial hypertension or valvular heart disease were noted.

REFERENCES

1. Caccia S, Conforti I, Duchier J, et al. Pharmacokinetics of fenfluramine and norfenfluramine in volunteers given D- and DL-fenfluramine for 15 days. Eur J Clin Pharmacol. 1985;29:221–224.
2. Baumann MH, Ayestas MA, Dersch CM, et al. Effects of phentermine and fenfluramine on extracellular dopamine and serotonin in rat nucleus accumbens: therapeutic implications. Synapse. 2000;36:102–113.
3. 10. Fitzgerald LW, Burn TC, Brown BS, et al. Possible role of valvular serotonin 5-HT2B receptors in the cardiopathy associated with fenfluramine. Mol Pharmacol. 2000;57:75 81.
4. Weintraub M. Long-term weight control study: conclusions. ClinPharmacol Ther. 1992;51:642–646.
5. Rothman RB, Elmer GI, Shippenberg TS, Rea W, Baumann MH. Phentermine and fenfluramine: preclinical studies in animal models of cocaine addiction. Ann N Y Acad Sci. 1998;844:59–74.
6. Connolly HM, Crary JL, McGoon MD, Hensrud DD, Edwards BS, Schaff HV. Valvular heart disease associated with fenfluramine-phentermine. N Engl J Med. 1997;337:581–588
7. Abenhaim L, Moride Y, Brenot F, Rich S, Benichou J, Kurz X, Higenbottam T, Oakley C, Wouters E, Aubier M, Simonneau G, Begaud B. Appetite suppressant drugs and the risk of pulmonary hypertension. N Engl J Med. 1996;335:609–616.
8. Gurtner HP. Aminorex pulmonary hypertension. In: Fishman AP, ed. The Pulmonary Circulation: Normal and Abnormal. Philadelphia, Pa: University of Pennsylvania Press; 1990:397–411.
9. Herve P, Launay J-M, Scrobohaci M-L, Brenot F, Simonneau G, Petitpretz P, Poubeau P, Cerrina J, Duroux P, Drouet L. Increased plasma serotonin in primary pulmonary hypertension. Am J Med. 1995;99: 249–254.
10. Sanders-Bush E, Bushing JA, Sulser F. Long term effects of p-chloroamphetamine and related drugs on the central serotonergic mechanisms J Pharmacol Exp Ther. 1975;192:33-41.
11. Harvey JA, McMaster SE. Fenfluramine: evidence for a neurotoxic action and a long-term depletion of brain serotonin. Commun Psychopharmacol. 1975;1:217-228.
12. Clineschmidt BV ,Totaro JA ,McGuffin JC,etal. Fenfluramine: long-term reduction in brain serotonin(5-hydroxytryptamine).Eur J Pharmacol.1976;35:211-214.
13. Harvey JA, McMaster SE, Fuller RW. Comparison between the neurotoxic and serotonin-depleting effects ofvarious halogenated amphetamine derivatives in the rat. J Pharmacol Exp Ther 1977; 202:581-589.
14. Fuller RW, Snoddy HD, Hemrick SK. Effects of fenfluramine and norfenfluramine on brain serotonin metabolism in rats. Proc Soc Exp Biol Med. 1978;157:202-205.

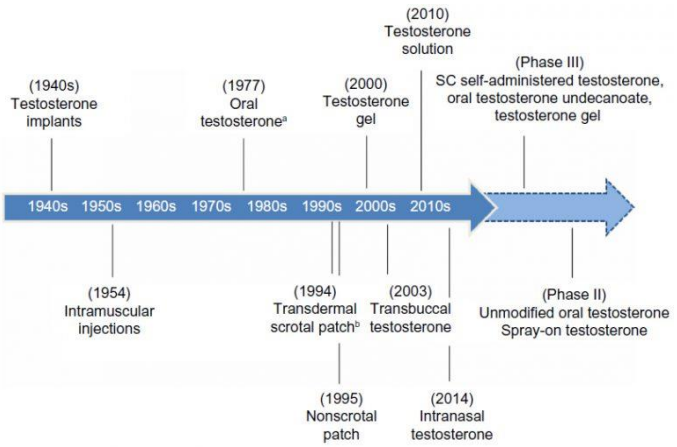
STEROIDS- DRUG ABUSE

Ms. Gayatri Patil
Department of Pharmacology, Dr. D.Y. Patil College of Pharmacy, Akurdi Pune.

ABSTRACT
Steroids are the most commonly used drugs by athletes to improve the strength of muscle but their overuse may result in addiction contributing to adverse effects on the body. This article summarizes the history of steroids, their neurobiology, mechanism of action, overdose effect, withdrawal syndrome, treatment for overdose, and non-pharmacological treatment.

INTRODUCTION
The International Day against Drug Abuse and Illicit Trafficking is observed every year on 26 June. Anabolic–androgenic steroids (AAS) are a class of hormones that can be obtained naturally or synthetically. They derive their name from both the biological effects they produce (androgenic and anabolic) and their chemical structure, the steroid nucleus. The term "anabolic" indicates how AAS builds skeletal muscle. As an oxymoron, the term "androgenic" refers to the production and maintenance of male secondary sexual traits, which in theory includes anabolic action. [1] The four androgens that are most frequently abused are testosterone, methandienone, ND, and methenolol. AAS is widely used since it minimizes androgenic effects while enhancing muscle growth for athletes' performance and aesthetic goals. While professional bodybuilders were the first to utilize androgens, recreational athletes are now more likely to do the same. Androgens can, in fact, improve both the size and strength of muscle fibers.[2] Males between the ages of 20 and 40 who lift weights are the typical AAS users. Illegal AAS can be simply and affordably acquired from local dealers via the Internet. The majority of AAS use occurs in cycles lasting six to eighteen weeks. Several drugs are used concurrently in most AAS cycles at doses significantly higher than substitution doses. Human growth hormone, thyroid hormone, tamoxifen, clomiphene citrate, and human chorionic gonadotrophin are among the many other performance- and appearance-enhancing medications that are frequently utilized. [3] Some female bodybuilders also utilize it to gain muscle, which is challenging for women to achieve without hormonal preparations. Women are nonetheless susceptible to adverse effects even though they often consume smaller amounts of AAS than males. According to research, women who use AAS frequently worry about male-stigmatizing side effects (such as a deeper voice, a more masculine appearance, and infertility). [4] Around the world, the rate of abusing AAS is 5%; men between the ages of 18 and 35 typically use AAS. AAS abuse was reported to occur in several nations around the world, including the United States (0.9% in males and 0.1% in women), Poland (0.6% in men and 0.3% in women), and Norway (3% in men and 1% in women). Long-term use of high dosages of AAS can lead to substantial organ damage and dysfunction, including cardiac problems, bone and tendon damage, decreased sperm production, diminished sexual function, kidney damage, brain cell apoptosis, depression, anxiety, aggression, addiction, and dependence. Thus, it is thought that education and understanding will be crucial in reducing the abuse of AAS.[5]

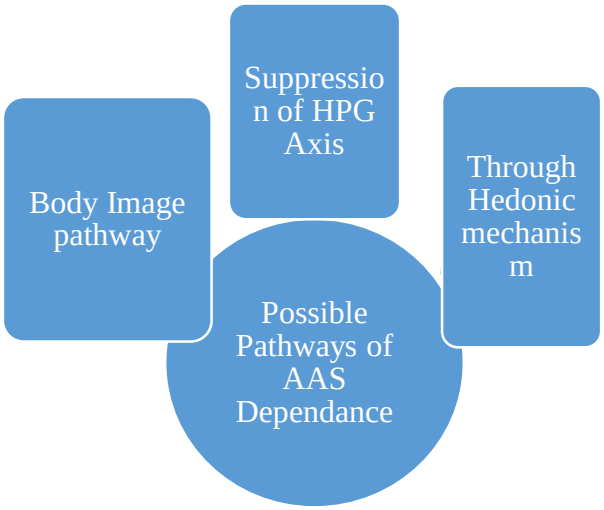
HISTORY OF DRUG WITH COMMON NAMES OF DRUG



NEUROBIOLOGY OF DRUG ABUSE OR ADDICTION

Physical and psychological dependence

Anabolic steroids cause pharmacological effects in the central nervous system (CNS) in two different ways: directly by regulation of their intracellular receptors, and indirectly through altering the binding site at the neurotransmitter receptor or releasing neuropeptides. The expression of certain neurotransmitter receptors, including dopamine (DA), glutamate (GLU), serotonin (5-HT), and gamma-aminobutyric acid (GABA), can be impacted by these processes. These receptors are highly expressed in brain regions linked to a variety of behavioural and physiological states. [6]



Body Image pathway- This occurs when a person becomes afraid that stopping AASs may cause him to lose muscle mass, making him reluctant to quit taking the medication, even for a brief period of time.Suppression of HPG Axis- It occurs via inhibition of pulsatile GnRH release and a subsequent decrease in LH and FSH. Through Hedonic mechanism- Repertoire sites on cell membranes mediate it instead of the traditional genomically mediated anabolic or androgenic effects. [7]

MECHANISM OF DRUG ACTION OR ABUSE

Steroid hormones can cross the target cell's membrane. The cytoplasmic receptor that the steroid hormone binds to is particular. The steroid hormone attached to the receptor enters the nucleus and attaches itself to a different particular receptor on the chromatin. Messenger RNA (mRNA) molecules, which code for the synthesis of proteins, are produced in response to the steroid hormone-receptor complex. Overdose effect with clinical manifestation

The overdose of steroids can result in many adverse effects like-

Burning/itchy skin, Agitation or psychosis, Convulsions, High blood pressure, Muscle and bone weakness, Nausea or vomiting, Extreme sleepiness, worsening health conditions, Nervousness, Depression, Swelling in the legs.

Extended anabolic steroid abuse can result in a serious set of negative effects, such as:

Kidney/liver damage, Increased blood pressure, Enlarged heart, Dangerous cholesterol changes, even in younger users, Major mood swings, Aggression and irritability, Delusions, Stunted growth in young users.[8] Clinical manifestations are- depressed mood, anorexia, fatigability, akathisia, decreased sex drive, insomnia, suicidal tendencies, body image dissatisfaction, abuse liability, and headache.

TREATMENT OF OVERDOSE

Treatment for steroid overdose may include:

Activated charcoal, Breathing support (oxygen or a ventilator), Intravenous fluids, Laxatives, Medication to treat symptoms, Skin and eye washing if the product touched these tissues and they are irritated or swollen Reducing or stopping corticosteroid use, **Supportive care,** Fluid management [9]

WITHDRAWAL SYNDROME

Two phases of AAS withdrawal syndrome are acute and chronic. The acute phase includes sympathetic activation leading to somatic symptoms of headache, tremors, palpitations, and nausea. The chronic symptoms include hypogonadism,low libido, erectile dysfunction, and fatigue.[10] Some of the syndromes related to topical steroids are “red skin syndromes”, described as a distinct pattern of chronic worsening eczematous rash including red face syndrome, post-peel syndrome, status cosmeticus, red scrotum syndrome, vulvodynia,

peri anal atrophoderma, chronic actinic dermatitis and chronic severe eczema. [11]

Non-pharmacological treatment of steroids It includes exercise and physical therapy, Weight management, Cognitive Behavioral Therapy, Yoga, Acupuncture, Heat and cold therapy, etc.

LEGAL STATUS IN INDIA

The usage of performance-enhancing drugs (PEDs) and anabolic steroids is a complicated topic in India. Some steroids are severely regulated or forbidden, while others are acceptable and available for medicinal usage. It is against the law to sell, possess, or use steroids in the nation without a legitimate prescription from a licensed healthcare provider. Additionally, the Indian government has passed strict legislation prohibiting the use of these drugs in sports, and those found guilty of doping face harsh punishments.

CONCLUSION

Anabolic steroid use is on the rise and users continue to exhibit lack of understanding regarding its potential effects. This review shows that long-term administration of high doses of AASs may lead to serious consequences, such as hypogonadism, cardiac impairment, neurodegeneration, coronary artery disease, and sudden cardiac death. Information and education are fundamental tools for AAS misuse prevention. As long as anabolic steroid misuse is popular among young athletes, information campaigns regarding AASs and other doping agents should be encouraged in high schools. It can be concluded that awareness regarding drug abuse should be enhanced with proper diagnosis and effective management.

REFERENCES

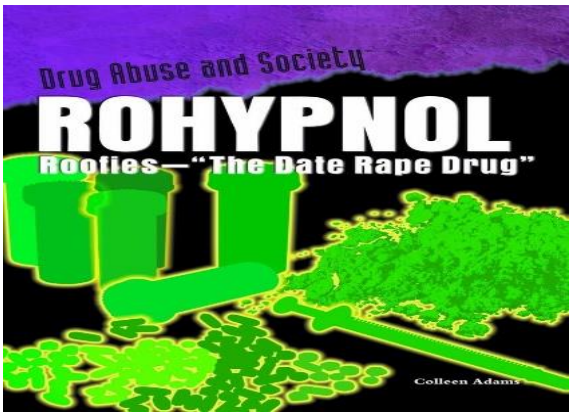
1. Bond P, Smit DL, de Ronde W. Anabolic–androgenic steroids: How do they work and what are the risks? Frontiers in Endocrinology. 2022 Dec 19;13:1059473.
2. Albano GD, Amico F, Cocimano G, Liberto A, Maglietta F, Esposito M, Rosi GL, Di Nunno N, Salerno M, Montana A. Adverse effects of anabolic-androgenic steroids: a literature review. InHealthcare 2021 Jan 19 (Vol. 9, No. 1, p. 97). MDPI.
3. de Ronde W, Smit DL. Anabolic androgenic steroid abuse in young males. Endocrine connections. 2020 Apr 1;9(4):R102-11.
4. Havnes IA, Jørstad ML, Innerdal I, Bjørnebekk A. Anabolic-androgenic steroid use among women–A qualitative study on experiences of masculinizing, gonadal and sexual effects. International Journal of Drug Policy. 2021 Sep 1;95:102876.
5. Ayubi N, Kusnanik NW, Herawati L, Komaini A, Cholik T, Syafawi A. Abuse of anabolic-androgenic steroids and adverse effects on human organ health: a review. Biointerface Res Appl Chem. 2023 Jun 15;13(3):1-.
6. Belchior santos jp, baêta lacerda fr, almeida de oliveira le, borcard fialho br, nogueira assunção is, gonçalves santana ma, ferreira gomides li, do carmo cupertino ma. Neurological consequences of abusive use of anabolic-androgenic STEROIDS. Brazilian Journal of Surgery & Clinical Research. 2020 Sep 1;32(2).
7. Pope Jr HG, Kanayama G. Neurobiology and treatment of anabolic-androgenic steroid-related disorders. Brady KT, Levin FR, Galanter MC, Kleber DH, editos. The American Psychiatric Association Publishing Textbook of Substance Use Disorder Treatment. Washington, DC: American Psychiatric Association. 2021 Jan 15:315-.
8. Symptoms of Steroid Overdose | Corticosteroid & Anabolic (drugabuse.com))
9. Ericson-Neilsen W, Kaye AD. Steroids: pharmacology, complications, and practice delivery issues. Ochsner Journal. 2014 Jun 20;14(2):203-7.
10. Sharma A, Grant B, Islam H, Kapoor A, Pradeep A, Jayasena CN. Common symptoms associated with usage and cessation of anabolic androgenic steroids in men. Best Practice & Research Clinical Endocrinology & Metabolism. 2022 Sep 1;36(5):101691.

ROHYPNOL® - FLUNITRAZEPAM

Dr.(Mrs.) Pallavi Chaudhari
Department of Pharmaceutics, Dr. D.Y. Patil College of Pharmacy, Akurdi Pune

ABSTRACT

Worldwide, drug abuse has become a common problem. Any part of the globe is now affected by drug addiction. The country faces drug abuse as a major concern, with grave impact on physical health and socio-economic status. Public health is greatly affected by it across different spheres of life. In India, the youth are entrenched in an epidemic of drug abuse that has reached disturbing proportions. Substance abuse is a consequence of pressures associated with immense complexity of modern life which makes people more susceptible to this issue. This results in alcoholism/drug dependency not only affecting individuals but also their family members and the society at large. Approximately 190 million individuals globally are estimated to be using drugs, and this issue has been escalating at a concerning pace, particularly among young adults under the age of 30.



INTRODUCTION

As per the General Assembly, resolution 42/112 dated 7th December 1987, 26th June has been observed as International Day against Drug Abuse and Illicit Trafficking. This day serves as a commitment to combat drug abuse and promote awareness for drug-free world [1]. The implementation of effective drug policies should be embedded in research, human rights and understand the implications of drug abuse on social, economic life.

This year's 2024, World Drug Day is observed with the following objectives:

Raise awareness for prevention strategies, emphasize impact for drug use.

Advocate for investment: Encourage prevention efforts by governments, policymakers, and law enforcement professionals, highlighting the long-term benefits of early intervention and prevention.

Empower communities: The communities need to be equipped with the tools and resources to implement evidence-based prevention initiatives, foster resilience against drug use and promote community-led solutions.

Facilitate dialogue and collaboration: Promote dialogue and collaboration between stakeholders to enhance evidence-based prevention practices and policies, that foster supportive environment for knowledge sharing and innovation. Promote evidence-based policymaking: Advocate for evidence-based policymaking at the national and international levels, to ensure drug policies are grounded in scientific research and informed by best practices. Engage communities: Importance for prevention of drug abuse can be done by awareness programs and preventive efforts.

Empower youth: Youth should be provided with the knowledge, skills to act as mediators of change in the communities, that advocate for drug prevention initiatives and amplify their voices in the conversation. Promote international cooperation: Fostering of international cooperation, collaboration among governments, organizations, and communities for development and implementation of evidence-based strategies to combat drug trafficking, crime, recognizing the global nature of the drug problem and the need for coordinated action[2].

HISTORY OF DRUG WITH COMMON NAMES OF DRUG

Uses & Possible Health Effects	
Short-term Symptoms of Use	Drowsiness, sedation, sleep; amnesia, blackout; decreased anxiety; muscle relaxation, impaired reaction time and motor coordination; impaired mental functioning and judgment; confusion; aggression; excitability; slurred speech; headache; slowed breathing and heart rate.
Long-term Consequences of Use and Health Effects	Physical and psychological dependence; cardiovascular collapse; and death
In Combination with Alcohol	Exaggerated intoxication, severe sedation, unconsciousness, and slowed heart rate and breathing, which can lead to death.
Withdrawal Symptoms	Headache; muscle pain; extreme anxiety, tension, restlessness, confusion, irritability; numbness

Rohypnol®, ®, trade name for Flunitrazepam, a benzodiazepine that slows the central nervous system. As compared to Valium, it's 10 times stronger. In countries other than the U.S., Rohypnol®, is made by Hoffman-LaRoche, Inc., and can only be obtained with a doctor's order for the brief management of intense sleep problems. It's easily found in many parts of Europe, Mexico, and Colombia.

Lawless use of Rohypnol®, began in the 1970s in Europe and appeared in the United States in the early 1990s. important of the concern girding Rohypnol®, is its abuse as a" date rape" medicine. Rohypnol®, is a tasteless and odorless medicine and, until recent manufacturer sweats, dissolved clear in liquid, which masked its presence. Rohypnol®, comes in lozenge form and is generally vended in the manufacturer's bubble packaging, which can mislead druggies in the United States into believing the medicine is safe and legal. Since February 1999, reformulated Rohypnol®, tablets, which turn blue in a drink to increase visibility, have been approved and retailed in 20 countries. The old noncolored tablets are still available [3].

COMMON NAMES FOR ROHYPNOL®

Street names for Rohypnol®,		
Rophies	Reynolds	Circles
Rophy	Roach-2	Forget-me pill
Ropies	Roaches	Forget pill
Row-shay	Roachies	La rocha
Ruffies	Roapies	Lunch money drug
Wolfies	Robutal	Mexican valium

MECHANISM OF DRUG ACTION

Benzodiazepines (Benzos) attach to benzodiazepine receptors BNZ1 and BNZ2 without discrimination. BNZ1 controls sleep, while BNZ2 affects muscle relaxation, stops seizures, coordinates movement, and influences memory in the brain. Scientists think benzodiazepine receptors connect to gamma-aminobutyric acid-A (GABAA) receptors. When benzos bind, they boost GABA's effects and make GABA stick better to its receptor. GABA, an inhibitory neurotransmitter, binds to its site and opens it up. This allows chloride to enter cells

making it harder for those cells to fire an action potential (get excited) [4-5].

Methods of Abuse

The predator may drop Rohypnol®, in liquid, because the drug is dissolved rapidly, tasteless, odourless and colourless. The predator also can mix Rohypnol®, in snacks or foods by crushing tablet in powder form. The victim on consuming the liquid can get the effect within 10 minutes, although the complete effect does not hit her for at least an hour [6].

Overdose effect with clinical manifestation

If Rohypnol®, is used in combination with CNS depressants – opioids, alcohol, life threatening effects are increased. Overdose of Rohypnol®, include – reduced heart rate, slowed or stopped breathing, loss of consciousness and severe sedation

TREATMENT OF OVERDOSE [7]

The treatment from addiction of Rohypnol®, includes therapy and detox – that may include 3 to 5 days' detoxification program, with 24-hour medical monitoring and provide comfort and minimizes the health risks.

Integrated Mental Health Care – There are number of rehab centres that provide mental health screening, diagnosis and treatment for the disorders. Holistic therapies can be used for recovering the addicts with these conditions.

Behavioural therapies – Two therapies namely Cognitive Behavioral Therapy (CBT) and Dialectical Behavioral Therapy (DBT) improve addict's behavior. CBT promotes positivity and belief, while DBT focus n helping to make healthy choices. These therapies help to overcome the drug craving.

Individual and Group Counseling – Counseling can help to resolve the trauma, conflicts, struggles through one to one treatment. While group counseling help to share the thoughts, experiences and develop social connections.

Psychotherapy – This can help to manage the withdrawal process, detox, reduce addictive behaviors.

LEGAL STATUS

Rohypnol®, is illegal and is Schedule IV under Controlled Substances Act. Rohypnol®, is banned in India [8]

CONCLUSION

Drugs are powerful drugs but club drugs or drugs of abuse are menace to the society. Careful use of the drugs depends on appropriate awareness and legislation. As India being country with teenage population, they are targeted by foreigners for their business purpose, hence there is a need to arrange certain awareness programs to avoid such hazards. Collective efforts of health professionals, regulatory authorities and stringent laws can combat this menace from the society.

REFERENCES:

[1] https://www.un.org/en/observances/end-drug-abuse-day

[2] https://www.unodc.org/unodc/en/drugs/index-new.html

[3] https://www.ojp.gov/pdffiles1/Digitization/193976NCJRS.pdf

[4] Oelschlager H: [Chemical and pharmacologic aspects of benzodiazepines]. Schweiz Rundsch Med Prax. 1989 Jul 4;78(27-28):766-72.

