Indian Psychiatric Society Publication

PSYCHIATRY

Spectrums in PSYCHIATRY

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CHAPTER 5

Addiction Disorders on a Spectrum

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INTRODUCTION

The concept of spectrum or a dimensional view is gaining popularity in psychiatry. The reason for this is evident by taking the example of schizophrenia, where the correlation between presenting symptoms and its correspondence to outcome is not consistent. When we consider affective disorder, boundaries between schizophrenia and affective disorders are not well defined. Similarly, research related to prodromal states, clinically at high-risk individuals and general population has not given us an exact delineation between normal states, or nonpathological deviations in cognitive function and schizophrenia.[1] There have been arguments that addiction is also dimensional in nature with varying degrees of severity.[2] There are further arguments that a dimensional classification serves better than enclosing addiction in arbitrarily defined categories of harmful use or dependence which results in diagnostic orphans.[3]

Addiction is best defined by the recent description by the American Society of Addiction Medicine which states that "Addiction is a treatable, chronic medical disease involving complex interactions among brain circuits, genetics, the environment, and an individual's life experiences. People with addiction use substances or engage in behaviors that become compulsive and often continue despite harmful consequences. Prevention efforts and treatment approaches for addiction are generally as successful as those for other chronic diseases."[3] Hence, addiction is best defined as the result of a complex interaction between biological vulnerabilities and environmental factors resulting in differing severities of substance use and outcomes.

NOSOLOGY

Diagnostic and Statistical Manual

Across its various iterations, changes are evident in both Diagnostic and Statistical Manual (DSM) and International Classification of Diseases (ICD) classificatory systems. In DSM-I and DSM-II, due to the prevailing influence of psychoanalysis and prevalent psychosocial models, substance use disorder was seen arising from a primary personality disorder (sociopathic personality disorder), with alcoholism and drug addiction considered a "reaction."[3]

Recognition of differing patterns in alcohol use and subsequent proposal of a classificatory system acknowledging alcohol use as a disorder was made by Jellinek in 1960. He divided alcohol users into five categories based on concepts such as physical and psychological dependence, tolerance, loss of control, and medical complications arising out of alcohol use.[4] In DSM-II (1968), addictions were placed alongside, rather than under, the personality

disorders, and some definitions were added. DSM-II did encourage separate diagnoses for alcoholism and drug addiction "even when it begins as a symptomatic expression of another disorder." Patterns of alcohol use were classified into—(1) episodic excessive drinking (intoxicated up to 4 times in a year), (2) habitual excessive drinking (persons who become intoxicated more than 12 times a year or are recognizably under the influence of alcohol more than once a week), and (3) alcohol addiction (defined in terms of dependency).[3]

Robins and Guze criteria for defining validity in psychiatric disorders, the Feighner Criteria (1972), and later on Spitzer and Endicott's Research and Diagnostic criteria (1978) heavily influenced the diagnosis of SUD in DSM-III (1980). DSM-III created a separate category of substance use disorders. It broke with psychoanalytic tradition and instituted consensus-based symptomatology approach. Taking into account the varying severity of substance use disorders, two categories of "abuse" and "dependence" were arbitrarily defined. DSM explicitly acknowledged differences in cultural perspectives on the acceptability of substance use; it also attempted to anchor the diagnostic criteria in terms of behavioral changes "almost all subcultures would view as extremely undesirable." In its revised version DSM-IIIR (1987), the definition of abuse was broadened (hazardous use, legal problems, neglected major roles due to use, social and interpersonal problems related to use, and has never met criteria for dependence). There was a reversal of the DSM-III stance that physiological use was, in most cases, the hallmark of the disorder and resulted in grouping of behavioral dysfunctions with physiological processes in a polythetic diagnostic set.[3,5]

In 1992, American Society of Addiction Medicine (ASAM) recognized addiction as a chronic relapsing condition. Thus, DSM-IV (1994) recognized SUD as a heterogeneous construct implying influence of multiple biopsychosocial factors. It specified that "Neither tolerance or withdrawal is necessary or sufficient for a diagnosis of Substance Dependence" and added specifiers "with" and "without" physiological dependence.[6]

Abuse and dependence categories were shown to have significant limitations, including—differences in reliability and external validity and the problem of "diagnostic orphans." With numerous studies favoring unidimensionality across the bi-axial spectrum, DSM-V combines abuse and dependence into a unified category and measures severity across a continuous scale.[7] There are four larger groupings, viz., impaired control, social impairment, risky use, and pharmacological criteria under which the features are grouped. Based on the number of criteria satisfied, severity ranges from into mild, moderate, to severe.[3]

