Faculty of Medical and Health Sciences, University of Poonch Rawalakot
Journal of Pharma and Biomedics
ISSN: 3007-1984(online), 3007-1976 (Print)
https://www.jpbsci.com/index.php/jpbs

Neurobiology and Management of Drug Addiction and Dependence: A Multidisciplinary Review

Abu Sulman, Muhammad Akmal Farooq, Rana Dawood Naseer, Anam Hanif, Zunaira Afzal, Muzammil Zaman Khan, Muhammad Saad Naeem, Hafiz Muhammad Ahmad, Saman Mahmood, Hafiz Aamir Ali Kharl*

Faculty of Health & Pharmaceutical Sciences, Department of Pharmacy, University of Agriculture, Faisalabad, Pakistan.

Received: May 18, 2025; *Revised: June 28, 2025;* *Accepted: June 30, 2025*

A B S T R A C T

Drug addiction and dependence are chronic, relapsing disorders influenced by a complex interplay of neurobiological, psychological, environmental, and social factors. Central to the addictive process is the dysregulation of the brain's reward system, particularly the mesolimbic dopamine pathway, which reinforces compulsive drug-seeking behavior and contributes to craving, tolerance, and withdrawal. This article provides a comprehensive overview of drug addiction, exploring definitions, pharmacology, prevalence, and societal impact. It outlines the neurobiological basis of addiction, including neurotransmitter systems, neuroadaptations, and affected brain circuits, with emphasis on the binge/intoxication, withdrawal/negative effect, and preoccupation/anticipation stages of the addiction cycle. Commonly abused drug classes such as opioids, stimulants, depressants, cannabinoids, and hallucinogens are discussed in terms of their mechanisms of action and physiological and psychological effects. Risk factors for addiction include genetic predisposition, psychiatric comorbidities, peer and family influences, low socioeconomic status, and environmental exposures. The article also reviews validated screening tools and diagnostic criteria for substance use disorders (SUDs). Management strategies include pharmacological treatments like methadone and buprenorphine-naloxone, and non-pharmacological interventions such as cognitive behavioral therapy (CBT) and cue exposure therapy (CET). Prevention efforts are categorized into universal, selective, and indicated approaches, targeting families, schools, communities, and healthcare settings. Despite advances, challenges such as stigma, relapse, limited resources, and lack of trained professionals persist. Future directions in research focus on personalized treatments, translational models, neurocircuitry mapping, and innovative techniques like optogenetics and single-cell profiling. A multidisciplinary and evidence-based approach remains vital to effectively address the complexities of addiction and mitigate its public health burden.

Keywords: Drug addiction, Dysregulation, Cognitive behavioral therapy, Cue exposure therapy.

Corresponding Author: Hafiz Aamir Ali Kharl*
Email: hafiz.kharl@uaf.edu.pk

INTRODUCTION

Drug dependent person is defined as a person who undergoes in a psychic or sometimes under physical state due to the use of any harmful drug which is characterized by some behavioural and other responses that may include urge to use that drug persistently or in a cyclic pattern to get its psychoactive effect or to avoid its withdrawal symptoms (West *et al.*, 2013). Drug dependant is commonly known as drug addict or drug abuser. Drug abuse is the consumption of drugs continuously and immensely to gain self-pleasure and reward, but not for medicinal purpose (Glatt *et al.*, 2012). A person with positive tested for drug without any legal justification is charged and sentenced under section 15 of DDA on self-administration of drugs. Drug addiction can

be defined as a chronic, relapsing disorder characterized by compulsive drug-seeking and consumption behaviors, impaired ability to limit intake, emergence of negative affective states (e.g., dysphoria, anxiety, irritability) during drug abstinence (Koob *et al.*, 2016). The term has changed from "addiction" to "substance use disorders (SUDs)" in modern classification systems. Drug dependence means presence of drug is necessary for normal functioning and reduction or discontinuation of that abrupt dose will result in withdrawal symptoms (Juurlink *et al.*, 2012). It depends upon the class of drug used. The term physical dependence represents neuroadaptation to sustained drug exposure while psychological dependency means drug craving, driven by either continuous rewarding effects or avoiding anticipated withdrawal effects.

Prevalence and societal impact

An estimated 149-271 million people world widely used an illicit drug; 125-203 million users of cannabis; 15-39 million problem users of opioids, amphetamines or cocaine and 11-21 million people who inject drugs. Opioid misuse is the leading cause of mortality, primarily through fatal overdose and dependence related problems. Other risks among injection drug users are Blood borne diseases (HIV, hepatitis C, hepatitis B) and associated with unsafe injection practices (e.g. opioid, amphetamine, cocaine injectors) (Degenhardt *et al.*, 2012). Major challenge exists in determination accurate prevalence rates of illicit substance use because of associated social stigma and behavioural concealment tendencies. Especially these challenges are nominated in cultural setting where drug use may result in legal results (Murphy *et al.*, 2016). The illegality status of substances (e.g. amphetamines, cocaine, cannabis, opioids) creates methodological limitations to determine population sizes of users, identify problems associated with usage patterns and quantify related health and social harms.

Major Type of Illicit Drugs

Amphetamine-type stimulants sympathomimetic amines, cause potent central nervous system stimulation, Cannabis (e.g., marijuana, hashish, and hash oil) produce euphoria and relaxation, sensory enhancement and increase sociability. Its botanical source is *Cannabis sativa*, Cocaine is an alkaloid that cause potent central nervous system stimulation and obtained from the *Erythroxylum coca* plant, Opioids such as heroin and morphine, and their synthetic analogues (e.g., methadone, fentanyl). Their botanical source is Opium Poppy (*Papaver somniferum)* plant. Opioids are analgesics and cause euphoria at therapeutic doses but respiratory depression and comma at high doses (Chou *et al.*, 2016).

Mechanisms of drug action in addiction

The study of addiction's transcriptional mechanisms focuses on drug-induced regulation of gene expression (a critical process through which chronic drug exposure induces persistent neuroadaptations) (Müller *et al*., 2011). Some psychoactive substances modify transcription factors within the brain's reward pathways, which normally govern responses to natural reinforcers (e.g., food, sex, and social interactions) but dysregulated following prolonged drug exposure. This reward system includes dopaminergic neuron present in midbrain's ventral tegmental area (VTA) and projection targets of limbic forebrain including ventral striatum, prefrontal cortex, amygdala, hippocampus and related structures (Miller *et al*., 2012)

The mechanism involves:

Mesolimbic Dopamine Pathway

The mesolimbic dopamine pathway (especially the nucleus accumbens and ventral tegmental area (VTA)) is central to the augmentation of drug taking behaviour (Volkow *et al*., 2016). Mesolimbic dopamine pathway especially ventral tegmental area (VTA) and nucleus accumbens, is stimulated by addictive substances which results in increase of dopamine. As a result of which feeling of euphoria and boosted drug taking behaviour takes.

Neuroadaptation

With the repeatedly use of these drugs brain undergoes neuroadaptations (altering receptor sensitivity and neurotransmitter levels) that leads to tolerance, dependence and cravings (Wise *et al.*, 2014).

Changes in Brain Circuits

Their long-term use affects the areas of brain that are responsible for decision-making, impulse control, and memory (e.g., prefrontal cortex, amygdala, hippocampus) and impairing judgment.

Conditioning and Craving

Environmental signals associated with drug usage can trigger conditioned responses and eager cravings that make relapse more easily even after long periods of refraining (Nestler *et al*., 2012) (Figure 1).

Types of drugs commonly associated with addiction (e.g., opioids, stimulants, alcohol, and benzodiazepines)

Stimulants: (e.g. cocaine, amphetamine)

MOA: increase the dopamine and noradrenaline level by inhibiting their reuptake or by enhancing their release.

Effect: Elevates mood, causes alertness. Long term use can lead to paranoia, anxiety and dependency (Koob *et al.*, 2016).

Depressants: (e.g. benzodiazepines, barbiturates and alcohol) (Volkow *et al.*, 2015).

MOA: Enhance the effect of inhibitory neurotransmitter (GABA) and reduce neuronal excitability.
Effect: Relaxation, anxiolysis and sedation. Chronic use can lead to tolerance, dependence and withdrawal symptoms like seizures.
Opioids: (e.g. heroin, morphine and codeine)
MOA: Bind to opioid receptors (μ, δ, κ) in brain and spinal cord (Brunton *et al*., 2006).
Effect: relieve pain, causes euphoria and sedation. Their repeated use leads to tolerance, physical dependence and severe withdrawal effects.
Cannabinoids: (e.g. THC from cannabis) (Anatolevna *et al*., 2013).
MOA: Act on cannabinoid receptors (CB1 in the brain and CB2 in the immune system).
Effect: Altered perception, causes relaxation and appetite stimulation. Chronic use can cause impaired memory and motivation.
Hallucinogens: (e.g. LSD, psilocybin) (Everitt *et al*., 2016).
MOA: Primarily act as a receptor agonist of serotonin (5-HT2A).
Effect: Altered consciousness, cause hallucinations and emotional swings. Physical dependence is lower but can cause psychological effects.