[5] Maxwell JC, Spence RT. Profiles of club drug users in treatment. Subst Use Misuse 40(9–10):1409–1426, 2005

[6] Drug Facts, Club Drugs, National Institute on Drug Abuse, retrieved from, www.drugabuse.gov

[7] https://michaelshouse.com/blog/4-common-treatment-methods-for-Rohypnol®, /

HEROIN: PHARMACOLOGICAL MECHANISM, ABUSE POTENTIAL, AND THERAPEUTIC CHALLENGES

Mr. Mukesh Mohite, Ms. Priyanka Gawali,
Department of Pharmaceutical Quality Assurance, Dr. D.Y. Patil College of Pharmacy, Akurdi Pune.

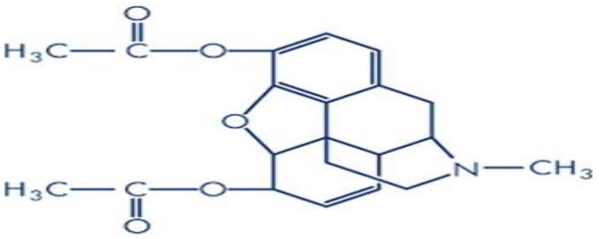
ABSTRACT

Heroin is a crude preparation of diamorphine. It is a semisynthetic product obtained by acetylation of morphine, which occurs as a natural product in opium: the dried latex of certain poppy species (e.g. Papaver somniferum L.). Diamorphine is a narcotic analgesic used in the treatment of severe pain. Illicit heroin may be smoked or solubilised with a weak acid and injected. Whereas opium has been smoked since historical times, diamorphine was first synthesised in the late nineteenth century. Heroin is under international control.

CHEMISTRY

MOLECULAR FORMULA: C21H23NO5

Molecular weight: 369.4 g/(IUPAC) Diamorphine (diacetylmorphine; CAS-561-27-3) is produced by the acetylation of crude morphine.



The systematic name (IUPAC) is (5α,6α)-7,8-didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol acetate. Although five pairs of enantiomers are theoretically possible in morphine, only one occurs naturally (5R, 6S, 9R, 13S, 14R)

PHARMACOLOGY

Diamorphine, like morphine and many other opioids, produces analgesia. It behaves as an agonist at a complex group of receptors (the μ, κ and δ subtypes) that are normally acted upon by endogenous peptides known as endorphins. Apart from analgesia, diamorphine produces drowsiness, euphoria and a sense of detachment. Negative effects include respiratory depression, nausea and vomiting, decreased motility in the gastrointestinal tract, suppression of the cough reflex and hypothermia. Tolerance and physical dependence occur on repeated use. Cessation of use in tolerant subjects leads to characteristic withdrawal symptoms. Subjective effects following injection are known as 'the rush' and are associated with feelings of warmth and pleasure, followed by a longer period of sedation. Diamorphine is 2–3 times more potent than morphine. The estimated minimum lethal dose is 200 mg, but addicts may be able to tolerate ten times as much. Following injection, diamorphine crosses the blood–brain barrier within 20 seconds, with almost 70 % of the dose reaching the brain. It is difficult to detect in blood because of rapid hydrolysis to 6-monoacetylmorphine and slower conversion to morphine, the main active metabolite. The plasma half-life of diamorphine is about three minutes. Morphine is excreted in the urine largely as the glucuronide conjugate. Diamorphine is associated with far more accidental overdoses and fatal poisonings than any other scheduled substance. Much morbidity is caused by infectious agents transmitted by unhygienic injection.

ORIGIN/EXTRACTION

The latex from the seed capsules of the opium poppy (Papaver somniferum L.) is allowed to dry. This material (opium) is dispersed in an aqueous solution of calcium hydroxide (slaked lime). The alkalinity is adjusted by adding ammonium chloride, causing morphine base to precipitate. The separated morphine is boiled with acetic anhydride. Sodium carbonate is added, causing the crude diamorphine base to separate. Depending on the region, this may be used directly, further purified or converted into the hydrochloride salt. Until the late 1970s, nearly all heroin consumed in Europe came from south-east Asia, but now most originates from south-west Asia, an area centered on Afghanistan and Pakistan. Heroin is also produced in certain parts of South America, but that material is rarely seen in Europe. Acetic anhydride, an essential

precursor in the manufacture of heroin, is listed in Table I of the United Nations 1988 Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances. The corresponding EU legislation is set out in Council Regulation (EEC) No 3677/90 (as later amended), which governs trade between the EU and third countries. As with other naturally occurring drugs of misuse, total synthesis of the active principles is not currently an economic proposition.

MODE OF USE

Heroin from south-west Asia may be 'smoked' by heating the solid on a metal foil above a small flame and inhaling the vapour. Those intending to inject this form of heroin must first solubilise it with, for example, citric acid or ascorbic acid. Heroin from south-east Asia is suitable for direct injection of a solution. A typical dose is 100 mg at street level purity. Except when used therapeutically as an analgesic drug, ingestion of diamorphine/heroin is a much less effective route of administration.

CONTROL STATUS

Heroin is listed in Schedule I of the United Nations 1961 Single Convention on Narcotic Drugs. Diamorphine is also included in a generic sense since the 1972 Protocol, which revised the 1961 Convention, extended control to esters and ethers of scheduled substances. Thus, diamorphine is the diacetyl ester of morphine (Schedule 1).

ABUSE OF HEROIN

It took a long time for the medical profession to realize the full danger of heroin addiction. On the other hand, very little time passed after the drug had become readily available before the underworld and smugglers discovered that heroin possessed properties even beyond those of other narcotics, which have since made it the main drug of addiction in many parts of the world. The analgesic and euphoric properties of heroin are much greater per gram than those of morphine. Here is no depression of the alimentary tract as is found in morphine. Whereas morphine usually is administered by a hypodermic needle, heroin can be sniffed into the system. [22] This is an important fact since many people are, to start with, repelled by the use of a hypodermic needle. However, persons addicted to heroin soon come to use it hypodermically and even intravenously. As the sensible effect wanes with increasing addiction, they try larger doses and more drastic methods of self-administration, always trying to recapture the stimulation of the drug.

Opioids Act on Many Places in the Brain and Nervous System

Opioids can depress breathing by changing neurochemical activity in the brain stem, where automatic body functions such as breathing and heart rate are controlled. Opioids can reinforce drug taking behavior by altering activity in the limbic system, which controls emotions.

HEROIN EFFECTS

How long does it take heroin to kick in? You may feel the effects within seconds of injecting or smoking heroin. The rush can take around 10 to 15 minutes if you snort it. But everyone reacts to drugs differently.

The effects of heroin depend on things such as:

Your weight and overall health
How often you use heroin
If you mix it with other drugs

Short-term effects of heroin

The immediate effects of heroin may include:
Euphoria
A dry mouth
Warm, flushed skin
Arms and legs that feel heavy
Upset stomach and vomiting
Itching

Long-term heroin effects

Opioids, including heroin, can change how your brain works. You may need to use more of the drug to get the same high. This is called tolerance. If you continue to use heroin often, you may become dependent and need to take the drug to avoid feeling bad when you're not on it.

Regular and long-term heroin use can also lead to:

Strong feeling of sadness
Collapsed veins
Insomnia, Constipation

Heroin Use Complications challenges

Short or long-term heroin can cause medical problems that can change your brain and damage your body.Over time, you may lose the ability to control your actions or make good decisions. You may get paranoid or have strange mood swings. If you snort heroin a lot, you may damage the lining of your nose or airways. You may destroy the tissue that separates your nasal passages (called the septum). If you use a needle to inject heroin, you may Scarred or collapsed veins. Bacterial infections in your blood vessels and heart valves. Pockets of pus caused by an infection (abscess or boil) Other infections in the soft tissue under your skin.

Infections

People who use drugs do things that raise the odds of exposure to viruses that live in blood or body fluids, including sharing needles and having risky sex. And if you get sick, you may pass the infection (hepatitis B and C, HIV) to your sexual partners or kids.

Blood vessel and organ damage

When people "cut" heroin, these extra substances can get into the bloodstream and block blood vessels. This can harm the cells that keep vital organs like your lungs, liver, kidneys, or brain working properly. Your immune system might also react to these additives, causing arthritis or other joint problems. Your medical team can help you find the treatment plan that works best for you. It will probably include medication and behavioral therapy. Experts say this medication-assisted treatment (MAT) is the "gold standard" of care for people who have heroin addiction.

REFERENCE:

1. https://www.euda.europa.eu/publications/drug-profiles/heroin_en

2. https://www.unodc.org/unodc/en/data-and-analysis/bulletin/bulletin_1953-01-01_2_page004.html

3. https://www.webmd.com/mental-health/addiction/heroin-use

4. Report of the Committee of Experts concerning Diacetylmorphine (Heroin) Records of the Conference for the Limitation of the Manufacture of Narcotic Drugs, League of Nations, Geneva, May 27th to July 13th, 1931. Vol. II. 529.

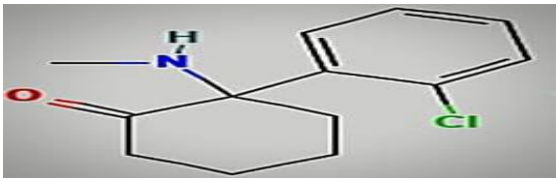
5. Woods, Arthur: Dangerous Drugs, The World Fight against illicit traffic in Narcotics, New Haven, Yale University Press, 1931, 14.

DRUG ABUSE: KETAMINE

Ms. Ankita Dudhal, Mr. Shrenik Dungarwal, Mr. Vinod Thakare,
Department of Pharmacology Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune

ABSTRACT

Ketamine is known for its dissociative anaesthetic properties and hallucinogenic effects. It can distort perceptions of sight and sound, leading to feelings of disconnection from one's surroundings. Commonly administered as an injectable, ketamine is a short-acting anaesthetic used for inducing sedation, immobility, pain relief, and amnesia in both humans and animals. However, it is often misused for its dissociative and hallucinogenic effects, and has unfortunately been used in instances of sexual assault. The term "dissociative anaesthetic" describes its ability to create a sense of detachment from pain and the environment.Ketamine, a less toxic alternative to phencyclidine, was developed decades ago. It is now approved by the FDA for treatment-resistant depression in adults. Esketamine, a derivative of ketamine, is also available as a liquid or off-white powder, known as Special K, K, super K, or Vitamin K.In this review paper we are mainly going to review origin, chemical and physical properties, mechanism of action, side effects of Ketamine. Also we ae going to review 'Drug Abuse'.



Ketamine (chemical structure and marketed preparation) Fig. no. (1)

INTRODUCTION

Ketamine is a Schedule III non-narcotic medication used by doctors to induce loss of consciousness. It is approved by the FDA for general anaesthesia but can also be prescribed for "off-label" uses like depression. Some people use ketamine for its hallucinogenic properties, which can cause sedate, incapacitate, and short-term memory loss, making it a date-rape drug.[1] While ketamine is safe for controlled medical use, it becomes hazardous for recreational use due to potential life-threatening adverse effects. It is important to understand its uses, side effects, risks, and interactions with alcohol and other drugs.[2]. Ketamine, a cyclohexanone, is a compound with a 2-chlorophenyl and methylamino group substituting hydrogens at position 2. It serves as an anaesthetic, NMDA receptor antagonist, analgesic, neurotoxin, environmental contaminant, and xenobiotic. It is a secondary amino compound and a member of monochlorobenzenes.[3]

HISTORY OF KETAMINE AND ITS COMMON NAMES:

Medical professionals have been researching post-surgery pain treatment methods for over 50 years. Ketamine, once used as an anesthetic, has been found to treat various mental health conditions. Recent scientific breakthroughs have led to the discovery of new treatment options, highlighting the potential of ketamine in various medical and psychological applications.[4] In 1962, ketamine, a structural analog of PCP, was synthesized and tested on volunteer prisoners in 1964. Results showed similar anesthetic and analgesic properties to PCP but fewer adverse side effects. Ketamine was characterized as a dissociative anesthetic, with participants experiencing feelings of floating in outer space and dying.[5]

COMMON NAMES

Ketalar, Ketavet and Ketamine Hydrochloride Injection, Special K, K, Kit Kat, Cat Valium, Super Acid, Special La Coke, Purple, Jet, and Vitamin K. [1]

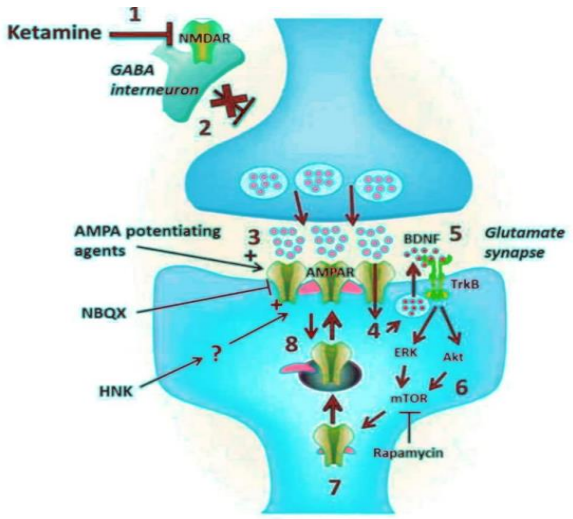
NEUROBIOLOGY OF KETAMINE ABUSE

Ketamine, initially anesthetic, is now recognized for its therapeutic effects, especially in treatment-resistant depression, but also has high abuse potential leading to neurobiological changes. Here's a detailed look at the neurobiology of ketamine abuse:

Mechanism of action: Ketamine, a neurotransmitter, acts as an NMDA receptor antagonist, blocking glutamate, reducing excitatory signaling and providing anesthetic and dissociative effects, but its effects extend beyond the NMDA receptor. [6] It also influences other receptors and pathways, including:

AMPA receptors: Ketamine's antidepressant effects are attributed to its indirect increase in activity at AMPA receptors.[7]

Opioid receptors: The substance may interact with opioid receptors, enhancing its analgesic properties and increasing its potential for abuse.[8]Dopamine system: Ketamine enhances dopamine release in the brain's reward pathways, particularly in the nucleus accumbens, which is crucial for reinforcing drug-taking behavior.[9]



Mechanism of action of Ketamine

Fig. no. (2)

OVERDOSE EFFECT OF KETAMINE

Ketamine overdose can be life-threatening, causing various symptoms based on the dose, administration route, and individual's tolerance and overall health, depending on the severity. Here's an overview of the effects and clinical manifestations of a ketamine overdose:

Neurological and Psychological Effects: Ketamine overdose can cause extreme dissociation, known as a "K-hole," characterized by intense hallucinations and out-of-body experiences.

Cardiovascular Effects:

Ketamine can significantly elevate blood pressure, which can pose a significant risk, particularly in individuals with pre-existing cardiovascular conditions.Elevated heart rate is a common issue, and in severe cases, it can lead to arrhythmias, irregular heartbeats that can be life-threatening.[10]Respiratory Effects: Ketamine, a less common sedative, can cause respiratory depression and, in severe cases, complete cessation of breathing. Death: Ketamine overdose is rare, but can occur when combined with other depressants like alcohol, benzodiazepines, or opioids, causing respiratory and cardiovascular depression. [11]

CLINICAL MANAGEMENT

Treatment of ketamine overdose primarily involves supportive care: Airway Management: The task involves maintaining an open airway and ensuring adequate breathing, potentially utilizing oxygen or mechanical ventilation if necessary.

Cardiovascular Support: The process involves monitoring and stabilizing blood pressure and heart rate, potentially using medications to manage hypertension or arrhythmias.

Activated Charcoal: Early detection of an overdose can be achieved by administering activated charcoal to restrict absorption in the gastrointestinal tract.[11]

WITHDRAWAL SYMPTOMS OF KETAMINE

Ketamine withdrawal occurs when a person stops or significantly reduces their ketamine intake, often leading to psychological and physical withdrawal symptoms. These symptoms vary in intensity depending on the duration and frequency of use, as

well as the individual's overall health and tolerance, and are not typically associated with severe physical dependence like opioids or alcohol.[12]

Psychological Symptoms:

Anxiety: Users may experience increased anxiety, restlessness, and nervousness after stopping ketamine, which is a common withdrawal symptom.

Depression: Ketamine withdrawal can cause depressive symptoms like low mood, hopelessness, and motivation, especially for those who self-medicate for depression.[12]

Cravings: Individuals may experience intense cravings for ketamine, making it challenging to resist the urge to re-use the drug.

Physical Symptoms:

Fatigue: Ketamine withdrawal can lead to significant fatigue and lethargy in many individuals.

Tremors: Ketamine withdrawal can lead to significant fatigue and lethargy in many individuals.

Sweating: Excessive sweating, particularly at night, may be a physical symptom of withdrawal. [13]

DURATION OF WITHDRAWAL:

Ketamine withdrawal symptoms can begin within hours to a day after the last dose, with the acute phase lasting a few days to a week. However, psychological symptoms like anxiety, depression, and cravings may persist for weeks or even months, especially if there is an underlying mental health disorder. [13]

TREATMENT OF KETAMINE DRUG ABUSE

Ketamine abuse treatment involves a holistic approach that addresses both physical and psychological aspects, involving detoxification, behavioral therapies, and ongoing support to prevent relapse. Here's an overview of the main strategies used in the treatment of ketamine abuse:

Detoxification: Detoxification is the initial treatment for ketamine abuse, allowing the drug to be eliminated under medical supervision. This process may involve:

Medical Supervision: Medical supervision during ketamine withdrawal helps manage discomfort and monitor complications, providing supportive care like hydration, nutrition, and sleep management.[14]

Symptom Management: Medications can be prescribed to manage withdrawal symptoms like anxiety, insomnia, or agitation, but no specific medications are approved for ketamine withdrawal.

Behavioral Therapies: Behavioral therapies are the primary method for treating ketamine addiction, focusing on addressing the psychological and behavioral aspects of the addiction and promoting healthier coping mechanisms.

Cognitive-Behavioral Therapy (CBT): CBT is a widely used treatment for addiction, assisting individuals in identifying and changing negative thought patterns, behaviors, and coping strategies to manage cravings and prevent relapse.

Motivational Interviewing (MI): MI is a counseling method that motivates individuals to change their behavior by encouraging self-reflection and fostering a desire to quit ketamine and seek treatment.

Dialectical Behavior Therapy (DBT): DBT, a combination of Cognitive Behavioral Therapy and mindfulness techniques, is particularly effective for individuals with co-occurring mental health disorders like borderline personality disorder or depression.[14]

Holistic and Complementary Therapies: Holistic approaches, which consider the physical, emotional, and spiritual aspects of recovery, can be beneficial for some individuals.

Mindfulness and Meditation: Mindfulness meditation is a practice that aids individuals in managing stress, reducing cravings, and maintaining focus on their recovery goals.

Exercise and Nutrition: Physical activity and a healthy diet can enhance overall well-being, support mental health, and decrease the likelihood of relapse. [15]

LEGAL STATUS OF KETAMINE IN INDIA

Ketamine is a controlled substance in India under the Narcotic Drugs and Psychotropic Substances (NDPS) Act of 1985. Here's a detailed overview of its legal status:

Classification:

Psychotropic Substance: Ketamine, classified as a psychotropic substance under the NDPS Act, is subject to government regulation in its production, distribution, sale, and use.

Medical Use:

Permitted for Medical Purposes: Ketamine, a widely used anesthetic in human and veterinary medicine in India, is legally available for medical use but is strictly regulated and only authorized by licensed practitioners.

Prescription Requirement: Ketamine is a drug that requires a valid prescription from a licensed healthcare provider and is illegal for unauthorised possession or use.(16)

Control and Regulation:

Licensing: Ketamine production, distribution, and sale require government-issued licenses, ensuring its use only for legitimate medical or scientific purposes under strict conditions.

Record-Keeping: Ketamine production and distribution entities are required to maintain detailed records of its use, including production, sales, and administration.(17)

Penalties for Illegal Use:

Illegal Possession: Ketamine possession without a prescription or license is a criminal offense under the NDPS Act, with penalties ranging from imprisonment to fines depending on the quantity involved.

Trafficking and Distribution: Ketamine trafficking, distribution, or production leads to severe penalties like long-term imprisonment and heavy fines, with the severity increasing with the substance quantity involved.(18)

Abuse and Recreational Use:

Illegal and Punishable: The Indian government is enforcing the law against the illegal recreational use of ketamine due to its potential for abuse and addiction.

Law Enforcement: India's law enforcement agencies are actively monitoring and enforcing regulations related to ketamine to curb its illicit use and distribution. (18)

Recent Developments:

Stricter Regulations: India has increased monitoring and control measures to prevent the diversion of ketamine for recreational use due to concerns about its abuse potential over the years.

CONCLUSION

Ketamine abuse is a global public health concern due to its potent dissociative and hallucinogenic effects, causing physical, psychological, and social harm. Despite its medical uses, its potential for abuse and addiction is a global concern.

Ketamine abuse poses significant risks to individuals and society, necessitating robust preventive measures, effective treatment strategies, and ongoing research. Public awareness, education, and accessible treatment are crucial for addressing the challenges and helping those affected recover and lead healthier lives.

REFERENCES

1. Morgan, Celia J. A., H. Valerie Curran, and the Independent Scientific Committee on Drugs (ISCD). "Ketamine Use: A Review." *Addiction* 107, no. 1 (January 2012): 27–38.
2. Sassano-Higgins, Sean, Dave Baron, Grace Juarez, Neevon Esmaili, and Mark Gold. "A REVIEW OF KETAMINE ABUSE AND DIVERSION: Review: Ketamine." *Depression and Anxiety* 33, no. 8 (August 2016): 718–27.
3. Marraffa, J.M. "Drugs of Abuse." In *Encyclopedia of Toxicology*, 248–51. Elsevier, 2014.
4. Domino, Edward F., and David S. Warner. "Taming the Ketamine Tiger." *Anesthesiology* 113, no. 3 (September 1, 2010): 678–84.
5. Chang, Lee C., Suman Rajagopalan, and Sanjay J. Mathew. "The History of Ketamine Use and Its Clinical Indications." In *Ketamine for Treatment-Resistant Depression*, edited by Sanjay J. Mathew and Carlos A. Zarate, 1–12. Cham: Springer International Publishing, 2016.
6. Aleksandrova, Lily R., Anthony G. Phillips, and Yu Tian Wang. "Antidepressant Effects of Ketamine and the Roles of AMPA Glutamate Receptors and Other Mechanisms beyond NMDA Receptor Antagonism." *Journal of Psychiatry and Neuroscience* 42, no. 4 (July 1, 2017): 222–29.
7. Abdallah, Chadi G., Gerard Sanacora, Ronald S. Duman, and John H. Krystal. "The Neurobiology of Depression, Ketamine and Rapid-Acting Antidepressants: Is It Glutamate Inhibition or Activation?" *Pharmacology & Therapeutics* 190 (October 2018): 148–58.