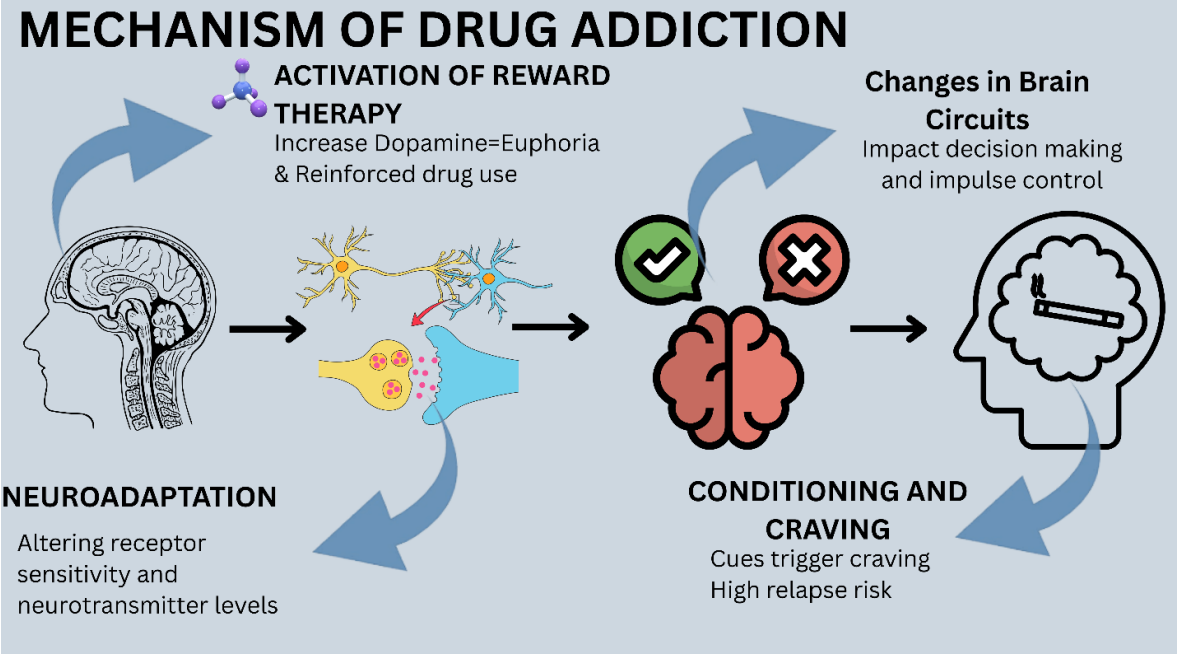

Figure 1: Mechanism of drug addiction.

Neurobiological Basis of Addiction

The neurobiological processes that take part in different states of drug addiction can be considered as distinct areas centred on brain pathways, and how these alterations sustain in the relapse vulnerability. Many neuroadaptations happen in these circuits of the brain during progression from drug use to addiction (NIDA et al., 2020). Different neuromodulators and neurotransmitters such as dopamine, opioid peptides along with GABA, serotonin, acetylcholine, glutamate and endocannabinoid systems show activity at the level either nucleus accumbens or ventral tegmental (Cremers *et al.*, 2021). Dopamine, GABA, enkephalins, glutamate, CRF, norepinephrine, dynorphin, neuropeptide Y and endocannabinoids are the principal neurotransmitters involved in neuroadaptations (Koob *et al*., 2016). SUDs (Substance Use Disorders) are multistage and complex disorders marked by dysregulation in three key neurocircuits (Uhl *et al*., 2019):

The binge/intoxication phase, mediated by the basal ganglia;
The withdrawal/negative affect phase, governed by the extended amygdala;
The preoccupation/anticipation phase, driven by the prefrontal cortex

Within three primary neural domains exhibit substance-induced neuroplasticity, characterized by neurotransmitter- and neuromodulator-specific adaptations including the mesocorticolimbic dopamine pathway, CRF signalling in the central amygdala, and corticostriatal glutamate projections (Koob *et al*., 2011). These circuits also functionally interact with other

networks involved in mood regulation, including stress reactivity circuit (involving amygdala, hypothalamus, and habenula) and interoceptive pathway (involving the insula and anterior cingulate cortex and collectively mediates the awareness of negative emotional states) (Noël *et al.,* 2013).

Risk Factors

Drug addiction has evolved a serious and multifaceted issue that impacts persons across biological, psychological and social aspects of their life. The consequences of drug addiction are equally severe, manifesting in academic performance decline among students, low workplace productivity, and strained professional relationships. It often creates household instability marked by interpersonal conflict and financial difficulties (Gardner *et al.,* 2011):

1. Family influences
2. Peer influences
3. Psychological factors
4. Socio-environmental factors

The family-related factors include genetic heritability, domestic violence and conflicts, parenteral education state and supervision etc. Peer pressure or influence affects through antisocial peer groups and experiences of peer rejection etc. At individual level, psychological issues including post-traumatic stress disorder (PTSD), depression, anxiety, conduct disorder and attention deficit/hyperactivity disorder (ADHD) etc increase the susceptibility to drug addiction. In the addition, Poverty, unemployment, low socioeconomic status (SES) and victimization histories further increase the risk of drug addiction. Risk of drug dependence is greater for adolescent recent onset users of cocaine, psychostimulant drugs other than cocaine, analgesics, anxiolytic medicines, inhalant drugs and cannabis as compared to adult recent onset users (Müller *et al.,* 2011; Devi *et al.,* 2023).

Genetic factors

It is well understood that the risk of many substance dependence traits is genetically influenced. It is determined by studying methods of genetic epidemiology, for which the most relevant is twin adoption study (Chen *et al*., 2009). Drug dependence disorders (cocaine, opioid and nicotine) are genetically influenced. Risk genes are located primarily on genetic linkage studies and identified primarily on genetic association studies (Benjamin *et al*., 2014). Despite of some conflicting results, overall data from adoption, twin and family studies confirms a substantial genetic contribution to drug dependence which also include the existence of genetic factors specific to each disorder (Gelernter *et al*., 2010).

Environmental factors

Drug abuse and drug dependence are fatal diseases and can have serious outcomes. It results in physical damage, behavioural problems and relationships with other people. Addiction can be spiritual illness (Mroziewicz et al., 2010). Environmental factors related to drug addiction to one or more family members are family conflict, lack of supervision by parents, parental unemployment (specially fathers) and parents with low literacy (Bierut *et al*., 2011).

Socio-economic factors

Socio-economic factors describe the position of the person in the society on the criteria such as income, level of education, occupation and value of owned property (Aghaii et al., 2012; Kadushin et al., 1998) . They include friends, unemployment, poverty, uncontrolled growth and migration, unhealthy entertainment and insufficient social acceptance. They also include easy access to drugs and residence near drug traffic routes (Spooner *et al.,* 2005).

Psychological factors

The presence of psychiatric issues is linked with enhanced risk for substance dependence that are further associated with mental issues, and it is bidirectional as this disorder enhances the risk of abnormal drug use to self-medication, as drugs affect neurocircuits associated with other mental diseases (Daniel et al., 2009). Psychiatric disorders include mood, anxiety, depression, psychotic, personality disorders, ADHD and individual factors includes lack of confidence, lack of character development, hopelessness, pleasure seeking, escape from the problems of life and low education etc. As psychiatric disorders enhance the risk for substance used disorders (SUDs) which can be prevented by early diagnosis and treatment of them (Kendler *et al.,* 2003; Manchikanti *et al*., 2007).

Pharmacokinetics and Pharmacodynamics of Addictive Substances

Humans consume many addictive substances mainly alcohol, cocaine and heroin. Understanding the effect of these drugs on nervous system involve the knowledge of pharmacology of the drug. In the case of alcohol, the two carbon molecules engage with other biomolecular targets through hydrogen bonding and weak hydrophobic interactions, lowering their pharmacological potency due to which ethyl alcohol is considered a nonspecific drug. Ethyl alcohol shows its effect on the brain that occurs in a range up to 100mM in users that occasionally drink. It causes about 11.8 billion deaths annually in the world that are much higher than deaths caused by cancer, and it is responsible for fifth of all deaths all around the world according to Global Burden of Disease study. Drug

addiction cycle is divided into three stages (Zuckerman *et al.*, 2012; Galizio *et al.*, 2013; Ando *et al.*, 1975) (Figure 2).