8. Krystal, John H., Alfred P. Kaye, Sarah Jefferson, Matthew J. Girgenti, Samuel T. Wilkinson, Gerard Sanacora, and Irina Esterlis. "Ketamine and the Neurobiology of Depression: Toward next-Generation Rapid-Acting Antidepressant Treatments." *Proceedings of the National Academy of Sciences* 120, no. 49 (December 5, 2023): e2305772120.
9. Shinohara, Ryota, George K. Aghajanian, and Chadi G. Abdallah. "Neurobiology of the Rapid-Acting Antidepressant Effects of Ketamine: Impact and Opportunities." *Biological Psychiatry* 90, no. 2 (July 2021): 85–95.
10. Chaves, Tharcila V., Bob Wilffert, and Zila M. Sanchez. "Overdoses and Deaths Related to the Use of Ketamine and Its Analogues: A Systematic Review." *The American Journal of Drug and Alcohol Abuse* 49, no. 2 (March 4, 2023): 141–50.
11. Green, Steven M, Richard Clark, Mark A Hostetler, Michael Cohen, Douglas Carlson, and Steven G Rothrock. "Inadvertent Ketamine Overdose in Children: Clinical Manifestations and Outcome." *Annals of Emergency Medicine* 34, no. 4 (October 1999): 492–97.
12. Chen, Lian-Yu, Chih-Ken Chen, Chun-Hsin Chen, Hu-Ming Chang, Ming-Chyi Huang, and Ke Xu. "Association of Craving and Depressive Symptoms in Ketamine-Dependent Patients Undergoing Withdrawal Treatment." *The American Journal on Addictions* 29, no. 1 (January 2020): 43–50.
13. Roxas, Nichole, Chaarushi Ahuja, Jessica Isom, Samuel T. Wilkinson, and Noah Capurso. "A Potential Case of Acute Ketamine Withdrawal: Clinical Implications for the Treatment of Refractory Depression." *American Journal of Psychiatry* 178, no. 7 (July 2021): 588–91.
14. Barik, Amiya K, Rajeev Chauhan, Ashwini Reddy, and Narender Kaloria. "Concerns on the Use of Ketamine in the Treatment of Depression." *Indian Journal of Psychological Medicine* 46, no. 1 (January 2024): 94–95.
15. Jones, Jennifer L., Camilo F. Mateus, Robert J. Malcolm, Kathleen T. Brady, and Sudie E. Back. "Efficacy of Ketamine in the Treatment of Substance Use Disorders: A Systematic Review." *Frontiers in Psychiatry* 9 (July 24, 2018): 277.
16. Radvansky, Brian M., Shawn Puri, Anthony N. Sifonios, Jean D. Eloy, and Vanny Le. "Ketamine—A Narrative Review of Its Uses in Medicine." *American Journal of Therapeutics* 23, no. 6 (November 2016): e1414–26.
17. Bloomfield, Andrew, Norine Chan, Leah Fryml, Reuben Horace, and Srinivas Pyati. "Ketamine for Chronic Pain and Mental Health: Regulations, Legalities, and the Growth of Infusion Clinics." *Current Pain and Headache Reports* 27, no. 10 (October 2023): 579–85.
18. Liao, Yanhui, Yi-lang Tang, and Wei Hao. "Ketamine and International Regulations." *The American Journal of Drug and Alcohol Abuse* 43, no. 5 (September 3, 2017): 495–504.

THE DUAL NATURE OF OPIUM: PHARMACOLOGICAL BENEFITS AND ADDICTIVE PROPERTIES

Mr. Lalit Nimekar, Ms. Poonan Mulay
Department of Pharmaceutical Quality Assurance, Dr. D.Y. Patil College of Pharmacy, Akurdi Pune.

ABSTRACT
Opium's history is rich. It has complex pharmacological properties and is significant. While there are therapeutic advantages, but addiction is a problem. This review article explores the various aspects of opium, covering its neurobiology, physiological effects, and potential for both physical and psychological dependence. it also examines clinical indicators of overdose, withdrawal symptoms, and possible treatments. These include both non-pharmacological and pharmacological methods. also focus on the legal status of opium in India, underlining the necessity to strike a balance between restrictions and its medical use. This review article aims to enhance comprehension and direct efficient handling of opium-related concerns.

INTRODUCTION
For many centuries, opium has been important in both medicine and society. It acts as a powerful pain reliever but can also be misused. The historical background along with the neurobiological aspects of addiction shows how complicated opium use really is. Grasping how physical plus psychological dependence works, as well as overdose and withdrawal effects, is vital for crafting good treatment plans.

HISTORY
The history of opium is a complicated interconnection of colonialism, economic aspirations, and public health. The poppy plant, Papaver somniferous, is the source of opium and has been utilized for generations. Egyptian documents from 1500 BC attest to the medicinal properties of the poppy plant. [1] However, the British East India Company's attempt to balance trade imbalances with China, mainly due to the demand for tea, marked the beginning of its transition into a worldwide commodity in the 17th century. Opium was smuggled into China despite a long-standing restriction on its importation as a strategic alternative in response to Chinese hostility to British goods [2][3].A significant turning point occurred during the First Opium War (1839–1842), when Britain used force to defend its lucrative trade. The Treaty of Nanking, which legalized the opium trade and gave Hong Kong to Britain due [3]. The growth of the opium trade had a fatal effect on Chinese society, causing social unrest and widespread addiction.

In the 19th century, the usage of opium shifted from being exclusively medicinal to being consumed recreationally, especially in Western countries. When morphine was introduced the situation got even more complicated even though at first it was believed to be a reliable and effective pain reliever. It was marked as a medical breakthrough [2][4]. But the emergence of heroin in the late 19th century—a drug made from morphine—sparked a new wave of addiction that would trouble all nations. Given the current opioid crisis in the United States, which has claimed over half a million lives in the last ten years alone, the legacy of the opium trade is still very much in evidence today. [3] Opium cultivation in India dates back to ancient times, with significant historical roots during the British colonial period. The British Raj relied heavily on opium production, which constituted a substantial portion of revenue. Post-independence, the cultivation of opium was retained under strict government control, primarily for medicinal and scientific purposes, in compliance with the United Nations Single Convention on Narcotic Drugs, 1961. [14]

NEUROBIOLOGY OF A OPIUM ABUSE AND ADDICTION
Opium addiction stems mainly from its powerful compounds, including morphine and heroin. These

drugs significantly change neurobiological pathways tied to reward, stress, & decision-making. The way opioids work is by attaching to mu-opioid receptors (MORs) found in the brain. These receptors are key in the reward circuitry. When opioids connect with them, dopamine is released in the nucleus accumbens, resulting in feelings of joy and strengthening the urge to use drugs [5].

Long-term use of opioids causes neuroadaptations that lead to tolerance & dependence. Over time, the brain gets used to having opioids around. Naturally occurring opioids are produced less, making the reward system less responsive to regular rewards—this condition is called "hypohedonia" [6]. As a result, individuals often find they need to take more of the drug just to get the same high, keeping them stuck in a cycle of addiction.

Another key player in opioid addiction is the lateral habenula. This brain region relates to feelings of aversion & negative reinforcement and shows increased activity during withdrawal phases. It seems to be vital in managing the bad emotional states that happen when someone stops using drugs[5]. Moreover, research highlights that genetic considerations—like variations in the OPRM1 gene—can affect how susceptible someone is to becoming addicted to opioids. This brings attention to how genetics and environmental factors work together in developing this complex problem[6].

Physical and psychological dependence

Opium addiction causes both physical & psychological dependence, which greatly changes how the brain's reward & systems work. When someone takes opium, compounds like morphine & heroin attach to mu-opioid receptors (MORs) in the brain. This process triggers dopamine release in a part called the nucleus accumbens. People feel euphoric, which makes them want to use drugs again. This behaviour helps build psychological dependence. [5]

When opioids are used over a long time, the brain gets used to them. This leads to tolerance & physical dependence. As it adapts, the brain lowers its own production of natural opioids. The reward system starts to respond less to everyday pleasures too [6]. People then need to take more of the drug just to feel the same high, which keeps them trapped in addiction.

Withdrawal symptoms can make things worse. These include feelings of dysphoria, anxiety, and hyperkatifeia—a really tough emotional state. They happen when opioid levels drop, causing discomfort that pushes people to seek out the drug again [5]. Stress response systems, especially the hypothalamic-pituitary-adrenal (HPA) axis, go out of whack too. This leads to stronger cravings and a desperate urge to use opioids again [6].

MECHANISM OF OPIUM ACTION

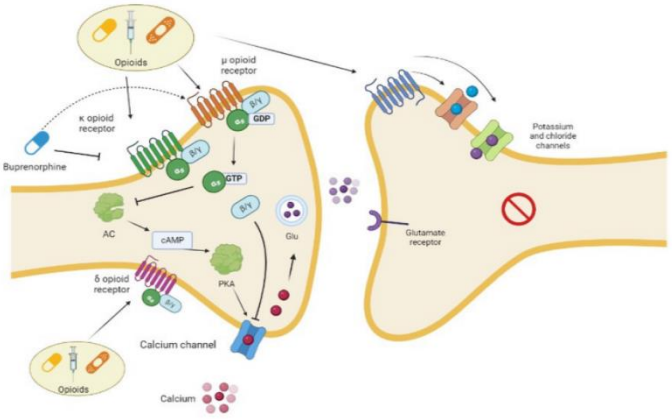
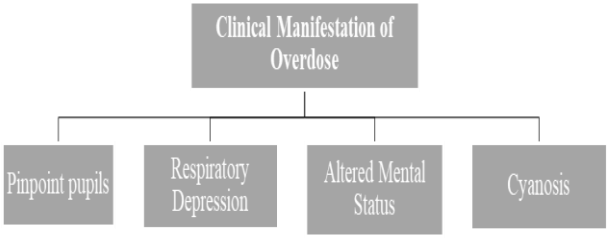


Fig 1: - Mechanism of opium action [7]

Opioids binds to their μ, κ, and δ receptors at the presynaptic level, leading to various effects. When they interact with a receptor, the α subunit of protein G blocks the adenylate cyclase (AC) pathway. This action results in decreased activity of calcium channels, which then leads to less glutamate release. Interestingly, this same channel is also blocked by the βγ subunit. Buprenorphine is unique because it partially activates the μ receptor but works as an antagonist on κ receptors. Furthermore, opioids stimulate activities on both calcium & chloride channels. This stimulation causes hyperpolarization at the postsynaptic level. To clarify terms: AC stands for adenylate cyclase; cAMP means cyclic adenosine monophosphate; GDP refers to guanosine diphosphate; Glu is shorthand for glutamate; GTP stands for guanosine-5'-triphosphate; and PKA is protein kinase A.[7]

OVERDOSE EFFECT WITH CLINICAL MANIFESTATION

Opium overdose is a serious medical emergency. It's marked by severe problems with the central nervous & breathing. If not treated quickly, it can lead to fatal results. When someone**.** overdoses on opium, they often show a triad of symptoms: pinpoint pupils (also called miosis), slow breathing, & a change in their mental state [8]. Patients might breathe very slowly. This can get worse and lead to apnea—when breathing stops altogether—causing hypoxia. And the brain might not get enough oxygen, which can harm it over time [9]. Also notice cyanosis on the skin, especially around lips & fingertips. This shows that oxygen levels are low. Other signs include drowsiness, confusion, and in severe cases, lose consciousness or coma [10]. When mu receptors are overstimulated, it can lead to less respiratory drive and confusion [5]. The risk of overdose goes up for people with a past history of using opioids. This is especially true after they haven't used them for some time since tolerance decreases and they can become sensitive to even normal doses [8].



TREATMENT OF OVERDOSE

Pharmacological treatment of Opium abuse.

The treatment of opium abuse mainly uses medication-assisted treatment (MAT). Thi approach to ease withdrawal symptoms & reduce cravings. It also works to prevent relapse. There are two main drugs used in MAT for opium abuse: methadone and buprenorphine.

Methadone: -Methadone is a long-acting synthetic opioid agonist. It can be given once a day, helping replace the need for many doses of opium. This medication supports stabilizing a patient's life by cutting down criminal activities, sharing needles, & risky sexual behaviours often linked to opium use. However, methadone is tightly controlled only

Buprenorphine:-

Buprenorphine serves as a

Naloxone is an opioid antagonist that can quickly counteract the effects of opioid toxicity. It helps restore normal breathing and consciousness [9]. However, since naloxone doesn't last long in the body, multiple doses might be needed. Naloxone can be given in different ways including intravenous intramuscular, subcutaneous, or even intranasal methods. The intranasal route works well in emergency. If patient doesn't respond right away, repeat doses of naloxone might be given every 2-3 minutes, up to a total of 10 mg[8][12].

Supportive care, including ensuring ventilation and checking vital signs, is important. Patients should be observed for re-sedation, as the effects of naloxone may end before the opioids are fully cleared from the body[8]. Patients who have had repeated doses or large infusions of naloxone should be admitted to a supervised setting since they are still susceptible to recurrent respiratory depression.[11]

WITHDRAWAL SYNDROME

Patients who acquire physiologically dependent on opioids and then decrease or stop using them experience opioid withdrawal syndrome.

Dysphoria, Insomnia, Muscle aches, Sweating, Yawning, Rhinorrhea (runny nose), Lacrimation (tearing), Nausea and vomiting, Diarrhea, Abdominal cramping, Piloerection (goosebumps), Dilated pupils (mydriasis) found in certain clinics. This can limit access for some patients [12].

NON - PHARMACOLOGICAL TREATMENT OF OPIUM ABUSE.

The non-drug treatment of opium abuse is very important as it deal with both psychological and behavioural parts of addiction. This includes different therapies that support people on their path to recovery.

Cognitive-Behavioural Therapy (CBT) is used to help people spot and change harmful thoughts & behaviours linked to substance use. It gives patients, tools to handle stress & cravings better. So it helps them make healthier choices [9]

Motivational Enhancement Therapy: -This therapy aims to boost a person's desire to change by tackling mixed feelings about treatment. By

encouraging patients to set their own goals, it strengthens their dedication to recovery. As a result, this improves how well they stick with treatment [9]

Contingency Management: - With contingency management, people receive rewards for good actions like staying sober or joining therapy sessions. This method has been effective in getting more people involved in treatment & lowering substance use [9].

Group Therapy: - Group therapy creates a safe space where individuals can share their experiences & difficulties with others who understand what they're going through. This collective method reduces loneliness & stigma, resulting in a sense of community and responsibility. [9]

Family Therapy: - Bringing in family members during treatment can strengthen communication & relationships. It addresses hidden issues that might lead to substance use. Family therapy fosters a supportive home that aids recovery. [9]

Peer Support Groups: - Programs such as Narcotics Anonymous (NA) offer ongoing help & motivation from peers who have faced similar problems. These groups encourage shared experiences & coping methods, which reinforces the recovery journey. [9]

LEGAL STATUS OF OPIUM IN INDIA

The legal status of opium in India is shaped by a complicated set of rules. These rules are aimed at controlling how opium is grown and used, strictly for legitimate medical or scientific reasons. India is among the few countries that allow the legal farming of opium poppy i.e. *Papaver somniferum*. This plant is crucial for producing important substances, like morphine & codeine. These are key in modern medicine, primarily for managing pain and coughs [13]. The main law guiding this is the Narcotic Drugs & Psychotropic Substances (NDPS) Act of 1985. This act power to the Indian government to oversee opium cultivation. The Central Bureau of Narcotics (CBN) handles the licensing. They make sure that farmers only grow opium in specific areas located in Madhya Pradesh, Rajasthan, & Uttar Pradesh. Every year, the government identifies these areas and sets rules for how opium can be cultivated. For farmers to keep their licenses, they must meet Minimum Qualifying Yield (MQY) standards [13]. Opium farming in India goes way back to ancient times and became especially important during British colonial rule. The British relied heavily on it because it was a significant source of income. After India gained independence, the country kept its legal framework for growing opium while emphasizing control over production. This control helps prevent misuse but also ensures that the pharmaceutical industry's needs are met [13].Even with these regulations in place, India has difficulties like illegal opium production and a strong black market. This situation makes India one of the world's largest producers of illegal opium. A major reason for this issue is the gap between government-set prices & those in the unlawful market. Often, farmers find it more profitable to sell their crops illegally rather than through official channels [13]. Thus, while the government enforces its strict policies and oversight, it faces the constant challenge of balancing legitimate medical usage with fighting against diversion and illegal trade.

CONCLUSION

Opium is a significant concern historically & today. Its complex background involves cultural,,& economic aspects. It can help as medicine but also lead to addiction. To truly grasp the issue of opium addiction, we must understand how it affects the brain. The processes behind physical & psychological dependence are complicated, making recovery challenging for many individuals. The signs of overdose and withdrawal show just how necessary effective treatment options are. Handling opium misuse requires both medication and other kinds of support. This points to the need for a thorough treatment plan that covers all angles. In India, the legal status of opium tries to find a middle ground. It allows for medicinal use while enforcing strict regulations to fight illegal trading. Overall, ongoing research & policy improvements are key to managing issues related to opium and promoting public health successfully.

REFERENCE:

[1]https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/opium

[2]https://www.pbs.org/wgbh/pages/frontline/shows/heroin/etc/history.html
[3]https://www.washingtonpost.com/books/2024/02/08/amitav-ghosh-smoke-ashes-opium-history-review/

[4]https://www.journals.uchicago.edu/doi/10.1086/705339

[5]https://www.sciencedirect.com/science/article/pii/S0006322319314350

[6]https://www.sciencedirect.com/science/article/pii/S2665945X2100019X

[7] The Pharmacological Treatment of Chronic Pain: From Guidelines to Daily Clinical Practice - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/Opioid-mechanism-of-action-Opioids-bind-to-their-m-k-and-d-receptors-at-presynaptic_fig1_369872688 [accessed 15 Aug 2024]

[8] https://bestpractice.bmj.com/topics/en-us/339

[9]https://medlineplus.gov/ency/article/002861.htm

[10]https://www.therecoveryvillage.com/opium-addiction/

[11]https://www.ncbi.nlm.nih.gov/books/NBK470415/

[12]https://emedicine.medscape.com/article/815784-treatment

[13]https://narcoticsindia.nic.in/Publication/2018.pdf

[14]https://en.wikipedia.org/wiki/Legal_opium_production_in_India

MORPHINE -DRUG ABUSE

Dr. Ramdas Shinde, Ms. Shreyasi Deshmukh, Ms. Sanika More
Department of Pharmacy Practice, Dr. D. Y. Patil College of Pharmay, Akurdi, Pune

ABSTRACT

Morphine addiction is a serious public issue. Morphine is typically used therapeutically for pain relief. Research has demonstrated a close relationship between their analgesic efficacy and their euphoric and physical dependency-producing properties. Recent developments in molecular biology, including quantitative (real-time) PCR and microarray analysis, have made it possible for us to investigate the changes in gene expression that arise during morphine withdrawal and in response to morphine therapies. Given how quickly tolerance to morphine builds, it has the potential to be extremely addictive. Morphine, a medication classified as Schedule II by the federal government, is used to treat moderate to severe chronic pain. In addition, it is used to treat cancer-related discomfort, relieve severe post-operative pain, and relieve dyspnoea in terminal patients.

INTRODUCTION

Opioid addiction, including morphine addiction, is a serious public health issue. Further research into the molecular underpinnings underlying opiate addiction may result in more effective treatment options down the road. It has long been recognised that morphine exposure alters a number of neuronal activity patterns, but until recently, little was understood about the underlying alterations in gene expression. Recent developments in molecular biology, including quantitative (real-time) PCR and microarray analysis, have made it possible for us to investigate the changes in gene expression that arise during morphine withdrawal and in response to morphine therapies.[1] Morphine-type pharmaceuticals are used therapeutically to relieve pain. Research has demonstrated a close relationship between their analgesic efficacy and their euphoric and physical dependency-producing properties (Eddy et al., 1956). Additionally, there is a general similarity in the order of effectiveness between analgesia and physical dependence. The physical abstinence syndrome, which consists of three elements: physical dependence, psychological dependency, and tolerance, is evidence of reliance on morphine-like substances. [2] morphine is an opiate used to treat pain. The euphoric state brought on by morphine is frequently compared to a dream state. The medication is available for injectable, syrup, or tablet form. Morphine can even be smoked under certain circumstances. Given how quickly tolerance to morphine builds, it has the potential to be extremely addictive. Morphine, a medication classified as Schedule II by the federal government, is used to treat moderate to severe chronic pain. In addition, it is used to treat cancer-related discomfort, relieve severe post-operative pain, and relieve dyspnoea in terminal patients. However, given of its relatively easy accessibility and enjoyable effects, morphine also has a high potential for abuse. [3]

HISTORY OF MORPHINE DRUG DEVELOPMENT

Opium has been used for both medical and recreational purposes by humans for thousands of years. Opium was referred to as "the plant of joy" by the Mesopotamians some 6,000 years ago. Documents spanning from 1100 to 800 B.C. demonstrate that Arab physicians mixed opium into concoctions believed to treat epilepsy, lunacy, and colds. Even in The Odyssey, the eighth-century B.C. Greek philosopher Homer makes reference to opium. The "father of toxicology," Paracelsus, a physician from Switzerland, is credited for bringing opium back to Europe around the year 1500. He made alcoholic solutions and tinctures of opium popular. Physicians and scientists began searching for a safer way to use opioids for pain treatment and cough suppression by the early 1800s, when they became aware of opium's addictive properties. At that point, 21-year-old pharmacy assistant Freidrich Sertürner began using opium in his tests. From a resinous gum in the opium poppy plant, he extracted

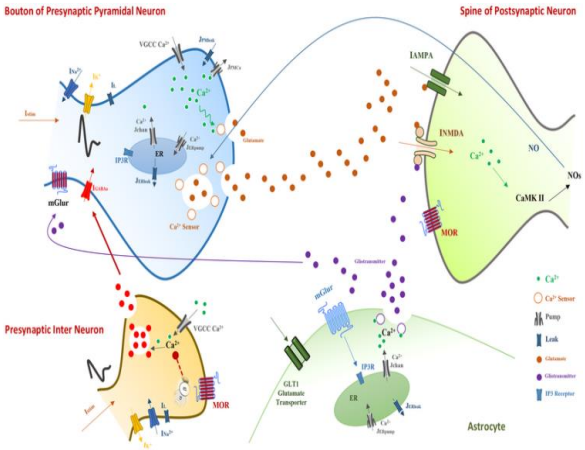
an organic alkaloid in 1803, a plant chemical with physiological effects on humans. Sertürner found the alkaloid to be a far more potent cough suppressant and pain reliever than opium itself after several years of testing (mostly on himself). Because the combination put people to sleep, he called it after the Greek god of slumber, Morpheus. By the middle of the 1800s, morphine was being produced commercially, and its administration grew simpler with the development of the hypodermic needle. Doctors frequently prescribed it for persistent pain, and it was even advertised as a means of kicking an opium addiction. Unfortunately, morphine's negative effects were felt very soon. After receiving morphine treatment for injuries sustained during the American Civil War (1861–1865), several troops went on to develop lifelong addictions that occasionally led to overdose deaths. Doctors continued to prescribe morphine to patients for chronic pain since there were few other options available to them. In addition, morphine addiction was viewed as a moral failing rather than a medical condition in 1880s culture. The per capita consumption of morphine tripled between 1870 and 1880.Scientists started searching for a less addictive painkiller at the end of the 1800s. Alder Wright, a scientist, combined morphine with other substances to produce heroin in 1874. It was quickly discovered that heroin was more powerful and addictive than morphine, despite the fact that heroin was once thought to be a therapy for morphine addiction. Opioid medicines were not heavily regulated prior to the 1900s. It was permissible to utilise opium poppy and morphine without a prescription from a doctor. Opium and opioid imports and distribution were also permitted. Nonetheless, governments all across the world started to think about laws to prevent the abuse of morphine. The Pure Food and Drug Act of 1906 mandated that medications containing intoxicants, such morphine, be labelled in the United States. The Harrison Narcotics Act, enacted by Congress in 1914, imposed taxes and regulations on the manufacture, importation, and sale of opiates. Additionally, it effectively limited the use of opioids to pain relief. It was decided that prescribers, such doctors and chemists, should oversee the dispensing of opioids. Modern medicine and drugs have come a long way since the 1920s. The 1940s saw the emergence of synthetic and semi-synthetic opioids, which were either entirely produced chemically or by modifying the natural opium plant chemically. In therapeutic practice, morphine is still utilised, but there are now a number of opioids that are much stronger—some of which are synthetic or semi-synthetic. Still, morphine is the benchmark used to evaluate painkillers. For instance, the semi-synthetic opioid hydromorphone is "four times stronger than morphine." The rules and regulations pertaining to morphine and all other opioids are still changing today. Morphine may be a safe painkiller in a therapeutic environment with updated patient care guidelines and increased awareness of opiate addiction. [4]

NEUROBIOLOGY OF MORPHINE DEPENDENCE

Many years of addiction study have led to the development of one theory of addiction. According to this idea, increased drug use follows a reward learning process as the initial stage of addiction in susceptible people with hypo-dopaminergic systems and compromised prefrontal cortex inhibitory control. It is hypothesised that allostatic drug-induced states in reward circuitry result in a high desire for drugs (incentive sensitisation), which sets off the third stage and the addiction phenotype. The focus of this paradigm is on positive reinforcement, and it suggests that altered synaptic plasticity in cortical striatal circuitry and a shift from goal-directed to habit circuitry are the main causes of addiction, along with a loss of inhibitory control.5 The desire to escape the withdrawal state (negative reinforcement) would serve as a driving force behind the continuous use of opioid drugs and is compatible with the widely circulated theory that opioid users use drugs in order to "avoid withdrawal." Apart from the physical withdrawal, prolonged abstinence syndrome is also associated with negative impact that fuels a prolonged yearning for drugs. That being said, yearning for drugs as a direct result of negative reinforcement to ease psychological withdrawal does not explain why addicted behaviours and cravings can occur

months or even years after stopping drugs, when withdrawal should have ended.

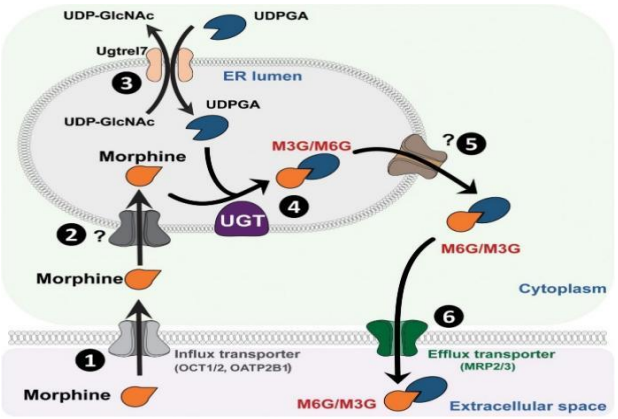
Many people are exposed to traumatic situations, but few go on to acquire PTSD. This is comparable to the epidemiology of addiction, where many people are exposed to substances but only a minority get addicted. The abnormal behavioural reactions in PTSD include avoidance and hypervigilance to avoid triggers from a conditioned fear memory, but in opioid addiction, the response to avoid unpleasant situations would just be the use of opioid drugs. An endophenotype common to many neuropsychiatric diseases is intrusive thought, which is a feature of both conditions. It's interesting to note that depressive drug misuse (opioids, alcohol, and benzodiazepines) and PTSD co-occur quite frequently, and recent studies have clearly shown that opioids protect against the development of terror memories in PTSD. [5]



Neurobiology of opioid signalling studied in this work The model consists of a pyramidal neuron's bouton and a GABAergic single compartment interneuron from CA3 layer, and a spine of a postsynaptic CA1 pyramidal neuron and an astrocyte. The astrocyte monitors the synaptic transmission, regulates presynaptic glutamate release and is involved in the postsynaptic transmission by releasing gliotransmitters. [11]

MECHANISM OF ACTION:

Roughly 85% of the reaction to morphine injection is caused by morphine-6-glucuronide. The mu and kappa opioid receptors are agonistically activated by morphine and its metabolites. The effects of morphine on the brain's ventral tegmental region depend critically on the mu-opioid receptor. Agonism of the delta-opioid receptor in the nucleus accumbens mediates the activation of the reward pathway by morphine, whereas antagonism of the mu-opioid receptor mediates the alteration of the respiratory system and addiction problem. [6] In terms of analgesic properties and adverse effects associated with other opiate derivatives, morphine is the quintessential opiate. It is excreted by the renal system and enterohepatic circulation, mainly as morphine-3-glucuronide, after being absorbed in the upper intestine and the mucosa of the rectum. Morphine can be taken orally, parenterally, epidurally, or rectally. It comes in both branded and generic forms, and it can be taken in many dosage forms.1. The degree of opioid tolerance of the patient, their overall health and medical status, their current medications, and the kind and intensity of their pain are all taken into consideration when determining the appropriate dosage of morphine. [7]



Glucuronidation process of morphine.

Morphine is first transferred from the extracellular space into the cytoplasm through active transporters such as OCT1 or OATP2B1. Then, morphine enters the lumen of the ER by way of an unknown transporter.

Concomitantly, UDPGA is transported across the ER membrane in exchange for UDP-GlcNac, due to UGTrel transporters, such as UGTrel7. Inside the lumen, UGT catalyzes the addition of a glucuronide moiety belonging to UDPGA onto morphine to form M3G and M6G. Metabolites are then transferred into the cytoplasm by unknown transporters. Finally, they are released into the extracellular space through active transporters such as MRP2 or MRP3. It is worth

noting that a significant proportion of morphine that enters the cytoplasm can be directly released into the extracellular space via P-gp. M3G, morphine-3-glucuronide; M6G, morphine-6-glucuronide; MRP, multidrug resistance-associated protein; OATP2B1, organic anion transporter polypeptides 2B1; OCT1, organic cation transporter 1; P-gp, P-glycoprotein; ER, endoplasmic reticulum; UDPGA, uridine diphosphate glucuronic acid; UDP-GlcNac, UDP-*N*-acetylglucosamine; UGT, UDP-glucuronosyltransferase. [12]

OVERDOSE SYMPTOMS

Loss of consciousness (e.g., the person cannot be awakened)
Slowed, shallow, or stopped breathing.
Pinpoint (i.e., tiny) pupils
Pale and clammy skin.Limp body.
Purple or blue fingernails.
Vomiting or gurgling noises.[6]

TREATMENT OF MORPHINE OVERDOSE

Naloxone: Naloxone is an opioid receptor antagonist that is semisynthetic, lipophilic, competitive, non-selective, and it reverses and blocks the effects of opioids, such as respiratory depression and analgesia. Naloxone can be given in a number of ways. When given IV, the time to maximum plasma concentration (tmax) is approximately 2-3 minutes; when given IM, it takes 10–20 minutes; and when given IN, it takes 15–30 minutes.

Nalmefene: A μ-opioid receptor antagonist called nalmefene can reverse the symptoms of an opioid overdose, including respiratory depression. In patients with substance use disorders or impulse control disorders, nalmefene (10–100 mg/day for 1–52 weeks) was compared to placebo or active control in eight randomised controlled trials. The meta-analysis found no evidence linking nalmefene to an increased risk of serious adverse events, indicating that nalmefene is safe. The study participants who were taking nalmefene had a 3.22-fold higher likelihood of withdrawing due to unfavourable side effects or adverse events; however, these effects are negligible when nalmefene is given rapidly during an emergency overdose incident.

Buprenorphine: The FDA has approved buprenorphine, a partial agonist of the μ-opioid receptor, for the treatment of opioid use disorder and as an analgesic at this time. Three accounts exist of bystanders who, in the absence of naloxone, used buprenorphine to reverse opioid overdoses. According to one report, a witness reversed a heroin overdose with an IV dosage of a transmucosal formulation (8 mg buprenorphine/2 mg naloxone), however naloxone may have played a role in this instance. [8]

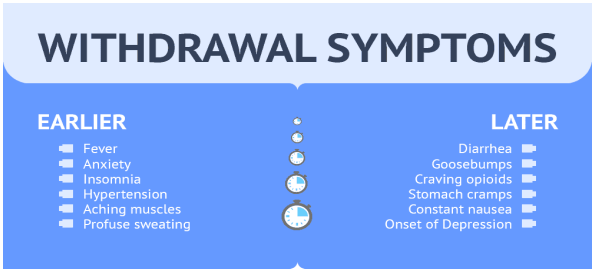
WITHDRAWAL SYNDROME

One of the few medications that can cause strong dependence and severe withdrawal symptoms when suddenly stopped abruptly is opioids. Chronic opioid usage alters central nervous system physiology, which can result in addiction, withdrawal symptoms, and dependence. Many patients who take long-term opioids for pain management would prefer to stop using them, but they keep taking them to prevent a severe withdrawal reaction. Nonetheless, there are recognised techniques for tapering off of opioids that, when followed carefully, can prevent the withdrawal symptoms. These techniques include inpatient detoxification for specific patients, outpatient Suboxone detoxification, and a gradual taper with the use of adjuvants to manage withdrawal symptoms. [9]

THE OPIOID WITHDRAWAL TIMELINE:

There are two phases to withdrawal: the acute withdrawal phase and the post-acute withdrawal phase. Acute withdrawal happens immediately after you stop taking your drug of choice (usually 6-24 hours after the last dose). It lasts up to two weeks. This is the most dangerous stage. During this time, seizures and other health complications are the most likely. It is also the most physically upsetting part of the process. Without help, most people relapse during acute withdrawal because they can not bear the discomfort of the symptoms. The post-acute withdrawal phase sets in about two to four weeks after you stop taking opioids. It can last for as long as six months. During this time, you will still not be fully restored to health. You will experience lingering withdrawal symptoms.

Cravings, anxiety, fatigue, and depression are typically the biggest obstacles to recovery during post-acute withdrawal. [13]



Physical symptoms: Increased blood pressure, Elevated heart rate, Chills, Insomnia, Irritability, Cravings, Abdominal cramping, Nausea and vomiting, Diarrhoea, Tremors.

Physiological symptoms: Agitation, Dysphoria, Anxiety, Memory loss, Depression, Irritability.

TREATMENT

Treatment for opioid use disorder (OUD) often involves a combination of:

Medications, such as methadone, naltrexone, or buprenorphine.Behavioural therapies, such as contingency management or cognitive-behavioral therapy (CBT).Evaluation and treatment for co-occurring disorders, such as anxiety or depression.Participation in support groups (e.g., 12-step programs). Aftercare planning.Patients with opioid use disorder (MOUD) may benefit from medications that block the effects of opioids and either completely or significantly reduce cravings and withdrawal symptoms. These drugs help many patients cease abusing opioids, and they can be continued once withdrawal symptoms have subsided. This gives patients the time and capacity to undertake the kind of life changes that are essential for long-term rehabilitation. When combined with MOUD, behavioural therapies are frequently utilised to assist patients in recognising and altering negative thought patterns and behaviours that lead to drug use. [6]

CONCLUSION

The various dangers and side effects of morphine abuse has been seen. The withdrawal symptoms have been proven fatal in various situations. The awareness has been implemented in various parts of the world. This article depicts the adverse effects of the drug addiction associated with morphine. Various medication regimen and therapies are found effectful in the treatment of morphine abuse.

REFERENCE

1. McClung CA. The molecular mechanisms of morphine addiction. Reviews in the Neurosciences. 2006 Aug;17(4):393-402.
2. Wilson CW. Drug Addiction: Pharmacological Aspects of Addiction to Morphine and other Drugs.
3. Addictioncenter.com/opiates/morphine/
4. Raspopin YS, Shifman EM, Feoktistova DA. History and prospects for the use of morphine in clinical practice: literature review. Regional Anesthesia and Acute Pain Management. 2024 Mar 26;18(1):33-40.
5. Evans CJ, Cahill CM. Neurobiology of opioid dependence in creating addiction vulnerability. F1000Research. 2016;5.
6. https://go.drugbank.com/drugs/DB00295
7. www.ncbi.nlm.nih.gov/pmc/articles/PMC8453761/
8. Britch SC, Walsh SL. Treatment of opioid overdose: current approaches and recent advances. Psychopharmacology. 2022 Jul;239(7):2063-81.
9. Wallace MS, Papp A. Opioid withdrawal. Challenging cases and complication management in pain medicine. 2018:15-20.
10. https://www.therecoveryvillage.com/morphine-addiction/withdrawal-detox/
11. https://www.researchgate.net/figure/Neurobiology-of-opioid-signaling-studied-in-this-work-The-model-consists-of-a-pyramidal_fig1_323622696
12. https://www.frontiersin.org/journals/molecular-neuroscience/articles/10.3389/fnmol.2022.882443/full

NAVIGATING THE COMPLEXITIES OF METHADONE ADDICTION: AN OVERVIEW OF ABUSE AND TREATMENT

Ms. Kajal Patil
Department of Pharmaceutics, Dr. D. Y. Patil College of Pharmacy Akurdi, Pune

ABSTRACT

Methadone is a synthetic opioid used primarily for opioid dependency treatment and pain management. While effective in reducing opioid cravings and withdrawal symptoms, methadone itself has the potential for abuse and addiction. Abuse of methadone often involves taking higher doses than prescribed or using the drug without a prescription, leading to serious health risks such as overdose, respiratory depression, and increased potential for addiction. Methadone addiction develops when individuals become physically dependent on the drug, leading to compulsive use despite negative consequences. Addressing methadone abuse requires a comprehensive approach, including strict regulatory measures, effective treatment strategies, and supportive interventions. Treatment options for methadone addiction often combine pharmacological therapies, such as tapering or substituting with other medications, and non-pharmacological strategies, including behavioral therapies, counseling, and lifestyle modifications. Early intervention and continuous monitoring are crucial for effective management and recovery from methadone abuse.

INTRODUCTION

Methadone is a synthetic opioid medication used to treat Opioid Use Disorder (OUD) and chronic pain management. [1,8] It is increasingly being used for its analgesic properties. Intraoperative methadone administration may be superior to intraoperative fentanyl for the control of pain during the 24-h cardiac surgery. Its unique properties make it a valuable tool in both medical and addiction treatment settings. Methadone is classified as a long-acting opioid agonist, meaning it binds to the same receptors in the brain as other opioids, such as heroin and morphine, but with a much longer duration of action. Intraoperative methadone administration may be superior to intraoperative fentanyl for the control of pain during the 24-h period following cardiac surgery.[2] This characteristic allows methadone to be used effectively in the management of opioid withdrawal symptoms and cravings, making it a cornerstone of opioid substitution therapy (OST).

HISTORY OF METHADONE

In 1937, scientists in Germany created methadone, a synthetic opioid, as a substitute for morphine during World War II. Known by its original name, "Dolophine," it was first brought to the US in 1947 as a painkiller. Methadone's use grew in the 1960s after doctors Marie Nyswander and Vincent Dole found that it could effectively cure heroin addiction. As a result, methadone maintenance therapy, or MMT, was developed and is now a vital kind of treatment for opioid addiction. Methadone treatment programs became widely available throughout the 1970s and played a crucial role in controlling the opioid crisis. Methadone has been controversial despite its success because of worries about dependency, but it is still an essential tool for treating addiction and managing pain.[13]

COMMON NAMES AND VARIANTS

Methadone is known by several common names, reflecting its widespread use and different formulations:

Table No. 1 Common names and variants of Methadone

Common Name	Variants
Dolophine	Oral Tablet Oral Solution Injection Extended-release tablets Dispersible tablets

	Liquid concentrates

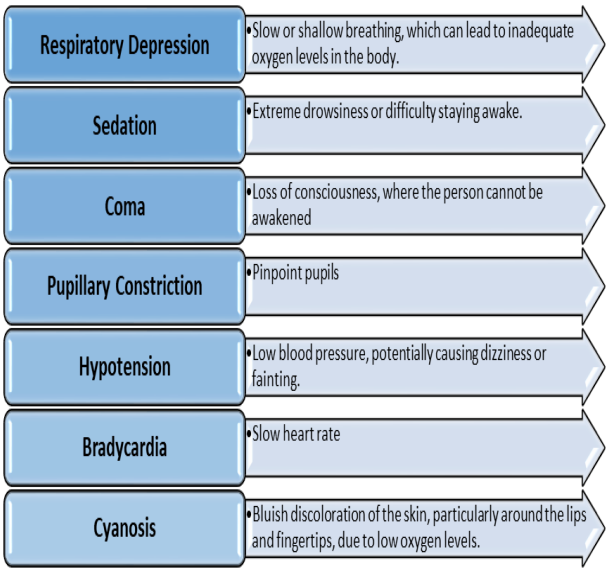
MECHANISM OF ACTION

Mu-Opioid Receptor Activation: Methadone binds to mu-opioid receptors in the brain and spinal cord, mimicking the effects of natural endorphins.[4] This leads to pain relief and feelings of euphoria.

Dopamine Release: The binding of methadone to these receptors increases dopamine levels in the brain's reward centers, such as the nucleus accumbens, contributing to its euphoric effects.[14]

Long Half-Life: Methadone has a long half-life, meaning it remains active in the body for an extended period. This helps prevent withdrawal symptoms in people with opioid dependence but also means it can accumulate to toxic levels if misused.[13]

CLINICAL MANIFESTATIONS OF METHADONE OVERDOSE



TREATMENT OF OVERDOSE

Treating a methadone overdose involves urgent medical interventions aimed at reversing opioid toxicity, stabilizing the patient, and preventing life-threatening complications.[6] Methadone is a long-acting opioid, which can lead to prolonged and severe respiratory depression.[12] Here's a structured approach to managing a methadone overdose:

SYMPTOMS OF METHADONE WITHDRAWAL

Methadone withdrawal can be particularly challenging due to the drug's long half-life, which means symptoms may start later and last longer compared to other opioids.[12] Common withdrawal symptoms include

Early Symptoms (within 24-48 hours)	Later Symptoms (peaking around 3-5 days and lasting up to 3 weeks or more)
Anxiety and restlessness	Nausea and vomiting
Insomnia	Diarrhea
Runny nose (rhinorrhea) and tearing (lacrimation)	Abdominal cramps
Yawning	Increased heart rate and blood pressure
Sweating	Dilated pupils
Muscle aches	Irritability and agitation

TREATMENT OF METHADONE ABUSE

Treating methadone abuse requires a comprehensive approach that addresses both the physical dependence on methadone and the underlying behavioral and psychological aspects of addiction.[10] The treatment process typically involves several steps, including detoxification, medication-assisted treatment (MAT), behavioral therapy, and ongoing support.[6]

Detoxification: Gradual tapering of methadone under medical supervision to reduce withdrawal symptoms.

Medication-Assisted Treatment (MAT): Using alternative medications like buprenorphine or naltrexone to manage dependence and prevent relapse.[11]

Behavioral Therapy: Cognitive-behavioral therapy (CBT), counseling, and support groups to address psychological aspects of addiction.

Aftercare: Ongoing therapy, support systems, and monitoring to prevent relapse and support long-term recovery.

Dual Diagnosis Treatment: Addressing any co-occurring mental health disorders alongside addiction.

NON-PHARMACOLOGICAL TREATMENT OF METHADONE

Exercise benefits for methadone dependence: [7]

Stress Reduction: Lowers stress hormones and boosts mood-enhancing endorphins.

Improved Mood: Alleviates depression and enhances overall well-being.

Better Sleep: Regulates sleep patterns and improves quality.

Reduced Cravings: Serves as a healthy distraction from cravings.

Increased Energy: Boosts energy levels and combats fatigue.

Physical Health: Enhances cardiovascular health and overall fitness.

Routine and Structure: Adds discipline and stability to daily life.

Social Support: Provides opportunities for social interaction and support through group activities.

Types of Exercise:

Aerobic: Walking, jogging, cycling

Strength Training: Weightlifting

Flexibility: Yoga, stretching

Mind-Body: Tai Chi, Pilates

LEGAL STATUS IN INDIA

In India, methadone abuse is treated as a serious legal issue due to the drug's classification as a controlled substance. Here's how the legal framework addresses methadone abuse:

Regulation: Methadone is regulated under the NDPS Act, 1985, which controls the production and use of narcotics and psychotropic substances. Abuse or illicit use is prohibited.

Penalties: Unauthorized possession, trafficking, or abuse of methadone can result in fines, imprisonment, or both, depending on the offense's severity.

Controlled Access: Methadone is available only through authorized medical channels. Unauthorized possession or distribution is illegal.

Enforcement: The Narcotics Control Bureau (NCB) enforces regulations to prevent methadone abuse and illegal distribution.

Treatment: The legal system includes provisions for the treatment and rehabilitation of substance use disorders, including methadone dependence.

CONCLUSION

Methadone abuse is a serious issue due to its potential for dependence and misuse. While it is effective for managing opioid dependence and pain, misuse can lead to health risks and legal consequences. Methadone is tightly regulated to prevent abuse. Effective treatment combines medication-assisted therapy, behavioral support, and non-pharmacological interventions like exercise and mindfulness. Addressing methadone abuse requires a comprehensive approach to ensure safe use and support recovery.

REFERENCES

1. Kreutzwiser D, Tawfic QA (2020) Methadone for pain management: A pharmacotherapeutic review. CNS Drugs. 34(8):827–39.
2. Murphy GS, Szokol JW, Avram MJ, Greenberg SB, Marymont JH, Shear T et al (2015) Intraoperative methadone for the prevention of postoperative pain. Anesthesiol 122(5):1112–22.
3. Bada Math S, Mohan A, Kumar NC. Opioid substitution therapy: legal challenges. *Addiction*. 2018;113(6):1201-1208.
4. Dhaliwal A, Gupta M. Physiology, opioid receptor. *In: StatPearls*. Treasure Island (FL): StatPearls Publishing; 2023.
5. Rettig RA, Yarmolinsky A, editors. *Federal Regulation of Methadone Treatment*.