1. Overconsumption
2. Detoxification with adverse symptoms
3. Urge phase/ Craving phase

Human and animal study models say that each stage affects various parts of the brain. In brief, VTA-NAc and dorsal striatum (Stimulus response habits) take part in the first stage, amygdala with brainstem and hypothalamus in the second stage and the dorsal striatum, cortical areas, the hippocampus, and basolateral amygdala affect the last stage of drug addiction.

The pharmacology of opioid receptors is to mediate receptors including analgesia, miosis, reduce gastrointestinal motility, anxiety, respiratory depression, physical dependence, and tolerance (Roth *et al*., 2018). Development of opioid use gradually increases by increasing higher use of opioids leading toward dependence and tolerance. Significant changes in certain brain areas and nerve circuits that affect various brain chemicals do not always occur in people who develop tolerance or physical dependence on opioids (Koob *et al*., 2010). Basic areas or two primary areas affected by the continuous increase of opioids use have been found by locus coeruleus and the mesolimbic system. One mesolimbic system arises from VTA in the midbrain to the prefrontal cortex and the amygdala and has abundant dopaminergic neurons. The projection reward via release of dopamine (neurotransmitter) which is indirectly enhanced by activation of opioids receptor that blocks release of GABA (γ-aminobutyric Acid) to disinhibit the release of dopamine.

The primary effect needed is anxiolysis and euphoria. Once tolerance and dependence is developed higher doses and more frequent doses is required to maintain the euphoric state .The withdraw pathway also act as same through reduce the dopamine production leading towards the dysphoria and anxiety .In opioids use disorder patients the desire of use to reward of euphoria and to avoid unpleasant dysphoric with drawl symptoms act unusual ways for example using opioids for the long time and taking it despite it causes problems at school, work, at home or in social activities (Stein *et al*., 2003).

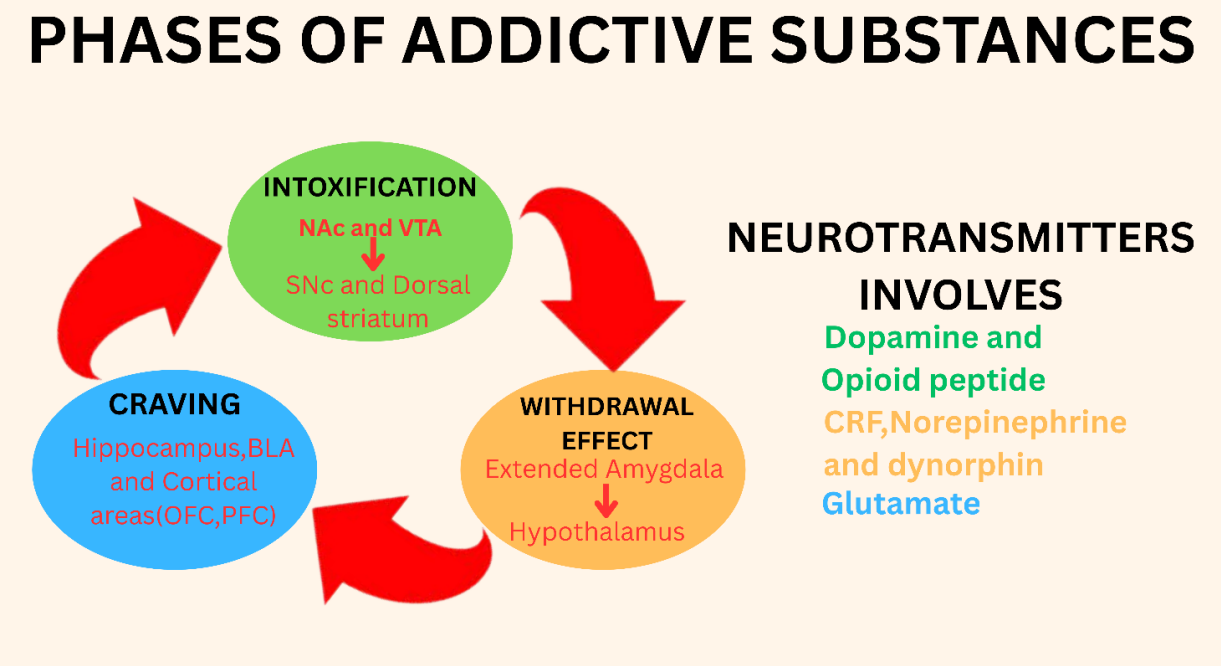

Figure 2: Phases of addictive substances.

Screening and Diagnosis of Drug Addiction

Diagnosis recognises that impaired decision-making (continued drug abuse despite of having knowledge about physical and psychological problems associated with them) and inhibitory control over behaviour (Persistent desire to lessen or control substance use). Diagnosis deal with physical behaviour as well as psychological problems. Hopefully advance information will help to manage any such deficits within routine clinical practice.

Pharmacological Management

At present many disorders which are caused by using psychoactive substances have been developed. So different

methods of treatment are present, but their effects are unsatisfactory. Actual achievement of long-term abstinence with medicine use has not been highly effective in drug use or criminal behavior (Chartoff *et al*., 2014). It is noted that about 85% of addicted people are relapse within 1 year after abstinence. However, the people who did not receive any medication have greater chances of mortality (Volkow *et al.,* 2024). OUD (Opioid use disorder) is a critical issue ranking the third most substance use disorder globally, contributes to morbidity and premature mortality (Kuhn *et al*., 2013). The estimated number of people with Opioid Use Disorder worldwide was estimated at 40.5million in 2017. In 2016 around 3.6 million years of life lost due to early death. Drug overdose is the leading cause of death among people with OUD (Brandon *et al*., 2007). Overdose are considered as a preventable cause of death by implementation of variety of techniques including OAT (Opioid Agonist Treatment) (Degenhardt *et al.,* 2019).

Table 1: Screening tools used for drug addiction and dependence.

Instrument	Type of instrument	Items	Recall Period	Time required (min)	Format	Completion	Availability
ASSIST[1]	Enquires about illicit drugs in a disaggregated manner.	8	Life-time experience Past 3 months	5–10	Printed version	Interviewer administered	Public domain for free
CAGE-AID[2]	Conjoint screening instrument	4	Life-time experience	5	Printed version	Self-administered	Public domain for free
DAST[3]	Enquires about illicit drugs in aggregate.	28 or 20 or 10	Lifetime experience	5–10	Printed version Online	Self-administered	Public domain for free
DHQ/PDHQ[4]	Enquires about illicit drugs in a disaggregated manner	5	Lifetime experience Past 6 months	5–10	Printed version	Self-administered	Public domain for free
DUDIT[5]	Enquires about illicit drugs in aggregate	11	Lifetime experience Past year	5–10	Printed version	Self-administered	Public domain for free
DUS[6]	Enquires about illicit drugs in a disaggregated manner	16	Past 30 days	5–10	Printed version	Interviewer administered	Public domain for free
NMASSIST[7]	Enquires about illicit drugs in a disaggregated manner	8	Lifetime experience Past 3 months	5–10	Printed version Online version	Interviewer administered Self-administered	Public domain for free
SMAST-AID[8]	Conjoint screening instrument	13	Lifetime experience.	5–10	Printed version	Self-administered	Public domain for free
SIP-AD[9]	Conjoint screening instrument	5	Lifetime experience 90 days	≤5	Printed version	Self-administered	Public domain for free
SDS[10]	Enquires about illicit drugs in aggregate	15	Anytime period	5–10	Printed version	Self-administered	Copyright information unavailable
SSI-SA[11]	Conjoint screening instrument	16	Lifetime experience	10	Printed version	Interviewer administered Self-administered	Public domain for free
TICS[12]	Conjoint screening	2	Past year	≤5	Printed version	Self-administered	Public domain for free

UNCOPE[13]	instrument Conjoint questions on illicit drugs and alcohol	6	Lifetime experience Past year	5–10	Printed version	Interviewer administered	Public domain for free

Methadone

Methadone along with Opioid agonist treatment is the main treatment for Opioid use disorder (Degenhardt *et al.*, 2011). It is effective and safe in suppressing illicit Opioid use as it reduces the injection behavior and it decreases the risk of HIV and Hepatitis C viral infection (Sordo *et al*., 2017; Jordan *et al*., 2019). It also improves mental and physical health and reducing mortality especially overdose death (Mattick *et al*., 2009). It is considered cost effective, with cost saving protocols when cost of imprisonment and the economic impact of criminal activities are considered (Platt *et al.*, 2018). Despite the evidence of benefits there is also evidence of a high mortality rate during the first month of treatment. Methadone (a full opioid agonist) cause severe respiratory depression, and it is the cause of overdose death during first month of treatment and could exceed the rate of thirty deaths per one thousand patients which much higher than individuals taking specialist addiction services in primary healthcare. In recent sixty-seven studies it is found that the Methadone maintenance treatment (MMT) decreases overtime. At six months, about 67% of patients remain in treatment at 2 years the 50% of patient remains in the program (Sordo *et al.*, 2017; Chetty *et al*., 2017).