Washington (DC): National Academies Press (US); 1995.

6. Ling W, Shoptaw S, Hillhouse M, et al. Methadone maintenance treatment: a review of the evidence. *J Subst Abuse Treat*. 2011;40(4):292-300.
7. Mangat AK, Schmölzer GM, Kraft WK. Pharmacological and non-pharmacological treatments for neonatal abstinence syndrome (NAS). *J Perinatol*. 2015;35(1):6-14.
8. Patel K, Bunachita S, Agarwal AK, Lyon A, Patel UK. Opioid use disorder: treatments and barriers. *Addict Sci Clin Pract*. 2021;16(1):12.
9. Cincotta JA. The role of methadone in opioid dependence treatment: a review. *Addict Sci Clin Pract*. 2014;9(1):7.
10. Korthuis PT, McCarty D, Weimer M, et al. The role of methadone in the treatment of opioid addiction: findings from a systematic review. *JAMA*. 2014;311(3):293-302.
11. Rosenblum A, Theodore L, Judd M, et al. Methadone maintenance treatment: a critical review of its effectiveness. *J Psychoactive Drugs*. 2012;44(3):219-228.
12. Pergolizzi JV Jr, Raffa RB, Rosenblatt MH. Opioid withdrawal symptoms, a consequence of chronic opioid use and opioid use disorder: current understanding and approaches to management. *Postgrad Med*. 2020;132(6):632-641.
13. Kreek MJ, Dole VP. Methadone: a review of its history and efficacy. *JAMA*. 1992;267(20):2834-2837.
14. Kosten TR, George TP. The neurobiology of opioid dependence: implications for treatment. *Sci Pract Perspect*. 2002;1(1):13-21.

MDMA: DRUG ABUSE

Dr. Prafulla Kadam.
Department of Pharm D, Dr. D Y Patil College of Pharmacy, Akurdi, Pune.

ABSTRACT:

MDMA (3,4-methylenedioxy-methamphetamine), commonly known as ecstasy, is a synthetic psychoactive substance renowned for its stimulant and empathogenic effects. Initially synthesized in 1912 by Merck, MDMA remained obscure until its rediscovery by American chemist Alexander Shulgin in the 1970s. Although primarily used recreationally, MDMA has garnered scientific interest for its potential therapeutic applications, particularly in treating PTSD, anxiety, and depression. However, its use poses significant risks, including hyperthermia, serotonin syndrome, and neurotoxicity. The drug's classification as a Schedule I controlled substance in many countries, including India, reflects its high potential for abuse and the severe legal consequences associated with its possession and distribution. Despite these concerns, ongoing clinical trials continue to explore MDMA's therapeutic potential, suggesting that it may soon gain approval for medical use. This article provides a comprehensive overview of MDMA's history, neurobiology, therapeutic research, risks, and legal status, particularly in India, offering insights into its complex role in both medical and recreational contexts.

INTRODUCTION TO MDMA

MDMA (3,4-methylenedioxy-methamphetamine) is a synthetic psychoactive substance primarily known for its stimulant and pathogenic effects. Chemically related to amphetamines, MDMA is popular in recreational settings under the name ecstasy, where it enhances mood, emotional connection, and energy. [1]. Pharmacologically, MDMA's effects are mediated through its ability to significantly increase the release of serotonin, as well as dopamine and norepinephrine, leading to its characteristic mood-enhancing and stimulant effects.[2] Clinical research is exploring MDMA's potential therapeutic uses, particularly in treating PTSD, anxiety, and depression, due to its impact on serotonin systems.[3] However, MDMA use is not without risks. It can lead to serious adverse effects including hyperthermia, dehydration, serotonin syndrome, and neurotoxicity, which are particularly concerning in non-clinical settings. [4]

EARLY HISTORY AND SYNTHESIS

1912: MDMA was first synthesized by the German pharmaceutical company Merck. It was initially developed as an intermediate compound for the synthesis of other pharmaceuticals. Merck patented MDMA in 1914, but it remained largely unnoticed for decades. [5]

1950s-1960s: During the Cold War, the U.S. military explored MDMA and other similar compounds as potential tools for psychological warfare, although it was never used in this capacity.

1970s: American chemist Alexander Shulgin re-synthesized MDMA and tested its psychoactive effects. Shulgin found MDMA to have unique properties that could facilitate psychotherapy. He introduced the drug to a small community of psychotherapists, who began using it in therapeutic settings under the name "Adam" for its supposed ability to foster empathy and communication.[6]

1980s: MDMA began to gain popularity as a recreational drug, particularly within the nightclub and rave scenes. Its ability to enhance mood, increase energy, and promote feelings of connection made it a popular choice at social events.

1985: The U.S. Drug Enforcement Administration (DEA) classified MDMA as a Schedule I controlled substance, which indicated that it had a high potential for abuse and no accepted medical use. This effectively banned the legal manufacture, distribution, and possession of MDMA. Despite this, its use continued to spread globally.

1990s-2000s: Despite its illegal status, research into the therapeutic potential of MDMA continued. Studies began to suggest that MDMA could be effective in treating conditions like post-traumatic

stress disorder (PTSD), anxiety, and depression when used in controlled, clinical settings.

2000s-2010s: Organizations like the Multidisciplinary Association for Psychedelic Studies (MAPS) led efforts to conduct clinical trials to investigate MDMA-assisted therapy for PTSD. These studies showed promising results, leading to a resurgence of interest in the drug's therapeutic potential.

2020s: Clinical trials continued, with some studies entering Phase 3, the final phase before potential approval by regulatory bodies. In 2021, the FDA granted "breakthrough therapy" designation to MDMA-assisted therapy for PTSD, recognizing its potential as a significant improvement over existing treatments.

CURRENT STATUS

As of 2024, MDMA remains a Schedule I controlled substance in many countries, but its use in clinical research is expanding. Regulatory approval for its therapeutic use in treating PTSD and other mental health conditions is being actively pursued, and some experts believe that it may be approved for medical use in the near future. [7]

COMMON NAMES

Ecstasy (or "E"): The most well-known name, often associated with the tablet form, Molly: Refers to the pure crystalline powder form of MDMA, often considered "more pure" than ecstasy tablets, X or XTC: Shortened versions, Adam: A name used by early psychotherapists, reflecting its intended use to promote empathy, Rolls: Refers to the experience of taking MDMA, Love Drug: Due to its effects of enhancing feelings of love, empathy, and emotional closeness. [8]

NEUROBIOLOGY OF MDMA

MDMA, derived from amphetamine, undergoes a complex absorption process in the body. After ingestion, it is partially absorbed in the stomach and rapidly absorbed in the small intestine, where it enters the bloodstream. A portion is metabolized in the liver, while the rest is pumped through the heart to the lungs for oxygenation. The oxygenated MDMA is then distributed throughout the body, including the brain. Despite the blood-brain barrier, MDMA easily crosses into the brain, triggering psychoactive effects within about 15 minutes, especially on an empty stomach. This process highlights MDMA's efficient absorption and rapid onset of effects. [9]

ADDICTION AND DEPENDENCE

Substance misuse and addiction arise from complex brain pathways, particularly within the reward system involving dopamine and serotonin. Understanding the neurobiology of addiction is crucial to grasping MDMA's effects.[9] Dr. George Ricaurte of Johns Hopkins University has conducted significant research on MDMA's neurotoxic and addictive properties, notably showing that monkeys frequently self-administer the drug, a strong indicator of its addictive potential in humans.[11]

MECHANISM OF ACTION

Ecstasy primarily affects the serotonin pathway, which regulates mood, emotions, sleep, and memory. By inhibiting serotonin reuptake and reversing transporter function, Ecstasy causes a surge in serotonin levels, leading to elevated mood, empathy, and altered perceptions. It also impacts dopamine pathways, increasing dopamine levels associated with pleasure and reward, which contributes to its addictive potential by reinforcing repeated use. [10]

PHYSICAL AND PSYCHOLOGICAL DEPENDENCE

Ecstasy affects both the body and mind by altering neurotransmitter systems, particularly serotonin and dopamine, inducing euphoria, emotional closeness, and empathy. These effects contribute to its addictive potential but also carry risks like anxiety, agitation, impaired cognition, hyperthermia, increased heart rate, hypertension, muscle spasms, and dehydration, which can lead to life-threatening conditions. The limbic system and brain's reward pathway, especially the amygdala, hippocampus, and basal ganglia, play key roles in Ecstasy's emotional effects and addiction potential. Research into these brain regions and neurotransmitter interactions is vital for developing addiction treatments and reducing harm.[12]

Pharmacokinetics

MDMA has a plasma half-life of approximately 7.6 hours, with effects beginning within an hour of ingestion and lasting 4 to 6 hours. Notably, individuals with similar blood levels of MDMA can experience vastly different symptoms, suggesting that adverse reactions depend more on individual differences and circumstances than on dosage alone. Fatalities have been reported at blood concentrations ranging from 0.1 to 2.1 mg/L, though some individuals have survived levels as high as 7.72 mg/L, experiencing only mild symptoms like tachycardia and hypertension, highlighting the unpredictable nature of MDMA toxicity. MDMA is metabolized through two primary pathways: O-demethylation, catalysed by CYP2D6 and followed by COMT-catalysed methylation and conjugation, and N-dealkylation, followed by deamination, oxidation, and glycine conjugation. Although CYP2D6 is crucial for O-demethylation, MDMA induces auto-inhibition of this enzyme after just two doses, rendering fast metabolizers functionally similar to slow metabolizers. Additionally, COMT, which varies genetically among individuals, converts HHMA (a metabolite of MDMA) into HMMA, a compound more potent than MDMA in triggering the release of ADH. This genetic variability in COMT activity may explain the diverse reactions to MDMA [9, 12]

Clinical Feature	Approximate Occurrence (%)	Dose Range (mg)
Euphoria	100%	50–150 mg
Increased Energy	80–90%	50–150 mg
Empathy and Emotional Warmth	85–95%	50–150 mg
Distorted Sensory Perception	70–85%	50–150 mg
Involuntary Jaw Clenching/Bruxism	60–80%	75–200 mg
Dry Mouth	50–70%	75–200 mg
Sweating	50–70%	75–200 mg
Increased Heart Rate	50–70%	75–200 mg
Nausea	30–50%	100–250 mg
Anxiety and Agitation	30–50%	100–250 mg
Hyperthermia (Elevated Body Temperature)	20–40%	100–300 mg
Hypertension (High Blood Pressure)	20–40%	100–300 mg
Confusion and Cognitive Impairment	15–30%	100–300 mg
Hallucinations	10–20%	150–300 mg
Muscle Rigidity	10–20%	150–300 mg
Panic Attacks	5–15%	150–300 mg
Serotonin Syndrome	1–5%	150–300 mg (or with polydrug use)
Seizures	<1%	>300 mg (or with polydrug use)

TREATMENT OF MDMA OVERDOSE

MDMA overdose presents a complex clinical challenge, often characterized by a constellation of symptoms including hyperthermia, agitation, and potential multi-organ dysfunction. The primary goal of treatment is to stabilize the patient and mitigate the acute complications associated with excessive MDMA consumption.

Initial Assessment and Stabilization

Airway, Breathing, and Circulation (ABC) Management: The initial focus in MDMA overdose cases is ensuring adequate airway patency, respiratory function, and circulatory support. In severe cases where the patient's ability to protect their airway is compromised, endotracheal intubation may be necessary. [13] Cardiovascular Monitoring: Continuous electrocardiographic monitoring is essential, as emphasized by the American Heart Association, due to the risk of tachyarrhythmia's and other cardiac complications associated with MDMA toxicity. [13]

Hyperthermia Management

Cooling Techniques: Aggressive cooling measures are critical in managing MDMA-induced hyperthermia. These include external cooling methods such as ice packs, cooling blankets, and evaporative cooling techniques. In severe cases, ice-water immersion may be employed. Pharmacological Interventions: Benzodiazepines serve a dual purpose in hyperthermia management, both as sedatives and to control shivering during cooling efforts. In some case reports, carvedilol has shown efficacy in managing hyperthermia and cardiovascular symptoms, though its routine use requires further research. [14

Neurological Symptom Management: Seizure Control: Benzodiazepines are the first-line treatment for seizures associated with MDMA overdose. They also play a crucial role in managing agitation and mitigating the hyper adrenergic state induced by MDMA. Hyponatremia Management: In cases of severe hyponatremia, which can lead to seizures and altered mental status, hypertonic saline (3% NaCl) may be indicated. Close monitoring of electrolyte levels is essential throughout treatment. [15, 16]

Supportive Care and Monitoring: Fluid and Electrolyte Management: Intravenous fluid administration is crucial for preventing dehydration and managing rhabdomyolysis. Careful monitoring and correction of electrolyte imbalances, particularly hyponatremia, is necessary throughout the treatment course. Rhabdomyolysis Management: Monitoring creatine kinase levels and renal function is essential in preventing acute kidney injury secondary to rhabdomyolysis. Aggressive fluid resuscitation plays a key role in this aspect of care.[15]

Pharmacological Interventions: While the mainstay of treatment remains supportive care, certain pharmacological interventions have been explored: Dantrolene has been used in some cases, though its efficacy in reducing end-organ damage remains uncertain. The use of activated charcoal may be considered if the patient presents within one hour of ingestion and has a protected airway.

Emerging Therapies: Recent case reports have described the use of the CytoSorb adsorber device in severe MDMA overdose cases. This therapy aims to reduce MDMA levels and associated inflammatory markers. However, further studies are needed to establish its efficacy and safety profile.

Admission Criteria and Ongoing Care: Patients presenting with significant complications such as persistent hyperthermia, altered mental status, seizures, severe hyponatremia, or respiratory depression should be admitted to an intensive care unit for close monitoring and management. [15, 16] The management of MDMA overdose requires a multifaceted approach, focusing on supportive care and targeted interventions to address specific complications. Rapid recognition and intervention are crucial in preventing severe outcomes. While current treatment strategies have shown efficacy in managing acute symptoms, further research is needed to develop targeted therapies and improve long-term outcomes for patients experiencing MDMA toxicity. [16]

WITHDRAWAL SYNDROME

MDMA is a synthetic psychoactive substance that primarily affects the serotonergic system, leading to profound alterations in mood, cognition, and behavior. Chronic use of MDMA can result in neuroadaptations that manifest as withdrawal symptoms when drug use is discontinued.

Understanding these symptoms and their underlying mechanisms is crucial for developing effective treatment strategies and harm reduction approaches.

Physical Symptoms: Fatigue and lethargy, Loss of appetite, Sleep disturbances (insomnia, vivid dreams), Muscle aches and cramps, Increased sweating, Headaches, Nausea, Dehydration and potential kidney problems.

Psychological Symptoms: Depression, Anxiety and panic attacks, Irritability, Mood swings, Drug cravings, Confusion, Decreased social behaviour, Loss of sex drive.

Cognitive Symptoms: Difficulty concentrating, Memory problems, particularly recognition memory, Impaired focus. [17]

LEGAL STATUS OF ECSTASY IN INDIA

Ecstasy is classified as a psychotropic substance under Schedule I of the Narcotic Drugs and Psychotropic Substances (NDPS) Act, 1985 in India. Schedule I drugs are deemed to have a high potential for abuse and no accepted medical use, making them illegal for all purposes except for certain limited research, medical, and scientific purposes authorized by the government. The NDPS Act imposes stringent penalties for the production, trafficking, possession, and consumption of MDMA. The penalties are divided based on the quantity involved. As defined under the NDPS Act, possessing up to 0.5 grams of MDMA is considered a small quantity. The penalty can include up to one year of rigorous imprisonment, a fine up to Rs. 10,000, or both. Commercial Quantity- Possession of 10 grams or more is considered a commercial quantity, with penalties including rigorous imprisonment for 10 to 20 years and a fine that can extend to Rs. 2 lakh or more.[14, 18] Indian courts have consistently upheld the stringent provisions of the NDPS Act in cases involving MDMA. In the case of State of Punjab vs. Balbir Singh, the Supreme Court ruled that strict adherence to procedural safeguards under the NDPS Act is essential, and any deviation could result in acquittal. This reflects the importance of following legal protocols strictly in drug-related cases.[19]

CONCLUSION

MDMA's journey from an obscure chemical compound to a widely recognized psychoactive substance highlights its dual nature as both a potential therapeutic agent and a drug of abuse. While research into its therapeutic applications, particularly in treating PTSD, shows promise, the risks associated with its use, especially in uncontrolled environments, cannot be understated. The stringent legal framework surrounding MDMA reflects these concerns, aiming to curb its misuse while allowing for scientific exploration under controlled conditions. As clinical research advances, the possibility of MDMA gaining acceptance as a legitimate medical treatment appears increasingly plausible. However, this potential must be balanced with robust harm reduction strategies and public education to mitigate the dangers associated with its non-medical use.

REFERENCES

1. Miller, M. A. (2019). MDMA and the Re-emergence of Psychedelic Therapy: Clinical Trials and the Therapeutic Potential. Journal of Psychoactive Drugs, 51(1), 26-32.

2. Parrott, A. C. (2013). The Psychobiology of MDMA: Neurotoxicity, Safety and Therapeutic Potential. Neuropsychology Review, 23(4), 275-290.

3. Mithoefer, M. C., Feduccia, A. A., & Jerome, L. (2019). MDMA-assisted psychotherapy for posttraumatic stress disorder: A systematic review and meta-analysis of randomized controlled trials. Journal of Psychopharmacology, 33(12), 135-150.

4. McCann, U. D., Szabo, Z., & Scheffel, U. (2008). Positron emission tomography and MDMA (ecstasy) research: A review. Journal of Psychopharmacology, 22(2), 115-124.

5. Sessa, B. (2017). The History of MDMA as an Underground Drug in the United States, 1960–1979. Journal of Psychoactive Drugs, 49(2), 114-120.

6. Passie, T., Benzenhöfer, U. (2018). The Early History of "Ecstasy". Drug Science, Policy and Law, 4, 1-8.

7. Doblin, R., et al. (2021). MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. Nature Medicine, 27, 1025-1033.

8. Inciardi, J. A., & McElrath, K. (2001). The American Drug Scene: An Anthology. Oxford University Press.

9. NIDA, N. I. (n.d.). The Neurobiology of Ecstasy.

10. Kish SJ. How strong is the evidence that brain serotonin neurons are damaged in human users of ecstasy? Pharmacology & Therapeutics. 2002;95(3):269-280.

11. Green AR, Mechan AO, Elliott JM, O'Shea E, Colado MI. The pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy"). Pharmacol Rev. 2003;55(3):463-508. doi:10.1124/pr.55.3.3.

12. Boyer EW & doi:10.1056/NEJMra041867.

13. Rietjens SJ, Hondebrink L, Westerink RH, Meulenbelt J. Pharmacokinetics and pharmacodynamics of 3,4-methylenedioxymethamphetamine (MDMA): interindividual differences due to polymorphisms and drug-drug interactions. Crit Rev Toxicol. 2012 Nov;42(10):854-76. doi: 10.3109/10408444.2012.725029. Epub 2012 Oct 3. PMID: 23030234.

14. Ghaffari-Rafi A, Eum KS, Villanueva J, Jahanmir J. Protracted hyperthermia and delayed rhabdomyolysis in ecstasy toxicity: A case report. Medicine (Baltimore). 2020 Oct 9;99(41):e21842. doi: 10.1097/MD.0000000000021842. PMID: 33031256; PMCID: PMC7544301.

15. Sandau KE, Funk M, Auerbach A, Barsness GW, Blum K, Cvach M, Lampert R, May JL, McDaniel GM, Perez MV, Sendelbach S, Sommargren CE, Wang PJ; American Heart Association Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; and Council on Cardiovascular Disease in the Young. Update to Practice Standards for Electrocardiographic Monitoring in Hospital Settings: A Scientific Statement From the American Heart Association. Circulation. 2017 Nov 7;136(19):e273-e344. doi: 10.1161/CIR.0000000000000527. Epub 2017 Oct 3. PMID: 28974521.

16. Lang CN, Sommer MJ, Neukamm MA, Staudacher DL, Supady A, Bode C, Duerschmied D, Lother A. Use of the CytoSorb adsorption device in MDMA intoxication: a first-in-man application and in vitro study. Intensive Care Med Exp. 2020 Jun 15;8(1):21. doi: 10.1186/s40635-020-00313-3. PMID: 32542550; PMCID: PMC7295925.

17. Kuypers KP, Ramaekers JG. Transient memory impairment after acute dose of 75mg 3.4-Methylene-dioxymethamphetamine. J Psychopharmacol. 2005 Nov;19(6):633-9. doi: 10.1177/0269881105056670. PMID: 16272186.

18. Parrott, A. C. (2013). MDMA, serotonin neurotoxicity, and the diverse functional deficits of recreational 'Ecstasy' users. *Journal of Psychopharmacology, 27(1), 2-13.* [Link](https://journals.sagepub.com/doi/10.1177/0269881112464829)

19. McCann, U. D., Mertl, M., Eligulashvili, V., & Ricaurte, G. A. (1999). Cognitive performance in (+/-) 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") users: A controlled study. *Psychopharmacology, 143(4), 417-425.* [Link](https://link.springer.com/article/10.1007/s002130050967)

KRATOM - DRUG ABUSE

Ms. Anju Kalyankar, Ms. Bhumika Zade
Department of Pharma Chemistry, Dr. D.Y. Patil College of Pharmacy, Akurdi Pune

ABSTRACT

Kratom, or *Mitragyna*, is a tropical plant indigenous to Southeast Asia having unique pharmacological properties. It is commonly consumed by preparing the leaves into decoction or tea, or by grinding them into a powder. Kratom has a unique pharmacologic profile that might offer advantages over other opioids, but its high abuse liability, potential for drug interactions and adverse events, and inadequate research into the balance of benefits to harm are concerning. The potential medical applications of Kratom extend beyond pain management. Some studies have suggested possible benefits in areas such as mood enhancement, anxiety and depression, and even cancer. Long term consumption of kratom leads to dangerous addiction. The pharmacological effect varies with the consumption of drug, low dose stimulates refreshing effect to the consumer whereas when consumed at ahigher dose it causes sedative effect. Toxicities associated with kratom consumption have focuses on hepatic, cardiac, and CNS effects. These are the reasons which play a major role on it being legally available. Hence, Kratom is an illegal drug/substance in Denmark, Finland, Ireland, Latvia, Lithuania, Poland, Romania, and Sweden

INTRODUCTION

Mitragyna speciose (Korth) is commonly known as “Kratom”, which refers to both the plant itself and the botanical products derived from its leaves- A native of Southeast Asia-Pacific, the Mitragyna speciosa tree is a tropical evergreen that has a close relation to the coffee plant in the Rubiaceae family. Traditionally, in certain regions of Southeast Asia, the chopped fresh or dried leaves of the tree are chewed or made into tea by local manual laborers to combat fatigue and improve work productivity[1]. For generations, indigenous people in Southeast Asia have used kratom to treat common health disorders (e.g. diarrhea, hypertension, cough, fever, etc.), enhance work performance, combat fatigue, alleviate pain, and manage opioid dependence (hereafter referred to as opioid use disorder (OUD))[2]. The effects of kratom in humans are dose-dependent where small doses produce stimulatory effects resembling the stimulant effect of drugs such as cocaine or amphetamines. At the same time, larger dosages tend to be associated with sedative-narcotic effects that resemble drugs such as opiates[3]. Fresh Kratom leaves can be consumed by chewing, smoking, or ingesting orally by brewing as a tea or juice [4] to minimize fatigue, enhance work performance, and improve physical tolerance to heavy workload [5], [6].

HISTORY AND BACKGROUND

This drug is commonly known as Kratom, Kakuam, Kraton, Ithang, or Thom in Thailand, and Ketum or biak-biak in Malaysia. Estimates of kratom users largely differ, but millions of people have been using this plant in the US where it is federally legal in all the constituent states apart from Alabama, Arkansas, Indiana, Vermont, Wisconsin, and Rhode Island[7,8]. In addition, kratom preparations have also been used for centuries during socio-religious ceremonies and to treat various medical conditions, such as morphine dependence in Thailand [9], and as an opium substitute in Malaya [9].According to certain theories, the reason the Dutch botanist Korthals named the genus "Mitragyna" was because the plant's stigmas and leaves resemble a bishop's miter. In addition, Kratom remains in use for its antispasmodic, muscle-relaxant, and antidiarrheal effects while both its brief stimulant and analgesic effects remain a popular home remedy in Southeast Asia[10,11].

PHARMACOLOGICAL ACTIVE ALKALOIDS OF KRATOM DRUG

There are forty alkaloids found in the leaves of Mitragyna speciosa. Its main active alkaloid, mitragynine (MG) was found to have unique morphine effects or opioid receptor agonist effects on guinea pig ileum [12]. MG is the most abundant active alkaloid derived from the leaves of Mitragyna speciosa, which constitutes up to 66% of the total alkaloid mixture. On the other hand, 7-hydroxy mitragynine was identified as a minor ingredient of kratom leaf extract[21] that makes up 0.04% of the alkaloids[22]. A drug therapy's pharmacokinetic (PK) and pharmacodynamic (PD) characteristics dictate its therapeutic efficacy. The pharmacokinetics and toxicity data of pure MG and alkaloid extract are still poorly known, even though the pharmacological effects of Kratom in humans and experimental animals are well-established. Opioids have been used extensively in treating pain for more than 100 years. Opioid receptors can be classified into three subtypes which are Mu (μ), kappa (κ), and delta (δ) opioid receptors [13]. Both mitragynine and 7-HMG target opioid receptors, though they have significant differences in binding affinity. Mitragynine was found to have less affinity than morphine, whereas 7-HMG is 46 times and 13 times more potent than mitragynine and morphine, respectively[19].

MECHANISM OF DRUG ACTION

The ability to target opioid receptors is shared by mitragynine and 7-hydroxy mitragynine, although there is a notable difference in their binding affinities. Its highly active oxidized metabolite, 7-OH-mitragynine, is in far lower quantities, generally under 0.02% [23]. While the affinity of mitragynine for opioid receptors is less than that of morphine, 7-OH-mitragynine is far more potent than either, approximately 46 times that of mitragynine and 13 times that of morphine[24,25]. The addition of a hydroxyl group at the C7 position of 7-hydroxymitragynine accounts for its increased binding affinity to opioid receptors. It has been shown that mitragynine and 7-hydroxy mitragynine are both agonists; mitragynine preferentially activates μ- and δ-receptors, while 7-hydroxy mitragynine primarily activates μ- and κ-receptors.Upon binding to opioid receptors, the indole alkaloids (such as kratom alkaloids) activate G-protein-coupled receptors. However, unlike conventional opioids (such as morphine), indole alkaloids do not initiate the β-arrestin pathway when they activate G-protein-coupled receptors[26]. This process refers to biased agonism that permits a single receptor to exert numerous distinct intracellular effects. Apart from its opioid-like analgesic actions, mitragynine appears to inhibit pain signals via other pathways than morphine. Implying a multimodal involvement in pain perception regulation. For example, mitragynine bears a high degree of structural similarity to yohimbine, another indole alkaloid with a well-documented adrenergic effect[27].

The seriousness of abuse and potential of Kratom Drug

Regular use of kratom, particularly at higher doses, can lead to tolerance and dependence [14]. Many of the respondents stated that they used kratom to treat symptoms including pain, low energy, and mood swings related to depression or anxiety. Furthermore, a significant amount of use, if not the majority was meant to replace prescription or over-the-counter medications for conditions for which kratom's adverse effect profile was more tolerable; such as sedation and opiate withdrawal. Kratom is often used in combination with other illicit drugs as well as prescription drugs such as opioids, benzodiazepines, and antidiarrheal medications such as loperamide, leading to serious side effects[15,16,17].In a few cases reported, the consumers complained of aspirational pneumonia, fever, and seizures after consumption. Kratom is not associated with an increased risk for sexually transmitted diseases. Other clinical presentations identified by the National Poison Data System include agitation (18%), confusion (8.1%), drowsiness (13.6%), hallucinations (4.8%), seizures (6.1%), and tachycardia (16.9%) that eventually progressed to cardiac arrest (0.6%) and coma[18].

KRATOM AND WITHDRAWAL SYMPTOMS

Kratom users in the West are using the leaf extract and its varied formulations for a range of health reasons that primarily relate to chronic pain, mood disorders, or mitigating the withdrawal symptoms

of a prescription or illicit drug dependency[20]. Regular usage of Kratom drug leads to withdrawal symptoms on abstinence, along with craving, tolerance, and cross-tolerance to morphine. The psychological withdrawal symptoms include depressed mood, anxiety, restlessness, irritability, and feeling tense. The physical withdrawal symptoms include myalgia and body aches, joint pain, lacrimation, running nose, yawning, insomnia, diarrhea, feverish sensation, loss of appetite, tremors, itching over the body, loss of concentration, and chills.

REFERENCE

1.Suwanlert S.,Study of kratom eaters in Thailand, Bulletin on Narcotics.(1975)27,no.3,21-27,2-s2.0-0016703532

2. (Adkins, Boyer, & McCurdy, 2011; Cinosi et al., 2015; Jansen & Prast, 1988; Vicknasingam, Narayanan, Beng, & Mansor, 2010)

3. Prozialeck W.C.,Jivan J.K.,and Andurkar S.V.Pharmacology of Kratom: an emerging botanical agent with stimulant, analgesic and opioid-like effects, Journal of the American Osteopathic Association.(2012)112,no.12,792-799

4.MacLaren E. The effects of kratom use. www.drugabuse.com/library/the-effects-of-kratom-use

5. Tanguay P. Kratom in Thailand: decriminalisation and community control? Legislative Reform of Drug Policies (Vol. 13). Amsterdam: Transnational Institute, 2011:1–16.10.2139/ssrn.1908849

6. Saingam D, Assanangkornchai S, Geater AF, Balthip Q. Pattern and consequences of kratom (Mitragyna speciosa Korth.) use among male villagers in southern Thailand: a qualitative study. Int J Drug Policy 2012;24:351–8.10.1016/j.drugpo.2012.09.004

7. Kruegel AC, Grundmann O. The medicinal chemistry and neuropharmacology of kratom: a preliminary discussion of a promising medicinal plant and analysis of its potential for abuse. Neuropharmacology. 2018;134(Pt A):108–20.

8. •• Swogger MT, Smith KE, Garcia-Romeu A, Grundmann O, Veltri CA, Henningfield JE, et al. Understanding kratom use: a guide for healthcare providers. Front Pharmacol. 2022;13:801855.

9. Ahmad K., Aziz Z. *Mitragyna speciosa* use in the northern states of Malaysia: a cross-sectional study. *Journal of Ethnopharmacology*. 2012;141(1):446–450. doi: 10.1016/j.jep.2012.03.009.

10. Suwanlert S. A study of kratom eaters in Thailand. *Bull Narc*. 1975;27(3):21–27.1041694

11. Singh D, Narayanan S, Vicknasingam B, Corazza O, Santacroce R, Roman-Urrestarazu A. Changing trends in the use of kratom (Mitragyna speciosa) in Southeast Asia. *Hum Psychopharmacol*.

12. Watanabe K, Yano S, Horie S, Yamamoto LT. Inhibitory effect of mitragynine, an alkaloid with analgesic effect from Thai medicinal plant Mitragyna speciosa, on electrically stimulated contraction of isolated guinea-pig ileum through the opioid receptor. Life Sci 1997;60:933–42

13. Al-Hasani R, Bruchas MR. Molecular mechanisms of opioid receptor-dependent signaling and behavior. Anesthesiology 2011;115:1363–81.

14. Galbis-Reig, 2016; Singh et al., 2014; Swogger & Walsh, 2018; Yusoff et al., 2016.

15. Kong WM, Chik Z, Ramachandra M, et al. Evaluation of the effects of mitragyna speciosa alkaloid extract on cytochrome P450 enzymes using a high throughput assay. *Molecules*. 2011;16(9):7344–7356.

16. Porrogi P, Kóbori L, Kõhalmy K, et al. Limited applicability of 7-methoxy-4-trifluoromethylcoumarin as a CYP2C9-selective substrate. *Pharmacol Rep*. 2008;60(6):972–979

17. Kikura-Hanajiri HR, Kawamura M, Maruyama T, et al. Simultaneous analysis of mitragynine, 7-hydroxylmitragynine and other alkaloids in the psychotropic plant “kratom” (mitragyna speciosa) by LC-ESI-MS. *Forensic Toxicol*. 2009;27:67

BUPRENORPHINE

Ms. Madhuri Kolhe, Ms Pooja Palandurkar
Dept. of Pharmaceutics, Dr. D. Y. Patil College of Pharmacy Akurdi, Pune

ABSTRACT
Opioid use disorder and its consequences are a major public health concern. The partial agonist buprenorphine is a safe and effective treatment for OUD, but concerns about abuse, misuse, and diversion of buprenorphine have been raised. This narrative review examined the rates and motives for use of illicit buprenorphine in the United States. Findings from the 17 included studies suggest the majority of study participants using illicit buprenorphine do so for reasons related to misuse. A smaller percentage of study respondents reported using buprenorphine for reasons related to abuse. There appears to be a gap between need for buprenorphine and access to adequate treatment. Attenuation of policy-related barriers and adoption of appropriate buprenorphine use by the treatment community are critical tools in the continued effort to reduce the burdens associated with OUD.

INTRODUCTION
Buprenorphine provides effective relief of moderate to severe pain. A potential side effect of all mu opioid receptor agonists is respiratory depression, which can be fatal with high doses. At an adult therapeutic dose buprenorphine can decrease respiratory rate in an equivalent manner to an equianalgesic dose of morphine. However, very high i.v. doses of buprenorphine do not lead to fatal overdose due to the partial mu agonist properties of buprenorphine. Buprenorphine is an effective and safe maintenance treatment for opioid dependence. Buprenorphineand methadone have similar effects in reducing illicit opioid use, and both retain subjects in treatment.

HISTORY
In 1969, researchers at Reckitt and Colman had spent 10 years attempting to synthesize an opioid compound "with structures substantially more complex than morphine [that] could retain the desirable actions whilst shedding the undesirable side effects". Physical dependence and withdrawal from buprenorphine itself remain important issues, since buprenorphine is a long-acting opioid. Reckitt found success when researchers synthesized RX6029 which had showed success in reducing dependence in test animals. RX6029 was named buprenorphine and began trials on humans in 1971. By 1978, buprenorphine was first launched in the UK as an injection to treat severe pain, with a sublingual formulation released in 1982.

ABUSE
Like many drugs, buprenorphine is subject to abuse, misuse, and diversion. In the years following FDA approval, reports of illicit buprenorphine use surfaced, and the occurrence of abuse, misuse, and diversion appear to have increased in conjunction with increases in buprenorphine prescribing frequency. There is a high prevalence of misuse, abuse, and diversion of buprenorphine products in the US and internationally, particularly among high-risk populations, such as people with OUD and drug injectors, which has been described extensively in comprehensive reviews of research on this topic. The paradoxical finding of a high prevalence of misuse and abuse Fpraof a product intended to treat OUD among individuals likely to be affected by this disorder raises questions about motivations for use of diverted buprenorphine. There are many likely reasons why buprenorphine may be used outside of a prescription, and understanding the scope and extent of these motives has important implications for policy and practice. Although international trends in buprenorphine injection have been summarized with discussion of motives for injecting buprenorphine injected buprenorphine can only occur outside of a

prescription and also represents a small portion of non-prescribed buprenorphine use.

EPIDEMIOLOGY

Over 16 million people worldwide and 3 million in the United States meet OUD criteria. Basically, OUD results in over 120,000 and 47,000 deaths per year worldwide and in the United States, respectively. In the United States, opioids have killed more people than any other drug in history. Recreational use of opioids was at its highest in 2010 and has gradually decreased as the opioid epidemic has gained attention in the United States.Up to 50% of patients on chronic opioid therapy meet the criteria for opioid use disorder.It varies by age and gender. Men are more likely to use and become dependent on opioids. Thus, men account for the majority of opioid-related overdoses. Women are prescribed opioids for analgesia more often than men. Opioid-related deaths are highest among individuals between the ages of 40 and 50 years, while heroin overdoses are most common among individuals between the ages of 20 and 30 years.

DRUG ADDICTION TREATMENT

Before January 2023, clinicians were required to obtain a DATA waiver, commonly known as an X-waiver, to prescribe buprenorphine for treating OUDs. This prerequisite was established under DATA 2000 to ensure clinicians had the necessary training and qualifications to prescribe buprenorphine for OUD treatment. However, following the enactment of the Consolidated Appropriations Act of 2023, the X-waiver requirement was eliminated. This change enables clinicians with Schedule III authority on their DEA registration to prescribe buprenorphine for the treatment of OUD without the necessity of a DATA waiver. This change is intended to increase access to buprenorphine treatment for individuals with OUD and to address the ongoing opioid epidemic in the United States. However, clinicians are still required to have the appropriate authorization under applicable state law to prescribe buprenorphine for OUD treatment.

Indications.

FDA-Approved Indications

Buprenorphine is approved by the U.S. Food and Drug Administration (FDA) to treat acute and chronic pain and opioid dependence. This drug is used in agonist substitution treatment, a method for addressing addiction by substituting a more potent full agonist opioid, such as heroin, with a less potent opioid, such as buprenorphine or methadone. Buprenorphine substitute treatment enables patients to focus on therapy rather than enduring uncomfortable withdrawals. The drug proves to be an effective choice for addressing opioid dependence by diminishing cravings and enhancing the overall quality of life during addiction treatment. By mitigating many distressing symptoms associated with opioid withdrawal, this approach facilitates the development of treatment plans that patients are more likely to adhere to, thereby reducing both morbidity and mortality rates.

Objectives:

Identify appropriate candidates for buprenorphine therapy based on a comprehensive assessment of opioid use disorders and patient history.Implement evidence-based buprenorphine treatment regimens, considering dosing, administration routes, and patient-specific factors. Select appropriate evidence-based treatment, adjunctive therapies, behavioral interventions, or counseling services to enhance the effectiveness of buprenorphine treatment. Collaborate with pharmacists, nurses, and other interprofessional healthcare professionals to ensure comprehensive and coordinated patient care on buprenorphine therapy.

CONTRAINDICATIONS

All Markets: Buprenorphine is contraindicated in those who are hypersensitivity to it.

Australia only: Buprenorphine is contraindicated in children under 15 years of age, those with severe respiratory or hepatic insufficiency, and those with acute intoxication with alcohol or other central nervous system (CNS) depressants. It is also contraindicated in pregnant women and in breast-feeding women.

Adverse Effects

Respiratory depression may occur with therapeutic doses of buprenorphine and it should be used with

caution in patients with compromised respiratory function. When used to treat opioid dependence, caution is advised regarding the possibility of severe potentially lethal reactions that may result from misuse of buprenorphine by injection with benzodiazepines and/or other central nervous system (CNS) depressants. Also, serious cases of acute hepatic injury have been reported in a context of intravenous misuse of buprenorphine exacerbated by pre-existing hepatic impairment due to chronic hepatitis C infection and alcohol abuse. The most frequent side effect is sedation, from which the patients can easily be aroused to an alert state. Other frequent side effects are nausea, dizziness/vertigo, sweating, headache, hypotension, vomiting, hypoventilation, and miosis.

CONCLUSION

Buprenorphine is an effective treatment of opioid addiction and can be safely prescribed by primary care physicians. The development of buprenorphine has helped physicians treat a variety of conditions, especially acute and chronic pain conditions and opioid dependence. Patient tolerability, lower risk of constipation, excellent half-life, and minimal respiratory depression are all superior to most other opioid class members. In this comprehensive review, a wide variety of buprenorphine formulations were elicited and described. Some formulations were specific for purposes of analgesia and others for opioid use disorder. It is the hope that, over time, more physicians become comfortable with the use of this medication in their armamentarium for treating these conditions.

REFERENCES

1.Preuss CV, Kalava A, King KC. StatPearls [Internet]. StatPearls Publishing; Treasure Island (FL): Apr 29, 2023. Prescription of Controlled Substances: Benefits and Risks. [PMC free article] [PubMed]

2.Noble F, Marie N. Management of Opioid Addiction With Opioid Substitution Treatments: Beyond Methadone and Buprenorphine. Front Psychiatry. 2018;9:742. [PMC free article] [PubMed]

3.Lyden J, Binswanger IA. The United States opioid epidemic. Semin Perinatol. 2019 Apr;43(3):123-131. [PMC free article] [PubMed]

4.Molfenter T, Fitzgerald M, Jacobson N, McCarty D, Quanbeck A, Zehner M. Barriers to Buprenorphine Expansion in Ohio: A Time-Elapsed Qualitative Study. J Psychoactive Drugs. 2019 Jul-Aug;51(3):272-279. [PMC free article] [PubMed]

5.Van Zee A, Fiellin DA. Proliferation of Cash-Only Buprenorphine Treatment Clinics: A Threat to the Nation's Response to the Opioid Crisis. Am J Public Health. 2019 Mar;109(3):393-394. [PMC free article] [PubMed]

6.Welsh CJ, Suman M, Cohen A, Broyles L, Bennett M, Weintraub E. The use of intravenous buprenorphine for the treatment of opioid withdrawal in medically ill hospitalized patients. Am J Addict. 2002 Spring;11(2):135-40. [PubMed]

7.Krishnan SH, Gilbert LA, Ghoddoussi F, Applefield DJ, Kassab SS, Ellis TA. Addition of buprenorphine to local anesthetic in adductor canal blocks after total knee arthroplasty improves postoperative pain relief: a randomized controlled trial. J Clin Anesth. 2016 Sep;33:432-7. [PubMed]

8.Ling W, Hillhouse MP, Saxon AJ, Mooney LJ, Thomas CM, Ang A, Matthews AG, Hasson A, Annon J, Sparenborg S, Liu DS, McCormack J, Church S, Swafford W, Drexler K, Schuman C, Ross S, Wiest K, Korthuis PT, Lawson W, Brigham GS, Knox PC, Dawes M, Rotrosen J. Buprenorphine + naloxone plus naltrexone for the treatment of cocaine dependence: the Cocaine Use Reduction with Buprenorphine (CURB) study. Addiction. 2016 Aug;111(8):1416-27. [PMC free article] [PubMed]

9.Wakhlu S. Buprenorphine: a review. J Opioid Manag. 2009 Jan-Feb;5(1):59-64. [PubMed]

10.Latif ZE, Solli KK, Opheim A, Kunoe N, Benth JŠ, Krajci P, Sharma-Haase K, Tanum L. No increased pain among opioid-dependent individuals treated with extended-release naltrexone or buprenorphine-naloxone: A 3-month randomized study and 9-month open-treatment follow-up study. Am J Addict. 2019 Feb;28(2):77-85. [PubMed]

11.Lake EP, Mitchell BG, Shorter DI, Kosten T, Domingo CB, Walder AM. Buprenorphine for

the treatment of posttraumatic stress disorder. Am J Addict. 2019 Feb;28(2):86-91. [PubMed]

12.Herring AA, Perrone J, Nelson LS. Managing Opioid Withdrawal in the Emergency Department With Buprenorphine. Ann Emerg Med. 2019 May;73(5):481-487. [PubMed]

13.Wang S. Historical Review: Opiate Addiction and Opioid Receptors. Cell Transplant. 2019 Mar;28(3):233-238. [PMC free article] [PubMed]

14.Coe MA, Lofwall MR, Walsh SL. Buprenorphine Pharmacology Review: Update on Transmucosal and Long-acting Formulations. J Addict Med. 2019 Mar/Apr;13(2):93-103. [PMC free article] [PubMed]

15.Shi JM, Henry SP, Dwy SL, Orazietti SA, Carroll KM. Randomized pilot trial of Web-based cognitive-behavioral therapy adapted for use in office-based buprenorphine maintenance. Subst Abus. 2019;40(2):132-135. [PMC free article] [PubMed]

16.Joshi P, Shah NK, Kirane HD. Medication-Assisted Treatment for Opioid Use Disorder in Older Adults: An Emerging Role for the Geriatric Psychiatrist. Am J Geriatr Psychiatry. 2019 Apr;27(4):455-457. [PubMed]

17Hollander MAG, Jarlenski MP, Donohue JM, Cole ES, Kelley D, Krans EE. Medical specialty of buprenorphine prescribers for pregnant women with opioid use disorder. Am J Obstet Gynecol. 2019 May;220(5):502-503. [PMC free article] [PubMed]

18.Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC Clinical Practice Guideline for Prescribing Opioids for Pain - United States, 2022. MMWR Recomm Rep. 2022 Nov 04;71(3):1-95. [PMC free article] [PubMed]

19.The ASAM National Practice Guideline for the Treatment of Opioid Use Disorder: 2020 Focused Update. J Addict Med. 2020 Mar/Apr;14(2S Suppl 1):1-91. [PubMed]

20.Lofwall MR, Walsh SL. A review of buprenorphine diversion and misuse: the current evidence base and experiences from around the world. J Addict Med. 2014 Sep-Oct;8(5):315-26. [PMC free article] [PubMed]

21.Davison SN. Clinical Pharmacology Considerations in Pain Management in Patients with Advanced Kidney Failure. Clin J Am Soc Nephrol. 2019 Jun 07;14(6):917-931. [PMC free article] [PubMed]

22.Filitz J, Griessinger N, Sittl R, Likar R, Schüttler J, Koppert W. Effects of intermittent hemodialysis on buprenorphine and norbuprenorphine plasma concentrations in chronic pain patients treated with transdermal buprenorphine. Eur J Pain. 2006 Nov;10(8):743-8. [PubMed]

23.Volkow ND, Jones EB, Einstein EB, Wargo EM. Prevention and Treatment of Opioid Misuse and Addiction: A Review. JAMA Psychiatry. 2019 Feb 01;76(2):208-216. [PubMed]

24.Quaye AN, Zhang Y. Perioperative Management of Buprenorphine: Solving the Conundrum. Pain Med. 2019 Jul 01;20(7):1395-1408. [PMC free article] [PubMed]

25.LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. National Institute of Diabetes and Digestive and Kidney Diseases; Bethesda (MD): Nov 24, 2020. Buprenorphine. [PubMed]

26.Post S, Spiller HA, Casavant MJ, Chounthirath T, Smith GA. Buprenorphine Exposures Among Children and Adolescents Reported to US Poison Control Centers. Pediatrics. 2018 Jul;142(1) [PubMed]

27.Tsui JI, Akosile MA, Lapham GT, Boudreau DM, Johnson EA, Bobb JF, Binswanger IA,

DEXTROMETHORPHAN (DXM) ABUSE: UNDERSTANDING PHARMACOLOGY, RISKS, AND MANAGEMENT APPROACHES

Mr. Yash Bhardwaj, Dr. Ramesh Katedeshmukh
Dept. of Pharm D, Dr. D. Y. Patil College of Pharmacy Akurdi, Pune

ABSTRACT

Dextromethorphan is a frequently used over-the-counter (OTC) medication for cold and cough, mostly due to its ability to suppress coughing. Despite its therapeutic effects, DXM also has considerable risks such as abuse potential and serious toxicity. This article aims to provide an in-depth review of DXM, looking at its pharmacological mechanisms, psychoactive effects, and the associated riskswith misuse. It analyzes the drug's dual role as an NMDA receptor antagonist as well as sigma-1 receptor agonist, how abuse affects neurological and systemic health while discussing treatment approaches for dependence and toxicity. The paper further addresses the regulatory landscape of DXM especially its status in various countries with a specific focus on India. The worries on abuse of dextromethorphan are increasing at alarming rates according to case studies and statistical data presented in this article which also calls for awareness and preventive measures.