Most of the dropouts happens early carefully assessing opioid tolerance and closely monitoring patients during the early phase can help lower the risk of death at the beginning of treatment, staying in MMT further reduce the risk of death both during the initial phase and long-term maintenance. This protection is lost if the person stops opioid agonist therapy, particularly if they are followed by relapses. Therefore, enhancing patient retention is essential to reduce fatalities (Sordo *et al.*, 2017; Durand *et al*., 2020) (Figure 3).

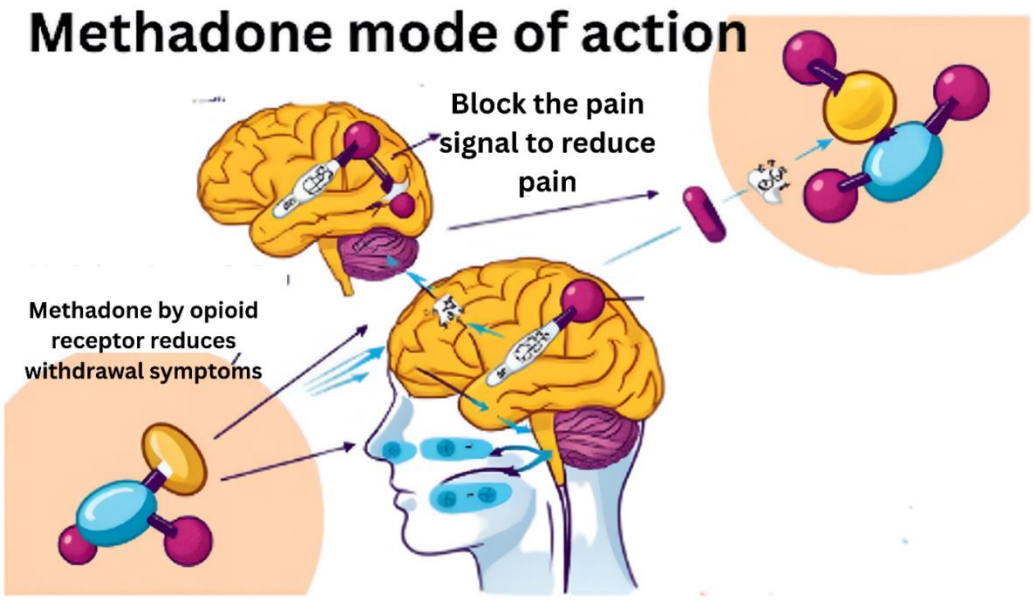

Figure 3: Mechanism by which Methadone reduces withdrawal symptoms.

Buprenorphine & naloxone

Buprenorphine is a partial μ-receptor agonist, currently under development as a pharmacotherapy for the treatment of the opioid dependence. It should remember that the buprenorphine itself has a potential to abuse. The administration of buprenorphine also shows opioid like

effects (O'Connor *et al*., 2020). The buprenorphine is taken by the parenteral route for abuse and is reported in Europe, India, and New Zealand etc. (Degenhardt *et al.*, 2019). One evidence-based strategy to minimize potential abuse and diversion is to use a combination of buprenorphine and short-acting opioid antagonist naloxone. Developing an optimal dosage form is suitable for typical use and by considering the poor oral bioavailability of buprenorphine (Bickel *et al*., 1995). Buprenorphine-naloxone is a partial agonist used for substitution therapy. These drugs are prescribed for the decrease craving and the frequency of use of full mu-receptors agonist which are heroin and fentanyl (Forsyth *et al*., 1993). Substitution using buprenorphine and naloxone decreases the intensity of euphoria than opioid agonists and reduces the adverse effects. This combination is associated with greater retention in drug treatment programs, a lower frequency of relapses and less opioid related overdose than placebo (Jasinski *et al.*, 1982). Patient prescribed buprenorphine-naloxone stays in treatment for a longer duration of time and the adverse effect of treatment appears to be less intense as compared to a-2 agonist (Coe *et al.*, 2019).

Non-pharmacological approaches in the treatment of Addiction

Many non-pharmacological therapies are introduced to treat drug addiction particularly in opioid use dependence.

Behavioral Treatment

Cognitive behavior and Cue expert (CBT and CET) therapies show activity in drug addiction treatment (Kakko *et al*., 2003). The base of the activity of CBT is hypothesis that behavior can be changed by changing the pattern of harmful thoughts and beliefs associated with addiction. According to reports CBT is effective in decreasing drug craving, so it is used in clinical settings, to treat many psychiatry diseases (Gowing *et al.*, 2017; Mellentin *et al.*, 2017) (Figure 4). It is not used commonly due to its protocols such as comparatively excessive cost and specialist requirement for its application, but both issues are resolved by using computer assisted CBT that is more useful, and its acceptance is increasing due to easy access of computer and internet. Studies prove the effectiveness of six-module computer-based training in cognitive behavioral therapy (CBT4CBT) for drug addiction (Zilverstand *et al*., 2016; Shafran *et al*., 2018; Carroll *et al.*, 2014).

CET is another approach in the field of addiction and psychiatry (Carroll *et al*., 2008). CET is based on the idea of pavlovian conditioning playing a role in craving and seeking behavior for drug. Through repeated exposure to drug related cue (both environmental and specific triggers) without actual drug use process known as extinction the conditioned response, such as craving and drug-seeking gradually decrease. CET operated on the theory that addiction hijacks the brain's normal learning and memory processes turning it into a persistent maladaptive memory (Carroll et al., 2014).

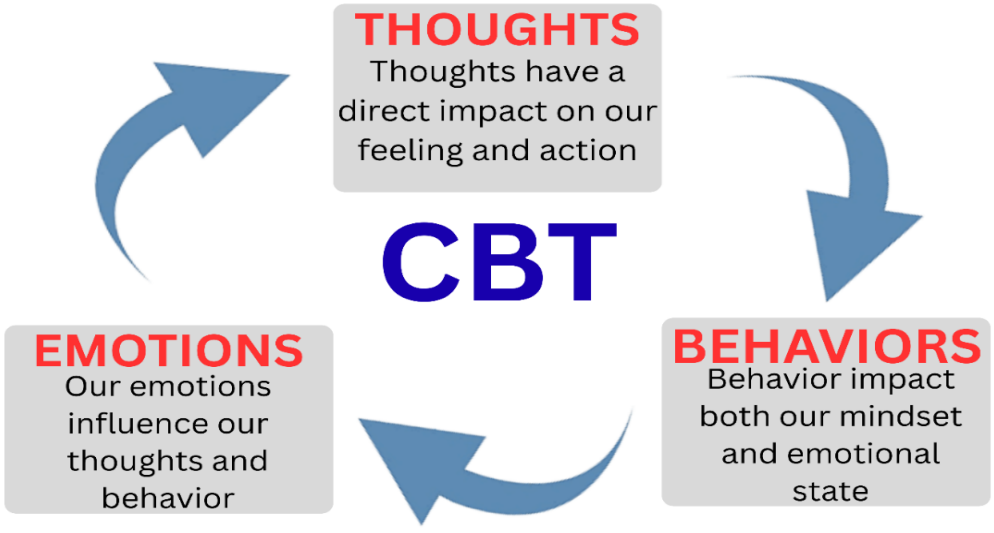

Figure 4: Drug addiction behavioural therapy.

Rehabilitation

The rehabilitation of narcotic users requires a comprehensive and sustainable approach rather than solely viewing them as lawbreakers. Rehabilitation interventions for drug abusers involve: (Figure 5).

Drug addiction therapy program which consists of:

Medical Rehabilitation phase involving Methadone maintenance program and complementary behavioral therapies.

Non-medical Rehabilitation program involves Therapeutic Communities with structured peer support.

After-Care rehabilitation stage such as integral boarding schools.

Prevention and Challenges in management of Drug Addiction

Various risk factors from childhood to adulthood decide the drug addiction (Liu *et al.,* 2019; BNN et al., 2017; Blanco *et al*., 2014). The purpose of preventive strategies is lessening the use of drugs and ensure that ability engagement of people with families, educational institutions and societies (Blanco *et al.*, 2014).

However risk is present during all stages of life and require preventive strategies, the stages of childhood and adolescence are main targets of these measures because major behavioural changes occur during these stages (García-Rodríguez *et al*., 2014; Bewley-Taylor *et al.,* 2018; Abuse *et al*., 2013; Chambers *et al*., 2003).

Evidence-based prevention programs are specifically designed for specific settings, age groups and populations. These programs may aim to:

Enhance protective factors such as self-control, parenting supervision and support, positive relationships, academic competence, anti-drug-use policies, and neighborhood social cohesion.