Keywords- Dextromethorphan (DXM) is a cough suppressant, NMDA receptor antagonist, sigma-1 receptor agonist, psychoactive effects, dextromethorphan toxicity, neurological impact, DXM misuse, substance use disorder, and regulatory landscape.

INTRODUCTION

Dextromethorphan is an over-the-counter drug that can suppress coughs. Its various forms include oral strips, lozenges, liquids, and liquid-filled capsules. In most of these formulations, it is usually combined with other drugs such as guaifenesin, acetaminophen or pseudoephedrine. For example, some people take it to get high on its dissociative and hallucinogenic effects. This is why it has received names like "Triple C", "Dex", "Orange Crush", "Red Devils," and "Poor Man's PCP." Excessive consumption of this drug leads to cardiovascular, neurological metabolic and musculoskeletal damage among others side effects. Therefore emergency department providers should be prepared for emergencies related to dextromethorphan poisoning because it could cause hypertension seizure tachycardia psychosis and rhabdomyolysis.[1]

MECHANISM OF ACTION

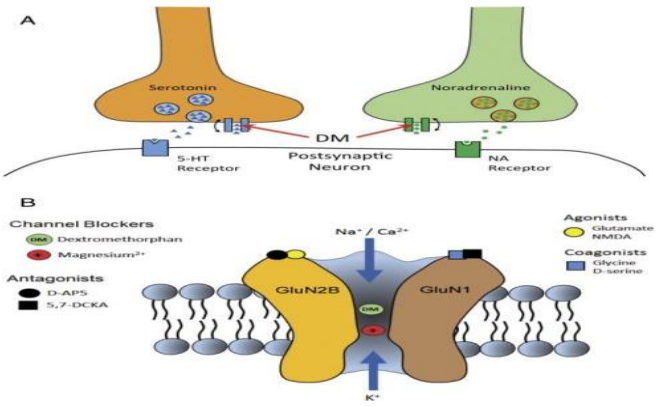


Figure 1

Dextromethorphan exhibits complex pharmacodynamic and pharmacokinetic properties. It is a lipophilic molecule with an ionizable amine group, structurally related to alkaloid opioids like morphine, although it does not interact with the mu-opioid receptor. Derived from levorphanol, which was initially developed as a morphine alternative, its primary mechanism of action in suppressing cough is not fully understood. One theory suggests that dextromethorphan acts on the nucleus tractus solitarius, a brainstem region thought to be involved in the cough reflex by acting as a gate for pulmonary vagal afferent fibers. Dextromethorphan has low oral bioavailability because of extensive first-pass metabolism, though this varies among different metabolic groups: ultrarapid, extensive, intermediate, and poor metabolizers, with most

people being extensive metabolizers. After a single 30mg oral dose, the drug has a median half-life of 2.4 hours with an oral bioavailability of 1 to 2%. The drug has a median half-life of 19.1 hours because nine percent of the population are poor metabolizers, and an oral bioavailability of 80%, which contributes to significantly higher plasma levels. Though structurally similar to opioids, dextromethorphan does not act on opioid receptors. Instead, it is primarily known to act as a non-competitive antagonist at N-methyl-D-aspartate (NMDA) receptors as illustrated in Figure1. Additionally, dextromethorphan and its metabolite dextrorphan interact with several other receptor sites, including:

- Sigma-1 receptors (as an agonist)
- Nicotinic receptors (antagonists at a3b4, a4b2, a7 subtypes)
- Serotonin transporter (inhibitor)
- Norepinephrine transporter (inhibitor)
- Voltage-gated calcium channels (inhibitor).

Dextromethorphan is a synthetic analog of codeine and undergoes rapid metabolism after absorption as shown in Figure2, primarily through the cytochromeP450 2D6 (CYP2D6) enzyme into its major metabolite, dextrorphan(DX). Dextrorphan is further processed into dextrorphan-o-glucuronide by uridine diphosphate-glucuronosyltransferase, which is the most common form of DX in the plasma and is less permeable to the blood-brain barrier due to its permanent charge. Additionally, dextromethorphan is metabolized into 3-methoxymorphinan by cytochrome P450 3A4.

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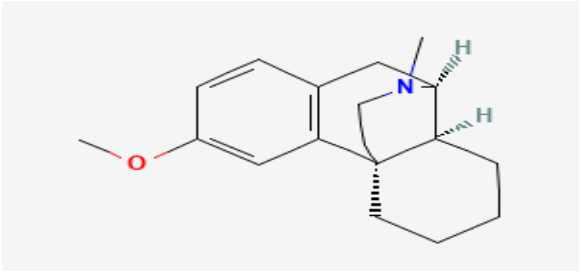
dextromethorphan is metabolized into 3-



methoxymorphinan by cytochrome P450 3A4.

Figure 2

PHARMACOLOGICAL CLASSIFICATION: UNDERSTANDING THE DRUG'S ROLE

- Substance Identifier: 7355X3ROTS
- Core Component: Dextromethorphan
- Pharmacological Classifications:
- Officially Recognized Pharmacologic Category:
- N-methyl-D-aspartate (NMDA) Receptor Antagonist (Uncompetitive)
- Sigma-1 Receptor Agonist Functional Mechanisms:
- NMDA Receptor Antagonism (Uncompetitive)
- Sigma-1 Receptor Activation
- Pharmacological Overview:
- Dextromethorphan is not just a sigma-1 receptor agoinst but also NMDA receptor blocker. Its therapeutic effects are attributed to these dual mechanisms of action.[3]

NEUROLOGICAL IMPACT OF DEXTROMETHORPHAN (DXM) MISUSE

Known for its psychoactive effects, dextromethorphan (DXM) is consumed in high doses. Effects may include confusion, inappropriate laughter, agitation and more severe symptoms like paranoia and hallucinations. Some users also indicate floating sensations, auditory changes and touch alterations among other sensory changes. DXM long-term abuse is particularly alarming because it can lead to severe psychological dependence.DXM abusers often claim to experience four distinct dose-dependent "plateaus" which are associated with varying degrees of

behavioral and psychological effects. A summary of these plateaus is provided in the table below.[4]

PLATEAU	DOSE (MG)	BEHAVIORAL EFFECTS
1st	100 - 200	Mild stimulation
2nd	200 - 400	Euphoria and hallucinations
3dr	300 - 600	Distorted visual perceptions Loss of motor coordination
4th	500 - 1500	Out-of-body sensations

CHRONIC EFFECTS OF DEXTROMETHORPHAN (DXM) MISUSE

Possible Long-Term Health Hazards Associated with DXM Abuse:

Liver Problems

The risk is higher when combined with products containing acetaminophen.

Respiratory Effects

Long term respiratory depression can lead to various problems.

Acid-Base Dysregulation

Dangerous amounts of acid may build up in the body. Organ Injury Related to Hypoxia May include important organs like, The heart, The lungs, The brain

Substance Use Disorder (SUD)

This can result in patterns of abuse or addiction[7].

APPROACHES TO ADDRESSING DEXTROMETHORPHAN (DXM) MISUSE

Demographic Trends:

Primary affected groups: Males and younger individuals Challenges: Tendency for denial and resistance to direct confrontation

Recommended Approach:

Professional Intervention

Utilize mental health experts specializing in addiction. Consider certified interventionists for family-involved approaches

Individualized Treatment Planning

Assess need for medically supervised withdrawal

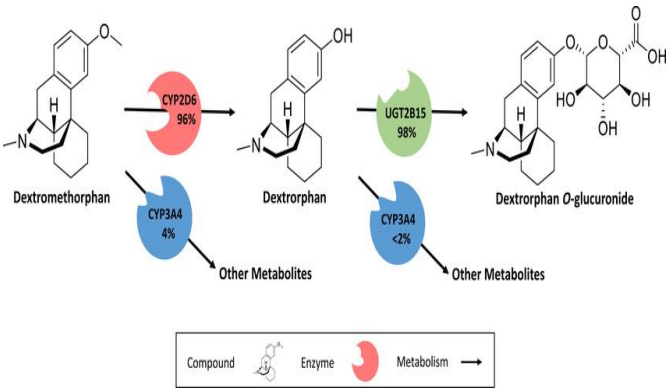


Figure 3

management, Evaluate polysubstance abuse patterns Tailor interventions to specific needs

Comprehensive Treatment Components

Address co-occurring mental health issues Implement substance use disorder therapy (group and/or individual) Incorporate social support networks (e.g., 12-Step programs) Provide medical management as needed Offer additional support services (e.g., tutoring, vocational rehabilitation)

Family Involvement

Consider family therapy, especially for younger individuals Focus on improving family dynamics and support systems

Peer Support Considerations

Recognize the impact of peer influence on substance use Facilitate positive peer interactions through age-appropriate group settings

Educational Elements

Provide information on substance abuse, mental health, and relapse prevention Utilize both formal therapy and support groups for education

Long-term Recovery Focus

Emphasize ongoing engagement beyond initial abstinence Encourage extended participation in therapy and support groups Aim for sustained recovery periods (5-7 years as a general guideline).[7]

Management of Dextromethorphan (DXM) Toxicity: Handling Emergencies

The following table represents a comprehensive approach to patient care, focusing on supportive measures, sedation strategies, gastrointestinal interventions, and other critical considerations

based on symptom severity and potential complications.[8]

Approach	Details
Primary Approach	Focus on supportive care Monitor ABCs and hemodynamics Consider ventilator support if required Consult a medical toxicologist
Sedation Strategies	- **Environment:** Quiet, dimly lit room - **Medication:** Benzodiazepines are preferred - **Suggested:** Lorazepam 2-4 mg IV/IM, repeat every 10 minutes - Use physical restraints if necessary
Gastrointestinal Intervention	**Activated Charcoal:** Administer within 1 hour of ingestion - **Dosage:** 1 g/kg (max 50g) orally or via NG tube - Avoid gastric lavage or induced emesis
Additional Pharmacological Interventions	**Naloxone:** For respiratory/CNS depression - **Dose:** 0.1 mg/kg IV (max 2mg)
Additional Pharmacological Interventions	**Naloxone:** For respiratory /CNS depression **Dose:** 0.1 mg/kg IV (max 2mg)
Hyperthermia Management	- Active Cooling Measures: - Evaporative cooling - Cold IV fluids - Cooled oxygen
Important Considerations	- Assess for co-ingestions (e.g., acetaminophen, decongestants, antihistamines) - Address associated toxicities as required
Disposition	- Discharge Criteria: - Asymptomatic for over 6 hours post-ingestion - Non-suicidal - Negative acetaminophen level - ICU Admission for: - Persistent symptoms - Complications (e.g., hyperthermia, serotonin syndrome, hypertensive crisis, rhabdomyolysis) - **Psychiatric Consultation:** For patients with suicidal intent

DXM ABUSE GROWING CONCERN

NCPC is reporting almost 6,000 visits per year to emergency rooms as a result of DXM abuse, about half of whom are aged between twelve and twenty-five years old. Just over 14,000 children aged 6-17 end up at poison control centers because they have been exposed to dextromethorphan and around sixty die from it each year (American Association on Poison Control Centers).[10]

Figure 4

DEXTROMETHORPHAN IN INDIA: LEGAL AND REGULATORY LANDSCAPE

Dextromethorphan is not allowed in fixed dose combination drugs in India. The drug itself is not banned, but its combination with other drugs is restricted. This was the outcome of an advisory committee formed to look into the dangers associated with the FDCs by government of India.[11]. There are no official boundaries between its sale and use as a result of recreational misuse such as taking a lot of OTC medications that contain dextromethorphan. In most countries dextromethorphan is available OTC but in places like HongKong, Denmark and Sweden access to it is more controlled.In India it can be bought over the counter from chemists [12].

CASE STUDY

LONG-TERM DEXTROMETHORPHAN MISUSE IN MIDDLE-AGED ADULT

Case 44-year-old male with severe dextromethorphan dependence

Background:

Dextromethorphan: An OTC cough suppressant available since the 1950s Known for cough relief and potential psychoactive effects comparable to certain hallucinogens

Usage Pattern:

Duration of misuse: Approximately 6 years

Peak daily consumption: 1800 mg (15 times the typical therapeutic maximum)

Financial impact: Over 300 euros spent monthly Consequences of Misuse:

Occupational and personal life neglect

Withdrawal symptoms upon cessation attempts: Sleep disruptions, nausea, perspiration

Diagnostic Criteria (Based on ICD-10):

Criteria met: Intense cravings, reduced self-control, withdrawal symptoms, increased tolerance, and neglect of life responsibilities.

Unmet criterion: Continued use despite clear harmful effects (insufficient evidence of harm)

Treatment Approach:

Initial contact: Outpatient addiction clinic

Inpatient detoxification:

Observed symptoms: Drug cravings, sweating, nausea, hypertension, tachycardia

Physical findings: Minor ataxia; normal neurological and ECG results

Therapeutic interventions:

Behavioral therapy focusing on relapse prevention, Social reintegration strategies, Stress management techniques

Symptom management: Achieved without pharmacological intervention. The patient should be referred to the nearest center for additional treatment following detoxification.

Key Insights:

Dextromethorphan's abuse potential linked to accessibility and psychoactive properties.Case illustrates need for:

Increased awareness of OTC medication risks

Potential reevaluation of dextromethorphan's regulatory status

Enhanced strategies to prevent and manage misuse.[6]

CONCLUSION

Although effective as a cough suppressant, Dextromethorphan has hidden dangers from its chances of being misused and causing side effects. Drugs that affect the NMDA receptor sites or agonists at sigma-1 receptors are important for its psychoactive properties hence the abuse risk. Prolonged abuse could lead to significant health problems such as neurological damage or substance use disorder. To manage DXM toxicity and dependence appropriately entails a multifaceted approach in which there is involvement of medical treatment, behavioral therapy and family support systems. Regulatory mechanisms, especially in countries like India, are vital in preventing DXM misuse risks. There is need for creating awareness while preventive measures must then follow so as to handle emerging issues on DXM misuse, ensuring that this widely-given medicine is used safely.

REFERENCES

1] Journey, Jonathan D. "Dextromethorphan Toxicity." StatPearls [Internet]., U.S. National Library of Medicine, 26 June 2023, www.ncbi.nlm.nih.gov/books/NBK538502/.

[2] -Oh, SaeRam. "Dextromethorphan." StatPearls [Internet]., U.S. National Library of Medicine, 22 May 2023, www.ncbi.nlm.nih.gov/books/NBK538216/.

[3]- "Dextromethorphan." National Center for Biotechnology Information. PubChem Compound Database, U.S. National Library of Medicine, pubchem.ncbi.nlm.nih.gov/compound/Dextromethorphan. Accessed 15 Aug. 2024

[4] ENFORCEMENT ADMINISTRATION, DRUG DEPARTMENT OF JUSTICE, U.S. "XI. Drugs of Concern." Drugs of Abuse, a DEA Resource Guide: 2017 Edition, LULU PRESS INC, S.l., 2020.

[5]-Akerman, Sarah C., et al. "Dextromethorphan abuse and dependence in adolescents." Journal of Dual Diagnosis, vol. 6, no. 3–4, 30 Dec. 2010, pp. 266–278, https://doi.org/10.1080/15504263.2010.537515.

[6]-Mutschler, Jochen, et al. "Dextromethorphan withdrawal and dependence syndrome." Deutsches Ärzteblatt International, 30 July 2010, https://doi.org/10.3238/arztebl.2010.0537.

CHRONIC EFFECTS OF DEXTROMETHORPHAN (DXM) MISUSE

[7]"DXM Abuse: Symptoms, Effects & Addiction Treatment: Oxford." Oxford Treatment Center, 30 Apr.2024,oxfordtreatment.com/substanceabuse/hallucinoges/dxm/.

[8]-Journey, Jonathan D. "Dextromethorphan Toxicity." StatPearls [Internet]., U.S. National Library of Medicine, 26 June 2023, www.ncbi.nlm.nih.gov/books/NBK538502/.

[9]DXM Abuse: Effects, Addiction & Recovery: Greenhouse." Greenhouse Treatment Center, 13 June24,greenhousetreatment.com/hallucinogens/dx

[10]-Hmpgloballearningnetwork.Com, www.hmpgloballearningnetwork.com/site/emsworld/article/10324941/drug-abuse-update-dextromethorphan#:~:text=The%20American%20Association%20of%20Poison,directly%20linked%20to%20this%20pharmaceutical. Accessed 16 Aug. 2024.

[11]-"List of Banned Medicines in India 2023." India Today, India Today, 10 Dec. 2023, www.indiatoday.in/information/story/list-of-banned-medicines-in-india-2023-2473522-2023-12-10.

[12]Kaur, Navpreet, et al. "Dextromethorphan abuse-a rising menace in India: Case review and its toxicokinetics." Indian Congress of Forensic Medicine & Toxicology, 2010.

PSILOCYBIN

Dr. Ashish Kulkarni, Ms. Nisha Patil
Department of Pharmacology, Dr. D. Y. Patil College of Pharmacy Akurdi, Pune

ABSTRACT

Psilocybin is the psychoactive component of hallucinogenic mushrooms. Due to its potential for therapeutic applications and its ability to mimic psychosis, it is currently garnering a lot of scientific interest. However, it's a highly used and often abused natural hallucinogen. This article aims to cover the history, pharmacodynamics, pharmacokinetics, symptoms and pharmacological and non-pharmacological treatments for psilocybin misuse.

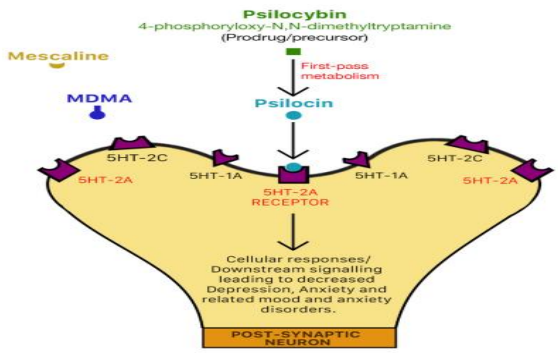
INTRODUCTION

Psilocybin is a naturally occurring psychedelic compound found in certain species of mushrooms, often called "magic mushrooms." Its history dates back thousands of years, particularly in Central and South America, where indigenous cultures like the Aztecs and Maya used these mushrooms in religious and healing ceremonies. The Aztecs referred to them as "teonanácatl," meaning "flesh of the gods."[1]In the mid-20th century, psilocybin was introduced to the Western world by R. Gordon Wasson, who published an account of his experiences with psilocybin mushrooms in a 1957 *Life* magazine article. Swiss chemist Albert Hofmann, who also discovered LSD, later isolated psilocybin and psilocin, leading to a wave of research into their effects on consciousness and mental health. During the 1960s, psilocybin became popular in the counterculture movement, but its use was criminalized in many countries, including the U.S., in 1970. However, starting in the 21st century, there has been renewed interest in psilocybin research, particularly for its potential therapeutic benefits. Recently, some places have moved to decriminalize or legalize psilocybin for medical use, signalling a shift in its cultural and legal status. [2] Most of the mushrooms that are known to produce psilocybin are members of the genus Psilocybe sensu stricto (s.s.) from which psilocybin and psilocin were initially isolated. There are currently thought to be more than 300 species in the genus Psilocybe, which is found all over the world (Figure 1). Psilocybe species that have been identified thus far are thought to be saprotrophic, and they can be found on a variety of substrates such as grasses, wood, dirt, roots, and the excrement of herbivores. [3]Psilocybe species intake is the foundation of modern syncretic rites and ceremonies that combine Catholic and Mesoamerican elements and are used to treat both physical and spiritual illnesses. It is believed that psilocybe mushrooms enable the soul to separate from the body by causing hallucinations and synesthesia, which results in a trance-like state. Consequently, traditional doctors can aid in the diagnosis of physical ailments, self-healing,introspection, and the discovery of missing individuals' locations. Furthermore, indigenous people have long employed psilocybe mushrooms as analgesics to alleviate stomachaches and anxiety as well as rheumatism. [4]

Figure 1. Psilocybe species diversity. (A) *Psilocybe serbica* (B) *P. mescalenroensis* (C) *P. cubensis* (D) *P. ovoideocystidiata* (E) *P. allenii* (F) *P. azurescens* (G) *P. cyanescens* (H) *P. subaeruginosa* (I) *P. angulospora*, (J) *P. baeocystis* (K) *P. pelliculosa* (L) *P. semilanceata (M) P. hoogshagenii*, (N) *P. mexicana* (O) *P. neoxalapensis* (P) *P. zapotecorum*

STRUCTURAL CHARACTERISTICS AND MECHANISM OF ACTION OF PSILOCYBIN

Psilocybin is an indole alkaloid. Chemically it is 4-phosphoryloxy-N, N-dimethyltryptamine. In the human body, liver and intestinal mucosal enzyme like alkaline phosphatase and nospecific esterase metabolise Psilocybin and converted it to the bioactive substance psilocin 4-hydroxy-N,N-dimethyltryptamine) by dephosphorylation. The neurotransmitter serotonin (5-hydroxytryptamine) is structurally similar to psilocybin and psilocin. psilocin interact with 5-HT (5-HT2A, 5-HT2C, 5-HT1A, 5-HT1B, and 5-HT1D) receptors disrupting serotonergic neurotransmission producing physiological effects (Figure 2) [5].



ABUSE

Although psilocybin is not considered physically addictive like opioids or alcohol, there is potential for psychological abuse. People may seek out the drug for recreational use to escape reality, leading to potential negative consequences. [8]

RISKS OF PSILOCYBIN ABUSE

Psychological Risks:

Bad Trips: Uncontrolled or excessive use of psilocybin can lead to intense fear, paranoia, and anxiety, sometimes referred to as a "bad trip." These experiences can be traumatizing and may lead to lasting psychological distress.

Hallucinogen Persisting Perception Disorder (HPPD): In rare cases, psilocybin users may experience ongoing visual disturbances, such as flashbacks or changes in perception, even after the drug's effects have worn off.

Worsening of Mental Health Conditions: Individuals with a predisposition to certain psychiatric disorders, such as schizophrenia or bipolar disorder, may experience worsening symptoms after using psilocybin, especially if taken without medical supervision.

Behavioral Risks:

Impaired Judgment: Psilocybin can impair decision-making abilities, which may lead to risky behavior, accidents, or unsafe situations.

Tolerance and Escalation: While psilocybin doesn't induce physical dependence, regular users can develop tolerance, leading to the need for higher doses to achieve the same effects. This could increase the risk of psychological distress or dangerous behaviour.

Physical Risks:

Nausea and Vomiting: Psilocybin can cause nausea and vomiting, especially when consumed in large amounts.

Toxic Mushroom Confusion: People seeking psilocybin mushrooms may accidentally consume poisonous mushrooms, which can be fatal or cause severe illness.

PSILOCYBIN IN CONTROLLED SETTINGS VS. RECREATIONAL USE

Psilocybin abuse is often tied to its unsupervised, recreational use. In controlled, therapeutic settings, the risks of abuse and negative psychological outcomes are minimized through careful dosing, preparation, and the presence of trained guides or therapists. However, in recreational use, where set and setting are often unpredictable, the risk of psychological harm increases.

SIGNS OF PSILOCYBIN ABUSE

Frequent Use: Using psilocybin mushrooms more frequently than intended or for purposes beyond self-reflection or growth (e.g., to escape reality).

Chasing Highs: Increasing doses to achieve more intense or longer-lasting experiences.

Neglecting Responsibilities: Neglecting work, school, or personal responsibilities in favor of using psilocybin.

Obsessive Focus: Becoming overly focused on the next trip or spending a lot of time acquiring or preparing mushrooms. Treating psilocybin misuse involves both pharmacological and non-pharmacological approaches, as misuse of this

hallucinogenic compound can lead to psychological and physical issues. Psilocybin, found in certain mushrooms, can induce altered perceptions, hallucinations, and emotional changes, which can be problematic when misused or taken in unsafe environments.

PHARMACOLOGICAL TREATMENTS [9]

Antipsychotic Medications:

Haloperidol or Risperidone may be used to manage acute psychotic episodes or agitation related to psilocybin intoxication. These drugs block dopamine receptors and can help counteract the hallucinogenic effects.

Benzodiazepines:

Lorazepam or Diazepam might be administered to calm anxiety, agitation, or panic that results from a bad trip or a psilocybin-induced psychotic episode. These medications act on the GABA system to induce sedation and reduce anxiety.

SSRIs (Selective Serotonin Reuptake Inhibitors):

In cases of chronic misuse or addiction (though addiction to psilocybin is relatively rare), SSRIs like Fluoxetine might be used to manage underlying conditions like depression or anxiety, which could contribute to misuse.

Symptomatic Treatment:

Patients may also receive medications to manage symptoms such as nausea, vomiting, or dehydration, which may accompany psilocybin intoxication.

NON-PHARMACOLOGICAL TREATMENTS [9]

Cognitive Behavioral Therapy (CBT):

CBT helps individuals identify and challenge thought patterns that lead to psilocybin misuse. It addresses maladaptive behaviors and teaches coping mechanisms for dealing with stress and underlying psychological issues.

Motivational Interviewing (MI):

This technique can be used to enhance a person's motivation to change their substance use behavior. It helps in addressing ambivalence about quitting or reducing psilocybin use and promotes commitment to treatment.

Psychoeducation:

Educating individuals about the risks of psilocybin misuse, including potential long-term psychological effects such as anxiety, depression, and the risk of triggering psychosis, can be a helpful tool in preventing future misuse.

Mindfulness-Based Therapies:

Mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy (MBCT) can help individuals cultivate awareness and control over their thoughts and emotions, reducing impulsive behaviours linked to psilocybin misuse.

Support Groups:

Peer-support groups, such as Narcotics Anonymous (NA) or groups specifically for psychedelic misuse, provide a space for individuals to share experiences, receive support, and maintain sobriety.

Contingency Management:

This behavioral therapy involves rewarding individuals for meeting treatment goals, such as abstinence from psilocybin or other substances.

Supervised Detoxification:

Although psilocybin is not physically addictive, supervised detoxification may be necessary for individuals who combine it with other substances or have developed psychological dependence.

Family Therapy:

involving family members in the treatment process can provide a supportive environment for recovery. Family therapy helps address relational issues that may contribute to substance misuse.

HOLISTIC AND LIFESTYLE INTERVENTIONS

Exercise and Nutrition:

Regular physical activity and a balanced diet can improve overall mental and physical health, which may help reduce cravings or the desire to misuse substances.

Stress Management:

Techniques like meditation, yoga, and breathing exercises can help manage stress and anxiety, which are common triggers for substance misuse.

Spiritual Counselling:

Some individuals misuse psilocybin in spiritual or recreational contexts. Counselling that explores these themes in a healthy, balanced way might reduce misuse. In most cases, a combination of both

pharmacological and non-pharmacological treatments is the most effective strategy for addressing psilocybin misuse. It's also important to tailor the treatment to the individual's specific psychological needs and the extent of their misuse.

CONCLUSION

Although there are risks involved with its usage, especially in unregulated recreational settings, psilocybin is not intrinsically addictive. Its psychological impacts and the drive to pursue altered states of consciousness are the primary sources of abuse potential. But when administered properly and under regulated circumstances, its therapeutic potential is still substantial. To maximize the positive effects and reduce the negative effects of psilocybin, responsible usage, education, and research are crucial.

REFERENCES

1. Gaston Guzman, Hallucinogenic Mushrooms in Mexico: An Overview, 62 ECON. BOTANY, 2008 404- 405
2. Abbas AI, Jeanne T, Knox R, Korthuis PT, Hamade A, Christopher S, Uehling J, Oregon Psilocybin Advisory Board Rapid Evidence Review and Recommendations. Oregon Psilocybin Advisory Board: Salem, OR, 2021 USA.
3. Guzman G., Species diversity of the genus Psilocybe (Basidiomycotina, Agaricales, Strophariaceae) in the world mycobiota, with special attention to hallucinogenic properties. Int. J. Med. Mushrooms, 2005; 7, 305e332.
4. Guzman G., The hallucinogenic mushrooms: diversity, traditions, use andabuse with special reference to the genus Psilocybe. In: Misra, J.K., Deshmukh, S.K. (Eds.), Fungi from Different Environments, 2009 pp. 256e277.
5. Tyls F, Palenicek T, Horacek J.,. Psilocybin–summary of knowledge and new perspectives. Eur. Neuropsychopharmacol. 2014; 24 (3); 342e356.
6. Hasler, F., Bourquin, D., Brenneisen, R., Bär, T., & Vollenweider, F. X. (1997). Determination of psilocin and 4-hydroxyindole-3-acetic acid in plasma by HPLC-ECD and pharmacokinetic profiles of oral and intravenous psilocybin in man. *Pharmaceutica Acta Helvetiae*, *72*(3), 175-184.
7. Goel DB, Zilate S. Potential Therapeutic Effects of Psilocybin: A Systematic Review. Cureus. 2022 Oct 12;14(10):e30214. doi: 10.7759/cureus.30214. PMID: 36381758; PMCID: PMC9650681.
8. Johnson MW, Griffiths RR, Hendricks PS, Henningfield JE. The abuse potential of medical psilocybin according to the 8 factors of the Controlled Substances Act. Neuropharmacology. 2018 Nov;142:143-166. doi: 10.1016/j.neuropharm.2018.05.012. Epub
9. 2018 Jun 5. PMID: 29753748; PMCID: PMC6791528
10. van Amsterdam J., Opperhuizen, A., & van den Brink, W. Harm potential of magic mushroom use: a review. Regulatory Toxicology and Pharmacology, 2011, *59*(3), 423-429.

GHB (Gamma aminobutyric acid)

Ms. Pranita Shankarrati, Ms Aditi Bhor
Department of Pharmaceutical Chemistry, Dr. D. Y. Patil College of Pharmacy Akurdi, Pune

ABSTRACT

Gamma-aminobutyric acid (GABA), the main inhibitory neurotransmitter in the brain, is the metabolic source of gamma-hydroxybutyric acid (GHB), a short-chain fatty acid that is found naturally in mammalian brains. Since GHB was first created more than 40 years ago, many ofits biological, pharmacological, and toxicological characteristics, as well as its presence in thebrain, have been clarified over the course of the previous 20 to 30 years. But only in the last five to ten years has there been a general interest in this compound, mostly because GHB has become a significant recreational drug and public health issue in the US. GHB may function asa neuromodulator in the brain, according to a large body of data. Gamma-aminobutyric acid type B (GABA(B)) receptor activation as well as a distinct GHB-specific receptor are two of the several neural pathways that GHB uses. In addition to the disruptions of learning and memory linked to supra-physiological concentrations of GHB in the brain that arise from the exogenous administration of this drug in the clinical context of GHB abuse, addiction, and withdrawal, this intricate GHB-GABA(B) receptor interaction is likely responsible for the diverse pharmacological, electroencephalographic, behavioral, and toxicological effects of GHB. Examining succinic semialdehyde deficiency (SSADH), an inborn error of metabolism,and the mouse model of this condition (SSADH knockout mice), where GHB is involved in a significant way, may aid in the dissection of pathways mediated by GHB and GABA(B) receptors. The processes involved in the molecular pathophysiology of GHB addiction and withdrawal, in particular, as well as the absence of seizures seen in the animals receiving GHB

INTRODUCTION

γ-hydroxybutyrate (GHB) is a particularly problematic recreational drug because to its easy accessibility, inexpensive price, and potential for negative interactions with other sedatives. Because the safety margin between a recreational dosage and a deadly dose is so small— between 5:1 and 8:1—mortality rates following GHB misuse are substantial. As a result, unintentional poisoning following recreational GHB use is not unusual, as shown by treatment admissions to hospital emergency rooms and by forensic medical examinations conducted on drug-related fatalities. Early in the 1990s, GHB became a popular recreational drug of abuse and garnered a lot of attention, particularly when it was linked to incidents of drug-facilitated sexual assault (DFSA), which the media sometimes refers to as "daterape." GHB's potential for abuse was reduced by its designation as a prohibited drug in the USA in 2000 (scheduled I), and in the EU in 2001 (scheduled III or IV). GHB is classified as a Class C drug under the UK'slegislation against drug usage. Possession of the substance is prohibited. Alternatively, GHB is produced from the unregulated organic solvents 1,4-butanediol (BD) and γ-butyrolactone (GBL). It is difficult to categorize GBL and BD as restricted drugs because they both have industrial and cosmetic uses. GHB is the primary analytical target in forensic toxicology. GBL and BD have pharmacological and behavioral effects because of their quick conversion into GHB. GHB's method of action includes binding to receptors for γ-aminobutyric acid (GABA),a significant inhibitory neurotransmitter. Specifically, the GABA-B

complex is involved in this interaction. Pharmacologically, GHB is categorized as a depressant of the central nervous system. This is not the case with other sedative-hypnotics like ethanol, barbiturates, and benzodiazepines, which act through the chloride ion channel of the GABA-A receptor subtype.Under US federal law, GHB is categorized as a schedule III restricted drug in the form of its sodium salt. The brand name of this medication is sodium oxybate, whereas its proprietary name is Xyrem ®.Adult patients with cataplexy related to narcolepsy are administered Xyrem®.Another name for GHB is 4-hydroxybutyrate, which means that this short-chain carboxylic acid has a hydroxyl (-OH) group on carbon number four. The close proximity of an alcohol (-OH) and a carboxylic acid (-COOH) group within the same molecule allowscyclization to the corresponding lactone(γ-butyrolactone). For GC-FID analysis of GHB in blood and urine, this chemical conversion of GHB into GBL via intramolecular esterification is used. When compared to GHB, the GBL derivative exhibits superior solvent extraction and chromatographic qualities. History of GHB and its common nameThe body creates little levels of GHB (gamma-hydroxybutyrate), a potent central nervous system depressant. In the 1920s, a synthetic (man-made) form of GHB was created for use as an anesthetic. Because synthetic GHB has euphoric and sedative effects, many misuse it. Sodium oxybate (Xyrem), a prescription drug, contains GHB as its active component. GHB is also known by the following names: G, goop, grievous bodily harm, Georgia home boy, and liquid ecstasy.

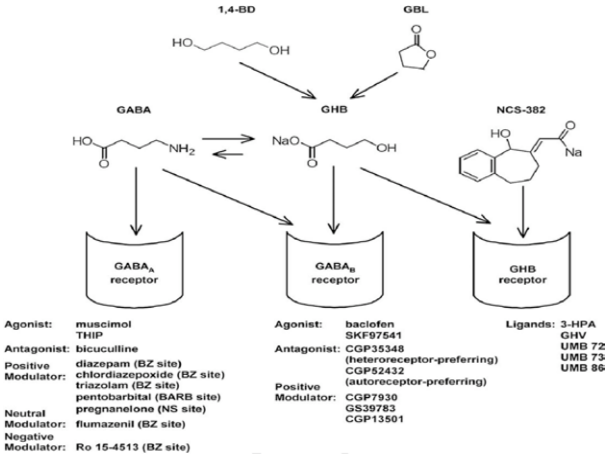
MECHANISM OF ACTION OF GHB

In order to produce its sedative effects, GHB stimulates GABA-B receptors in the brain, where it is found in far larger quantities. GHB binds to excitatory GHB receptors, which are highly expressed in the cotex and hippocampus among other areas of the brain, with a high affinity. Research has shown some evidence that the excitatory neurotransmitter glutamate is produced when GHB receptors are activated in specific brain regions. GHB acts on the GHB receptor to increase the release of dopamine at low concentrations, and this biphasic release of dopamine happens. GHB acts on GABA-B receptors at greater doses to suppress the release of dopamine, which is followed by GHB receptor signaling and an increase in dopamine release. This explains why GHB has a paradoxical combination of stimulatory and sedative effects, as well as the "rebound" effect that causes people taking the drug to wake up unexpectedly after many hours of deep slumber. It is hypothesized that with time, brain levels of GHB drop below the critical point at which GABA-B receptors become significantly activated, preferentially activating GHB receptors over GABA-B receptors and increasing wakefulness.

PHARMACOLOGICAL EFFECT OF THEDRUG GHB

GHB is a neuro-modulator linked to GABA that depresses the Central Nervous System (CNS). The CNS has at least two unique binding sites for GHB. It functions as an agonist at the excitatory GHB receptor and as a mild agonist at the inhibitory GABA-b receptor. GHB is a naturally occurring chemical that functions in the brains of mammals similarly to some neurotransmitters. In GABAergic neurons, GHB is most likely produced from GABA and released upon neuronal firing. The main source of GHB's sedative effects is its activation of GABA-b receptors, which occurs at far larger concentrations in the brain at pharmaceutical dosages.Antibodies of GABAB prevent GHB's sedative effects. Tryptophan accumulates in the extracellular area as a result of GHB. Peripheral GHB treatment increases tryptophan levels in the blood. Given its potential role in mood, anxiety, and sleep regulation, the serotonergic system may be stimulated by large doses of GHB, which may contribute to some of the neuropharmacological effects of GHB treatment. GHB has a biphasic effect on dopamine release. While greater quantities block dopamine release via GABA-b receptors, lower amounts promote dopamine release via the GHB receptor. The GHB receptor increases dopamine release following the first stage of inhibition. This explains why GHB has a paradoxical combination of stimulatory and sedative effects, as well as the phenomenon known as the "rebound" effect, which causes people to

wake up unexpectedly after many hours of deep sleep brought on by GHB. This is due to the fact that GHB primarily activates the GHB receptor when its concentration in the system falls below the threshold for considerable GABA-b receptor activation over time. A muscarinic acetylcholine receptor blocker mediates the growth hormone-raising actions of GHB



PATHOPHYSIOLOGY AND TOXICOKINETICS

As an endogenous neurotransmitter, gamma-aminobutyric acid (GHB) is a precursor to the inhibitory neurotransmitter GABA. It has an effect on GHB and GABA-B receptors. GHB affects dopamine in two phases. Lower dosages bind to GHB receptors and cause dopamine to be released. Increased dosages first cause neuro-inhibition and depression of the central nervous system (CNS) by blocking dopamine release through agonist actions on GABA-B receptors. However, they then cause an increase in dopamine release through the GHB receptor. The primary mechanism of GHB toxicity is central nervous system and respiratory depression, but this also explains the sedative and excitatory effects of GHB. The body absorbs GHB quickly, and it takes five to fifteen minutes for it to start working. Users frequently report feeling euphoric for a short while at first. GHB poisoning has dose-dependent clinical symptoms and a two- to four-hour half-life. Peak plasma concentrations and clinical effects are obtained between thirty and sixty minutes after exposure. There is a 20–60 minute range in the mg/kg). Treatments ranging from 20 mg/kg to 30 mg/kg induce REM sleep periods. Coma,respiratorydepression,vomiting,apnea,hypothermia and bradycardia are the effects at higher dosages (50 mg/kg). Co-intoxicants can intensify the effects and lengthen the duration of symptoms, particularly alcohol. Because of their changed mental state, patients frequently make it difficult to get a trustworthy history. Empty tiny shampoo bottles in their possession, party or nightclub attendance, or potential sexual assault are all indicators of GHB poisoning.

TOXIC EFFECTS/ SIDE EFFECTS

High amounts of GHB overdose can cause vomiting, nausea, coma, unconsciousness, seizures, decreased heart rate, significantly slower respiration, and reduced body temperature. Confusion, odd and unsettling thoughts, and despair can also be brought on by GHB. They also elicit sympathomimetic effects (increase in the mean atrial pressure and heart rate) when administered parenterally.

GHB WITHDRAWAL SYNDROME

Withdrawal from GHB or its analogs can result in GHB withdrawal syndrome (GWS), which is similar to other withdrawal symptoms, particularly those related to alcohol and benzodiazepines. Due to the brief duration of GHB activity and its quick clearance, GWS frequently follows a fulminant course, presenting with a sudden onset (1–6 hours after the last use) and a rapid development to severe withdrawal symptoms. Regular users usually take GHB every one to four hours to avoid the start of withdrawal, which is probably due to its fast oral absorption and half-life of 20 to 30 minutes. Withdrawal from GHB can occur over a period of 3-5 to 14-21 days (average 9 days). A minimum GHB dose of 18 g and 10 g for GBL previous withdrawal syndromes and polydrug use are two of the predictors of GHB withdrawal, as are the amount and frequency of use (e.g., > 4 mL of GBL on a daily basis or GBL use > 6 times daily every day or using GHB/GBL > 4 times per day during 2–4 weeks in higher doses). The initial signs and symptoms of GHB/GBL withdrawal include vertigo, nausea, vomiting, tremors, and sleeplessness. Additional symptoms during the course of the following 12 to 48 hours include tachycardia, hypertension, agitation, convulsions and/or myoclonic jerks, as well as aural or visual hallucinations. There are also descriptions of

confusion and paranoia. Although the most severe GHB withdrawal symptoms go away in two weeks, mood disturbance, anxiety, and sleeplessness might linger for a while after the conclusion of an acute episode, much as with other sedatives. Acute delirium, which is similar to what occurs after severe alcohol withdrawal, is a serious adverse event that can occur in some cases of GWS. However, compared to alcohol withdrawal (about 5%), the prevalence of GHB withdrawal might reach 12% greater. An additional effect of co-using stimulants on GHB withdrawal symptoms, such as more severe and persistent twitching of the muscles, agitation, and restlessness, was discovered in a recent research.

TREATMENT OF WITHDRAWAL FROM GHB

There are no established detoxification procedures for GHB. Case studies and uncontrolled open-label trials provide the basis of the research that is currently available. Characteristics of alcohol or benzodiazepine withdrawal syndrome typically necessitate a similar therapeutic strategy. A high-dose, long-acting benzodiazepine, such diazepam, is the first-line pharmaceutical therapy. To treat GHB withdrawal, high-dose benzodiazepines aren't always enough, though. Due to the increased risk of delirium and the requirement for larger dosages of medicine, the management of severe GHB withdrawal is more difficult than that of alcohol withdrawal. There have been suggested detoxification strategies that combine a set dosage with a symptom-triggered dosing schedule. Additionally, a scale utilized in the context of opioid withdrawal served as the foundation for the development of the Subjective and Objective Withdrawal Scale.

LEGAL STATUS OF GHB IN INDIA

The Narcotics, Drugs and Psychotropic Substances Act, 1985 includes GHB in India. According to Chapter VII-A of the NDPS Rules, 1985, GHB may be imported for medicinal and scientific reasons under the Special Provisions after receiving an import certificate from the Narcotics Commissioner in accordance with the proviso to Rule 53 of the NDPS Rules. Many nations laws classify GHB and its equivalents as controlled drugs.

CONCLUSIONS

Gamma Hydroxy Butyrate has a wide variety of abusive and addictive potentials, making it a possibly fatal naïve drug. It has been the go-to drug in the modern world for incidents of drug-facilitated sexual crimes, particularly in the west. It's difficult to gauge the extent of the devastation that such a medicine may bring about in poor nations. The problem is made worseby the fact that it has grown to be one of the drug mafia's most favored commodities due to its simple manufacturing methods, widespread usage, and probable availability of its designer pills, which make it simple to evade the law. It is urgently necessary to implement strict legal regulations, conduct extensive research on the treatment of acute intoxication and poisoning, assist addicts in their recovery, and develop methods for raising young knowledge of the health risks associated with substance misuse.

REFERENCES

1. https://www.betterhealth.vic.gov.au/health/healthyliving/GHB
2. https://www.dea.gov/factsheets/ghb-gamma-hydroxybutyric-acid
3. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8098080/
4. https://en.wikipedia.org/wiki/%CE%93-Hydroxybutyric_acid
5. https://emedicine.medscape.com/article/820531
6. https://karger.com/nps/article/73/2/65/233800/The-Neurobiological- Mechanisms-of-Gamma
7. https://www.dea.gov/sites/default/files/2020-06/GHB-2020_0.pdf

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Dr. D. Y. Patil College of Pharmacy, D. Y. Patil Educational Complex, Sector 29, Nigidi Pradhikaran, Akurdi, Pune 411044.