Reduce risk determents such as early-onset aggression, poor social skills, deficiency of parental supervision, drug accessibility and poverty.

Help people to avoid the onset of drug use.

Refrain progressing from low-risk higher-risk substance use.

Reduce substance use-related harms such as infections and injuries.

There are different categories of prevention programs such as Indicated (for people who are at risk stage of substance abuse), selected (for individuals or group with a known risk factor) and universal (broad approaches for everyone in a specific setting) (Casey *et al*., 2015; Blanco *et al.,* 2019; Volkow *et al.,* 2024). These programs are also usually designed to meet people's need at specific periods of life, prenatal period, early childhood or adulthood and in certain settings like communities, doctor's offices and family households (Cance *et al*., 2023). Family-based help parents and guardians access skills and resources associated with better substance use results in children (Haggerty *et al*., 1994; LeNoue *et al.,* 2016; Brody *et al.,* 2017).

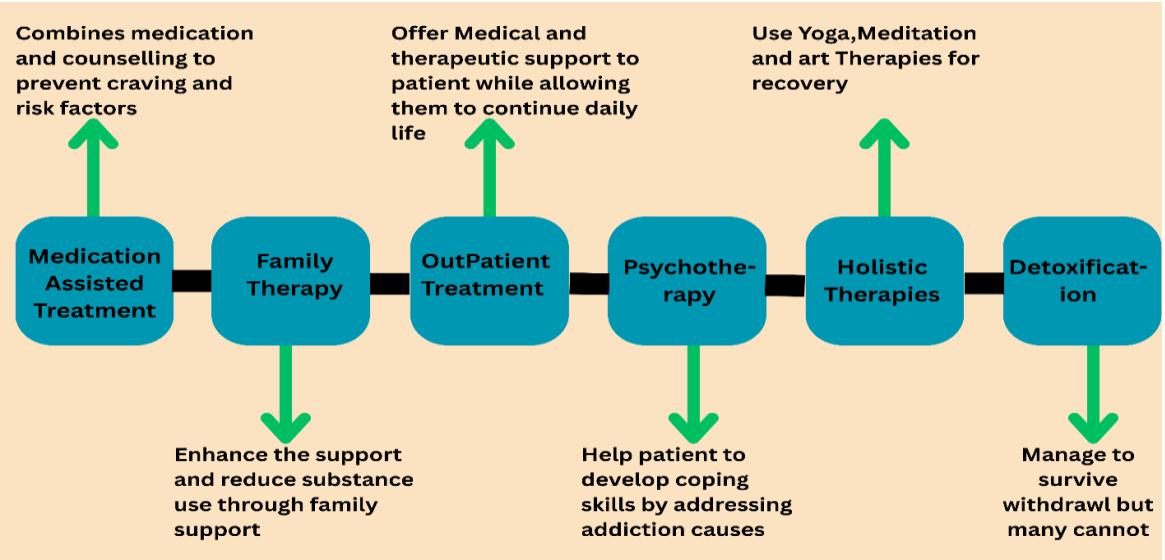

Figure 5: Different strategies to treat drug addiction.

These include, for instance, Nurse-Family partnership and parenting classes to teach them how to build a good and supportive relationship with children. The main targets of family-based preventions are risk factors that

are linked with social and family influence (Kitzman *et al.,* 2019). These programs have beneficial effects on adults (Kumpfer *et al*., 2003). There are also gender specific strategies present to target mothers and daughters (Yap *et al.,* 2017). If education of parenting skills and how to grow their children in vulnerable environment is provided to mothers during their pre-natal stage, it will be helpful in preventing substance use in future life (Newton *et al*., 2017; Bewley-Taylor *et al.,* 2018).

School-based drug education is most common strategy, and its effects are generally modest (Turnbull *et al.,* 2012; D'Onise *et al*., 2010; Faggiano *et al*., 2014). Furthermore, limitations of resources often hinder sustainable implementations (Sussman *et al*., 2004). School-based Programs provide students substance-refusal skill, accurate information on drugs, social and emotional skill training, connect at-risk students to good mentors or coordinate after school activities such as Classroom-Centred Interventions (Foxcroft *et al.,* 1996; Hawkins *et al.,* 2016). One example of this type of intervention is Preventure (Hill et al., 2020). As students can also become addict, high-risk individuals specially youth need continuously preventive measures (Spoth *et al*., 2013; Conrod *et al.,* 2016).

Community-based programs engage leaders and organizations to identify and implement evidence-based interventions that match needs and resources of that community (Oesterle *et al*., 2018).

Population-based programs help specific group of people with same circumstances and challenges (Blume *et al*., 2016). For example, a program for youth experiencing homelessness may deliver healthcare, education, job and housing to lessen the risk factors for worsening substance use. The best-known community-based strategy is Communities That Care (CTC) for adolescent prevention from drug addiction as it prevents multiple youth problems and it trains members of local community on how to select effective community-specific interventions to implement (Hawkins *et al*., 2014).

Strategies in health-care settings help clinicians determine if patient may be at risk and connect them to services that can help (Mitchell *et al*., 2013). This includes activities such a screening as part of routine primary care visit of paediatric e.g. S2BI, BSTAD tools etc (Matson *et al*., 2022).

Programs can also be arranged for workspaces and justice settings.

Digital media, which is basically developed for educational purposes, can also be utilized for the implementation of strategies especially among youth but subsequent systemic education is required to achieve efficacy and safety (Rodriguez *et al.,* 2014; Torous *et al*., 2021; Badawy *et al*., 2017). Lack of workforce skills and stigma towards addiction are most challenging areas of the field. Another common hurdle is insufficient grants and funds for preventive measures beyond the research field. But the implementation and evaluation of recommended preventive strategies is very difficult and create pressure on Health and treatment system (Volkow *et al*., 2023).

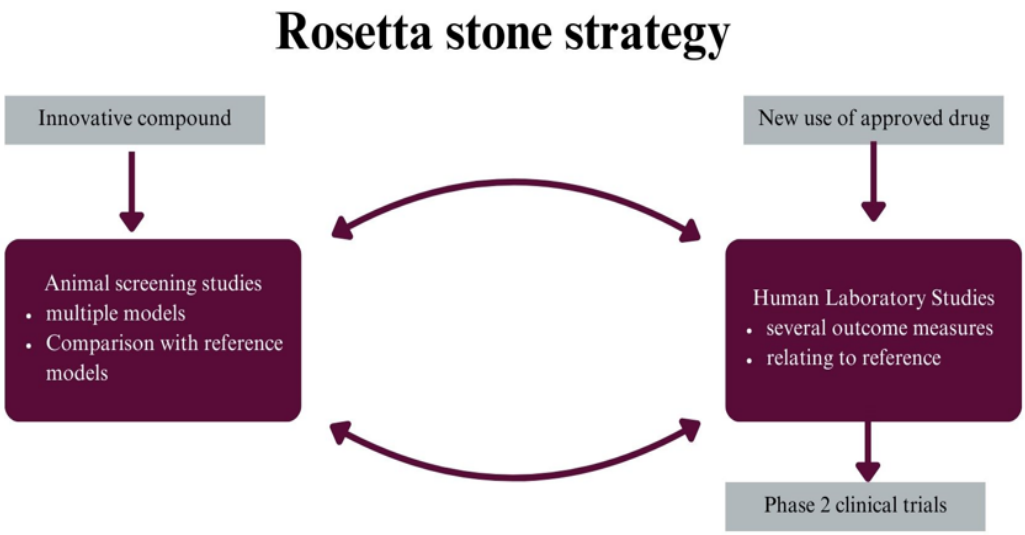

Figure 6: Rosetta stone strategy.

Future Directions in Management of Drug Addiction

Drug addiction is causing relapse in all over the world. A huge population is suffering from addiction this trend is globally increasing according to the reports of WHO (World Health Organization) (James *et al.,* 2018; Degenhardt *et al*., 2018; World Health Organization *et al.,* 2016). Currently available pharmacological research is reporting better treatment strategies and provide the basis for discovery of new drugs. Development and maintenance of addiction includes approved models of animals for addiction and a surge of describing neurocircuitry and different mechanisms of neuropharmacology. A crucial part of this approach is to ensure that the prediction derived from animal models are not constrained by the limitation inherent in those models. The Rosetta stone strategy tackles this challenge in several ways. Firstly, no single animal or human laboratory model can fully capture every facet of addiction, so a range of models is employees to represent different elements of the condition. Secondly the validation process follows a dynamic model allowing discoveries and adaptation to occur at both the input and output stages .Novel neurobiological targets are integrated into the system in a forward -flowing manner, while new medications whether emerging from this forward pipeline, clinical practice or unexpected findings .Third is that the specific symptoms and components for the addiction cycle serve as face-valid models enable the development of more targeted animal and human laboratory models.

Several elements that are required for development pharmacotherapy treatments for drug addiction, have been promoted by NIH. In recent years, major achievements have been done such as Neurobiology of addiction advancement and successful development and validation of pharmacological as well as behavioural treatment, for example, buprenorphine therapy and naltrexone with the support of NIDA and NIAAA respectively. Better results are expected by using Rosetta Stone approach that links human and animal studies (Figure 6). Development of pharmacotherapies for the treatment of drug addiction have considerable potential in future. Existing medication have not only demonstrated the possibilities for enhancing treatment outcomes but also serve as valuable benchmark for assessing the effectiveness of new therapeutic candidate (Koob *et al.,* 2009; Kreek *et al.,* 2002; Deroche-Gamonet *et al.,* 2004).

CONCLUSION

Drug addiction and dependence are chronic, multifactorial conditions involving complex interactions psychological, social, neurobiological and environmental factors. Central to the development of addiction is the brain's reward system. The mesolimbic dopamine pathway which reinforces drug taking behaviours and contributes the cycle of craving and relapse. Prolonged drug use can alter the neurotransmitter system of the body, affects the areas of brain working and impaired the decision-making process and impulse control**.** This article has highlighted how different drugs such as opioids, stimulants, depressants, hallucinogens and cannabinoids impact the brain differently but often lead to similar pattern of dependence and withdrawal. Neuroadaptations such as increased tolerance and changing in receptor sensitivity, underline long term effect of substance use and difficulty to achieve sustained recovery. The social and public health impact addiction is substantial with high rates of mortality and morbidity, and economic burden risk factor includes genetics, peer influence, trauma, mental illness poverty and family dynamics. Adolescents and vulnerable population are particularly at risk.

Treatment approach includes both pharmacological and non-pharmacological (behavioural techniques). Some drugs, for instance, buprenorphine, naloxone and methadone are essential in managing opioids use disorder, though challenges remain in this are patient retention and relapse prevention. Behavioural therapies like cognitive behavioural therapy and cue exposure therapy offer effective non-pharmacological support by targeting through patterns and conditions responses to drug cue. Prevention strategies target different age groups and settings including families, school and communities. The goal of the programme is to make protective factors stronger and decrease exposure. However, implementation is often hindered by stigma lack of resources and insufficient training.

Pharmacists, due to their accessibility, play a vital role in early detection for, patient education, and referral especially in underserved communities. Advancement in neuroscience and research tools offer promising directions for personalized treatment and better understanding of mechanism of addiction in human. A comprehensive and multidisciplinary approach remains essential to address the complexities of addiction of the drugs and lessen its individual as well as social effects.

FUNDING

This study acknowledges the absence of financial assistance or grants from any source to support its execution.

CONFLICT OF INTEREST

There are no conflicts of interest, whether of a financial

or non-financial nature, that could influence the impartiality of the research.

ETHICS APPROVAL

It is noted that this investigation did not entail the involvement of either animal subjects or human participants, thereby rendering ethics approval unnecessary.

CONSENT TO PARTICIPATE

The concept of obtaining consent for participation does not apply to the scope of this study.

CONSENT FOR PUBLICATION

All the authors have diligently examined and provided their approval for the final version of the manuscript, endorsing its readiness for publication.

AUTHORS' CONTRIBUTIONS

The research was conceptualized and designed through the collective efforts of all authors.

REFERENCES

Abuse, S., 2013. Mental health services administration. Results from the, 2(013), pp.55-68.

Aghaii, S.S.H., Kamaly, A. and Esfahani, M., 2012. Meta-analysis of individual and environmental factors that influence people's addiction tendencies. International Journal of High Risk Behaviors & Addiction, 1(3), p.92.

Anatolevna, B.I. and Rubenovich, A.V., 2013. Drug addiction. Drugs and their effects on man. Природные системы и ресурсы, (2 (6)), pp.22-27.

Ando, K., 1975. The discriminative control of operant behavior by intravenous administration of drugs in rats. Psychopharmacologia, 45(1), pp.47-50.

Badan Narkotika Nasional (BNN**)** (2017) National survey of drug abuse in 34 provinces in 2017. Jakarta: BNN.

Badawy, S.M. and Kuhns, L.M., 2017. Texting and mobile phone app interventions for improving adherence to preventive behavior in adolescents: a systematic review. JMIR mHealth and uHealth, 5(4), p.e6837.

Benjamin, A. and Chidi, N., 2014. Drug abuse, addiction and dependence. Pharmacology and therapeutics.

Bewley-Taylor, D.R. and Nougier, M., 2018. Measuring the 'world drug problem': 2019 and beyond. In Collapse of the Global Order on Drugs: From UNGASS 2016 to Review 2019 (pp. 65-83). Emerald Publishing Limited.

Bickel, W.K. and Amass, L., 1995. Buprenorphine treatment of opioid dependence: a review. Experimental and Clinical Psychopharmacology, 3(4), p.477.

Bierut, L.J., 2011. Genetic vulnerability and susceptibility to substance dependence. Neuron, 69(4), pp.618-627.

Blanco, C. and Volkow, N.D., 2019. Management of opioid use disorder in the USA: present status and future directions. The Lancet, 393(10182), pp.1760-1772.

Blume, A.W., 2016. Advances in substance abuse prevention and treatment interventions among racial, ethnic, and sexual minority populations. Alcohol Research: Current Reviews, 38(1), p.47.

Brandon, T.H., Vidrine, J.I. and Litvin, E.B., 2007. Relapse and relapse prevention. Annu. Rev. Clin. Psychol., 3(1), pp.257-284.

Brody, G.H., Gray, J.C., Yu, T., Barton, A.W., Beach, S.R., Galván, A., MacKillop, J., Windle, M., Chen, E., Miller, G.E. and Sweet, L.H., 2017. Protective prevention effects on the association of poverty with brain development. JAMA pediatrics, 171(1), pp.46-52.

Brunton, L.L., Lazo, J.S. and Parker, K.L., 2006. The pharmacological basis of therapeutics. Goodman Gilman's, 11th ed.-2006.-McGraw Hill, New York, P, pp.727-733.

Cance, J.D., Adams, E.T., D'Amico, E.J., Palimaru, A., Fernandes, C.S.F., Fiellin, L.E., Bonar, E.E., Walton, M.A., Komro, K.A., Knight, D. and Knight, K., 2023. Leveraging the full continuum of care to prevent opioid use disorder. Prevention Science, 24(Suppl 1), pp.30-39.

Carroll, K.M., 2014. Lost in translation? Moving contingency management and cognitive behavioral therapy into clinical practice. Annals of the New York Academy of Sciences, 1327(1), pp.94-111.

Carroll, K.M., Ball, S.A., Martino, S., Nich, C., Babuscio, T.A., Nuro, K.F., Gordon, M.A., Portnoy, G.A. and Rounsaville, B.J., 2008. Computer-assisted delivery of cognitive-behavioral therapy for addiction: a randomized trial of CBT4CBT. American journal of Psychiatry, 165(7), pp.881-888.

Carroll, K.M., Kiluk, B.D., Nich, C., Gordon, M.A., Portnoy, G.A., Marino, D.R. and Ball, S.A., 2014. Computer-assisted delivery of cognitive-behavioral therapy: efficacy and durability of CBT4CBT among cocaine-dependent individuals maintained

on methadone. American journal of Psychiatry, 171(4), pp.436-444.

Casey, B.J., 2015. Beyond simple models of self-control to circuit-based accounts of adolescent behavior. Annual review of psychology, 66(1), pp.295-319.

Chambers, R.A., Taylor, J.R. and Potenza, M.N., 2003. Developmental neurocircuitry of motivation in adolescence: a critical period of addiction vulnerability. American journal of psychiatry, 160(6), pp.1041-1052.

Chartoff, E. H., & Connery, H. S. (2014). It's MORe exciting than mu: crosstalk between mu opioid receptors and glutamatergic transmission in the mesolimbic dopamine system. Frontiers in pharmacology, 5, 116.

Chen, C.Y., Storr, C.L. and Anthony, J.C., 2009. Early-onset drug use and risk for drug dependence problems. Addictive behaviors, 34(3), pp.319-322.

Chetty, M., Kenworthy, J.J., Langham, S., Walker, A. and Dunlop, W.C., 2017. A systematic review of health economic models of opioid agonist therapies in maintenance treatment of non-prescription opioid dependence. Addiction science & clinical practice, 12(1), p.6.

Chou, R., Cruciani, R.A., Fiellin, D.A., Compton, P., Farrar, J.T., Haigney, M.C., Inturrisi, C., Knight, J.R., Otis-Green, S., Marcus, S.M. and Mehta, D., 2014. Methadone safety: a clinical practice guideline from the American Pain Society and College on Problems of Drug Dependence, in collaboration with the Heart Rhythm Society. The Journal of Pain, 15(4), pp.321-337.

Coe, M.A., Lofwall, M.R. and Walsh, S.L., 2019. Buprenorphine pharmacology review: update on transmucosal and long-acting formulations. Journal of addiction medicine, 13(2), pp.93-103.

Conrod, P.J., 2016. Personality-targeted interventions for substance use and misuse. Current addiction reports, 3(4), pp.426-436.

Cremers, S. and Wright, D.F., 2021. Nonmedical use of prescription drugs. British Journal of Clinical Pharmacology, 87(4).

Daniel, J. Z., Hickman, M., Macleod, J., Wiles, N., Lingford-Hughes, A. N. N. E., Farrell, M., ... & Lewis, G. (2009). Is socioeconomic status in early life associated with drug use? A systematic review of the evidence. Drug and alcohol review, 28(2), 142-153.

Degenhardt, L. and Hall, W., 2012. Extent of illicit drug use and dependence, and their contribution to the global burden of disease. The Lancet, 379(9810), pp.55-70.

Degenhardt, L., Bucello, C., Mathers, B., Briegleb, C., Ali, H., Hickman, M. and McLaren, J., 2011. Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta-analysis of cohort studies. Addiction, 106(1), pp.32-51.

Degenhardt, L., Charlson, F., Ferrari, A., Santomauro, D., Erskine, H., Mantilla-Herrara, A., Whiteford, H., Leung, J., Naghavi, M., Griswold, M. and Rehm, J., 2018. The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet Psychiatry, 5(12), pp.987-1012.

Degenhardt, L., Grebely, J., Stone, J., Hickman, M., Vickerman, P., Marshall, B.D., Bruneau, J., Altice, F.L., Henderson, G., Rahimi-Movaghar, A. and Larney, S., 2019. Global patterns of opioid use and dependence: harms to populations, interventions, and future action. The Lancet, 394(10208), pp.1560-1579.

Deroche-Gamonet, V., Belin, D. and Piazza, P.V., 2004. Evidence for addiction-like behavior in the rat. Science, 305(5686), pp.1014-1017.

Devi, S. and Singh, S., 2023. Risk Factors for Drug Addiction: A Review. Indian Journal of Health & Wellbeing, 14(3).

D'Onise, K., McDermott, R.A. and Lynch, J.W., 2010. Does attendance at preschool affect adult health? A systematic review. Public health, 124(9), pp.500-511.

Durand, L., O'Driscoll, D., Boland, F., Keenan, E., Ryan, B.K., Barry, J., Bennett, K., Fahey, T. and Cousins, G., 2020. Do interruptions to the continuity of methadone maintenance treatment in specialist addiction settings increase the risk of drug-related poisoning deaths? A retrospective cohort study. Addiction, 115(10), pp.1867-1877.

Everitt, B.J. and Robbins, T.W., 2016. Drug addiction: updating actions to habits to compulsions ten years on. Annual review of psychology, 67(1), pp.23-50.

Faggiano, F., Minozzi, S., Versino, E. and Buscemi, D., 2014. Universal school-based prevention for illicit drug use. Cochrane Database of Systematic Reviews, (12).

Forsyth, A.J., Farquhar, D., Gemmell, M., Shewan, D. and Davies, J.B., 1993. The dual use of opioids and temazepam by drug injectors in Glasgow (Scotland). Drug and alcohol dependence, 32(3), pp.277-280.

Foxcroft, D.R., Tsertsvadze, A. and Cochrane Drugs and Alcohol Group, 1996. Universal family-based prevention programs for alcohol misuse in young people. Cochrane database of systematic reviews, 2011(9).

Galizio, M. and Maisto, S.A. eds., 2013. Determinants of substance abuse: Biological, psychological, and environmental factors. Springer Science & Business Media.

García-Rodríguez, O., Blanco, C., Wall, M.M., Wang, S., Jin, C.J. and Kendler, K.S., 2014. Toward a comprehensive developmental model of smoking initiation and nicotine dependence. Drug and Alcohol Dependence, 144, pp.160-169.

Gardner, E.L., 2011. Introduction: addiction and brain reward and anti-reward pathways. Advances in psychosomatic medicine, 30, p.22.

Gelernter, J. and Kranzler, H.R., 2010. Genetics of drug dependence. Dialogues in clinical neuroscience, 12(1), pp.77-84.

Glatt, M.M. ed., 2012. Drug dependence: Current problems and issues. Springer Science & Business Media.

Gowing, L., Ali, R., White, J.M. and Mbewe, D., 2017. Buprenorphine for managing opioid withdrawal. Cochrane Database of Systematic Reviews, (2).

Haggerty, R.J. and Mrazek, P.J. eds., 1994. Reducing risks for mental disorders: Frontiers for preventive intervention research.

Hawkins, J.D., Jenson, J.M., Catalano, R., Fraser, M.W., Botvin, G.J., Shapiro, V., Brown, C.H., Beardslee, W., Brent, D., Leslie, L.K. and Rotheram-Borus, M.J., 2016. Unleashing the power of prevention. American Journal of Medical Research, 3(1).

Hawkins, J.D., Oesterle, S., Brown, E.C., Abbott, R.D. and Catalano, R.F., 2014. Youth problem behaviors 8 years after implementing the communities that care prevention system: a community-randomized trial. JAMA pediatrics, 168(2), pp.122-129.

Hill, K.G., Bailey, J.A., Steeger, C.M., Hawkins, J.D., Catalano, R.F., Kosterman, R., Epstein, M. and Abbott, R.D., 2020. Outcomes of childhood preventive intervention across 2 generations: A nonrandomized controlled trial. JAMA pediatrics, 174(8), pp.764-771.

James, S.L., Abate, D., Abate, K.H., Abay, S.M., Abbafati, C., Abbasi, N., Abbastabar, H., Abd-Allah, F., Abdela, J., Abdelalim, A. and Abdollahpour, I., 2018. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The lancet, 392(10159), pp.1789-1858.

Jasinski, D.R., Haertzen, C.A., Henningfield, J.E., Johnson, R.E., Makhzoumi, H.M. and Miyasato, K., 1982. Progress report of the NIDA Addiction Research Center. Problems of drug dependence, 7981, pp.45-52.

Jordan, C.J., Cao, J., Newman, A.H. and Xi, Z.X., 2019. Progress in agonist therapy for substance use disorders: Lessons learned from methadone and buprenorphine. Neuropharmacology, 158, p.107609.

Juurlink, D.N. and Dhalla, I.A., 2012. Dependence and addiction during chronic opioid therapy. Journal of Medical Toxicology, 8(4), pp.393-399.

Kadushin, C., Reber, E., Saxe, L. and Livert, D., 1998. The substance use system: social and neighborhood environments associated with substance use and misuse. Substance use & misuse, 33(8), pp.1681-1710.

Kakko, J., Svanborg, K.D., Kreek, M.J. and Heilig, M., 2003. 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo-controlled trial. The Lancet, 361(9358), pp.662-668.

Kendler, K.S., Jacobson, K.C., Prescott, C.A. and Neale, M.C., 2003. Specificity of genetic and environmental risk factors for use and abuse/dependence of cannabis, cocaine, hallucinogens, sedatives, stimulants, and opiates in male twins. American Journal of Psychiatry, 160(4), pp.687-695.

Kitzman, H., Olds, D.L., Knudtson, M.D., Cole, R., Anson, E., Smith, J.A., Fishbein, D., DiClemente, R., Wingood, G., Caliendo, A.M. and Hopfer, C., 2019. Prenatal and infancy nurse home visiting and 18-year outcomes of a randomized trial. Pediatrics, 144(6), p.e20183876.

Koob, G. F., & Volkow, N. D. (2016). Neurobiology of

addiction: a neurocircuitry analysis. The lancet psychiatry, 3(8), 760-773.

Koob, G.F. and Volkow, N.D., 2010. Neurocircuitry of addiction. Neuropsychopharmacology, 35(1), pp.217-238.

Koob, G.F., 2011. Neurobiology of addiction. Focus, 9(1), pp.55-65.

Koob, G.F., Kenneth Lloyd, G. and Mason, B.J., 2009. Development of pharmacotherapies for drug addiction: a Rosetta stone approach. Nature reviews Drug discovery, 8(6), pp.500-515.

Kreek, M.J., LaForge, K.S. and Butelman, E., 2002. Pharmacotherapy of addictions. Nature reviews Drug discovery, 1(9), pp.710-726.

Kuhn, J., Bührle, C.P., Lenartz, D. and Sturm, V., 2013. Deep brain stimulation in addiction due to psychoactive substance use. Handbook of clinical neurology, 116, pp.259-269.

Kumpfer, K.L., Alvarado, R. and Whiteside, H.O., 2003. Family-based interventions for substance use and misuse prevention. Substance use & misuse, 38(11-13), pp.1759-1787.

LeNoue, S. R., & Riggs, P. D. (2016). Substance Abuse Prevention. Child and adolescent psychiatric clinics of North America, 25(2), 297–305.

Liu, J.F., Tian, J. and Li, J.X., 2019. Modulating reconsolidation and extinction to regulate drug reward memory. European Journal of Neuroscience, 50(3), pp.2503-2512.

Manchikanti, L., Giordano, J., Boswell, M.V., Fellows, B., Manchukonda, R. and Pampati, V., 2007. Psychological factors as predictors of opioid abuse and illicit drug use in chronic pain patients. Journal of opioid management, 3(2), pp.89-100.

Matson, P.A., Ridenour, T., Ialongo, N., Spoth, R., Prado, G., Hammond, C.J., Hawkins, J.D. and Adger Jr, H., 2022. State of the art in substance use prevention and early intervention: Applications to pediatric primary care settings. Prevention Science, 23(2), pp.204-211.

Mattick, R.P., Breen, C., Kimber, J. and Davoli, M., 2009. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane database of systematic reviews, (3).

Mellentin, A.I., Skøt, L., Nielsen, B., Schippers, G.M., Nielsen, A.S., Stenager, E. and Juhl, C., 2017. Cue exposure therapy for the treatment of alcohol use disorders: a meta-analytic review. Clinical psychology review, 57, pp.195-207.

Miller, N.S., 2012. The pharmacology of alcohol and drugs of abuse and addiction. Springer Science & Business Media.

Mitchell, S.G., Gryczynski, J., O'Grady, K.E. and Schwartz, R.P., 2013. SBIRT for adolescent drug and alcohol use: Current status and future directions. Journal of substance abuse treatment, 44(5), pp.463-472.

Mroziewicz, M. and Tyndale, R.F., 2010. Pharmacogenetics: a tool for identifying genetic factors in drug dependence and response to treatment. Addiction science & clinical practice, 5(2), p.17.

Müller, C.P. and Schumann, G., 2011. Drugs as instruments: a new framework for non-addictive psychoactive drug use. Behavioral and Brain Sciences, 34(6), pp.293-310.

Müller, C.P. and Schumann, G., 2011. Drugs as instruments: a new framework for non-addictive psychoactive drug use. Behavioral and Brain Sciences, 34(6), pp.293-310.

Murphy, A.L., Phelan, H., Haslam, S., Martin-Misener, R., Kutcher, S.P. and Gardner, D.M., 2016. Community pharmacists' experiences in mental illness and addictions care: a qualitative study. Substance abuse treatment, prevention, and policy, 11(1), p.6.

National Institute on Drug Abuse (NIDA) (2020) Understanding drug use and addiction. Bethesda, MD: National Institutes of Health.

Nestler, E.J., 2012. Transcriptional mechanisms of drug addiction. Clinical Psychopharmacology and Neuroscience, 10(3), p.136.

Newton, N.C., Champion, K.E., Slade, T., Chapman, C., Stapinski, L., Koning, I., Tonks, Z. and Teesson, M., 2017. A systematic review of combined student-and parent-based programs to prevent alcohol and other drug use among adolescents. Drug and alcohol review, 36(3), pp.337-351.

Noël, X., Brevers, D. and Bechara, A., 2013. A neurocognitive approach to understanding the neurobiology of addiction. Current opinion in neurobiology, 23(4), pp.632-638.

O'Connor, A.M., Cousins, G., Durand, L., Barry, J. and Boland, F., 2020. Retention of patients in opioid substitution treatment: a systematic review. PloS one, 15(5), p.e0232086.

Oesterle, S., Kuklinski, M.R., Hawkins, J.D., Skinner, M.L., Guttmannova, K. and Rhew, I.C., 2018. Long-term effects of the communities that care trial on substance use, antisocial behavior, and violence through age 21 years. American journal of public health, 108(5), pp.659-665.

Platt, L., Minozzi, S., Reed, J., Vickerman, P., Hagan, H., French, C., Jordan, A., Degenhardt, L., Hope, V., Hutchinson, S. and Maher, L., 2018. Needle and syringe programmes and opioid substitution therapy for preventing HCV transmission among people who inject drugs: findings from a Cochrane Review and meta-analysis. Addiction, 113(3), pp.545-563.

Rodriguez, D.M., Teesson, M. and Newton, N.C., 2014. A systematic review of computerised serious educational games about alcohol and other drugs for adolescents. Drug and Alcohol Review, 33(2), pp.129-135.

Roth, G.A., Abate, D., Abate, K.H., Abay, S.M., Abbafati, C., Abbasi, N., Abbastabar, H., Abd-Allah, F., Abdela, J., Abdelalim, A. and Abdollahpour, I., 2018. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. The lancet, 392(10159), pp.1736-1788

Shafran, R., Wroe, A., Nagra, S., Pissaridou, E. and Coughtrey, A., 2018. Cognitive behaviour treatment of co-occurring depression and generalised anxiety in routine clinical practice. PloS one, 13(7), p.e0201226.

Sordo, L., Barrio, G., Bravo, M. J., Indave, B. I., Degenhardt, L., Wiessing, L., ... & Pastor-Barriuso, R. (2017). Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. bmj, 357.

Sordo, L., Barrio, G., Bravo, M.J., Indave, B.I., Degenhardt, L., Wiessing, L., Ferri, M. and Pastor-Barriuso, R., 2017. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. bmj, 357.

Sordo, L., Barrio, G., Bravo, M.J., Indave, B.I., Degenhardt, L., Wiessing, L., Ferri, M. and Pastor-Barriuso, R., 2017. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. bmj, 357.

Spooner, C. and Hetherington, K., 2005. Social determinants of drug use. Sydney: National Drug and Alcohol Research Centre, University of New South Wales.

Spoth, R., Trudeau, L., Shin, C., Ralston, E., Redmond, C., Greenberg, M. and Feinberg, M., 2013. Longitudinal effects of universal preventive intervention on prescription drug misuse: three randomized controlled trials with late adolescents and young adults. American journal of public health, 103(4), pp.665-672.

Stein, C., Schäfer, M. and Machelska, H., 2003. Attacking pain at its source: new perspectives on opioids. Nature medicine, 9(8), pp.1003-1008.

Sussman, S., Earleywine, M., Wills, T., Cody, C., Biglan, T., Dent, C.W. and Newcomb, M.D., 2004. The motivation, skills, and decision-making model of "drug abuse" prevention. Substance use & misuse, 39(10-12), pp.1971-2016.

Torous, J., Bucci, S., Bell, I.H., Kessing, L.V., Faurholt-Jepsen, M., Whelan, P., Carvalho, A.F., Keshavan, M., Linardon, J. and Firth, J., 2021. The growing field of digital psychiatry: current evidence and the future of apps, social media, chatbots, and virtual reality. World psychiatry, 20(3), pp.318-335.

Turnbull, C. and Osborn, D.A., 2012. Home visits during pregnancy and after birth for women with an alcohol or drug problem. Cochrane Database of Systematic Reviews, (1).

Uhl, G.R., Koob, G.F. and Cable, J., 2019. The neurobiology of addiction. Annals of the New York Academy of Sciences, 1451(1), pp.5-28.

Volkow, N.D. and Blanco, C., 2023. Substance use disorders: a comprehensive update of classification, epidemiology, neurobiology, clinical aspects, treatment and prevention. World Psychiatry, 22(2), pp.203-229.

Volkow, N.D. and Morales, M., 2015. The brain on drugs: from reward to addiction. Cell, 162(4), pp.712-725.

Volkow, N.D., 2024. Drugs and addiction science: NIDA celebrates 50 years of research and looks to the future. American Journal of Psychiatry, 181(5), pp.349-352.

Volkow, N.D., Koob, G.F. and McLellan, A.T., 2016. Neurobiologic advances from the brain disease model of addiction. New England Journal of Medicine, 374(4), pp.363-371.

West, R. and Brown, J., 2013. Theory of addiction.

Wise, R.A. and Koob, G.F., 2014. The development and maintenance of drug addiction. Neuropsychopharmacology, 39(2),

pp.254-262.

World Health Organization, 2016. World Health Statistics 2016 [OP]: monitoring health for the sustainable development goals (SDGs). World Health Organization.

Yap, M.B., Cheong, T.W., Zaravinos-Tsakos, F., Lubman, D.I. and Jorm, A.F., 2017. Modifiable parenting factors associated with adolescent alcohol misuse: a systematic review and meta-analysis of longitudinal studies. Addiction, 112(7), pp.1142-1162.

Zilverstand, A., Parvaz, M. A., Moeller, S. J., & Goldstein, R. Z. (2016). Cognitive interventions for addiction medicine: Understanding the underlying neurobiological mechanisms. Progress in brain research, 224, 285-304.

Zuckerman, M., 2012. Psychological factors and addiction: Personality

.