The DSM-V describes nine classes of substances which are alcohol, caffeine, cannabis, hallucinogens, inhalants, opioids, sedative hypnotics, stimulants, and tobacco. It also gives legitimacy to the concept of behavioral addiction by inclusion of gambling disorder in the chapter on Substance Use Disorder and Internet Gaming Disorder in the section on conditions for further study. Operationalization of criteria does vary across substances.[8] In view of cultural acceptability and easy availability of tobacco abuse is not generally defined for the same. Dependence is not generally described for hallucinogens due to the phenomenon of tachyphylaxis. There is also an addition of withdrawal syndrome for cannabis.[9]

International Classification of Diseases

The first classification published (ICD-8, 1967) grouped substance use disorders under personality disorders and neuroses. Current diagnostic criteria used in ICD-10 take origin from a seminal paper by Edwards and Gross in 1976, where they described features of alcoholism, viz., a narrowing in the repertoire of drinking behavior; salience of drink-seeking behavior; increased tolerance to alcohol; repeated withdrawal symptoms; repeated relief or avoidance of withdrawal symptoms by further drinking; subjective awareness of a compulsion to drink; reinstatement of the syndrome after abstinence.[10]

For assessment of alcohol use disorder, the drinker's pyramid gives a spectrum of "Abstainers", "No risk", "Hazardous use", "Harmful use", and "Dependence" in the general population, based on which interventions are planned. These five categories form a pyramid with abstainers forming the base in any population. This approach is indicative of the wide spectrum of severity in the general population.[11] Based on this, ICD-9 carried separate terminologies of abuse and dependence. As Babor, one of the architects of the revision concluded, alcohol abuse in the absence of dependence merits classification in view of its detrimental effects on health.[12] In the ICD-10, deviating from the DSM, the category of harmful use was defined, which is the physical or mental consequences of substance abuse so that health problems do not remain underreported.[13]

The ICD-11 has made major changes. The section is divided into disorders of substance use and addictive behaviors. Categorical classification is maintained. There is introduction of a category of single episode of harmful use. Harm to others has been introduced as a criterion to determine harmful use. Behavioral criteria have been given predominance while diagnosing dependence over physiological criteria. ICD-11 also mentions that craving is not an essential criterion. Hazardous use of substances has been coded elsewhere the chapter on "Factors Influencing Health Status or Contact with Health Services." There are other addition categories of substances included from the earlier nine groups including synthetic cannabinoids, synthetic cathinone, MDMA and associated substances including MDA, and classification of disorder due to ketamine and phencyclidine use, separate from hallucinogens. Harmful pattern of use of nonpsychoactive substances such as laxatives, nonsteroidal anti-inflammatory drugs (NSAIDs), and growth hormone is also classified in this section. Under the section of addictive behaviors, both gambling disorder and gaming disorder are included.[14]

Other Typologies

Other typologies which take into account differing profiles of alcohol use are Cloninger's Type 1 and II alcoholism and Babor's Type A and B alcoholism. Here, Type I and A individuals have a greater contribution of environment towards etiology, equal number of males and females, lesser childhood risk factors, later age of onset, less severe and episodic alcohol use, lower levels of novelty seeking, and reward dependence with lesser co-morbid psychopathology.[15] In comparison, persons with Type II/B alcoholism have a greater genetic influence, higher proportion of males, conduct disorder in childhood, earlier age of onset, more chronic and severe polydrug abuse, high impulsivity and novelty seeking, higher incidence of co-morbid psychopathology including dis-social personality.[16]

Research Domain Criteria

In the alcohol and addictions research domain criteria (RDoC) model, the addiction neuroclinical assessment battery evaluates three domains of executive function, negative emotionality, and incentive salience. The five major RDoC domains negative and positive valence, cognitive system, arousal and regulatory systems, and social processes could be conceptualized as risk or protective factors for addiction and interventions could be tailored to each domain.[17]

ADDICTION AS A COMORBID DIAGNOSIS

When DSM-V was introduced, researchers looked into the possibility of larger dimensions, including neurocognitive, neurodevelopmental, psychosis, emotional and externalizing spectrum. SUD is a co-morbidity along with many of the severe mental disorders and vice versa, co-occurring more frequently as compared to general population rates.[18]

Externalizing and Internalizing Disorders

Externalizing disorders involve emotional dysregulation and impulsivity that are manifested in dis-social behavior, aggression, and oppositional behavior. They include attention-deficit hyperactivity disorder (ADHD), oppositional defiant disorder, conduct disorder, and substance use disorders as various phenotypes within the spectrum. This model posits a spectrum of personality and psychopathology, united by an externalizing factor which is largely genetic. Additionally, there are other environmental factors such as parenting, poverty, and nutrition that account for distinct phenotypes within the spectrum. In a study comparing the fit of categorical and continuous models of externalizing liability in the NESARC cohort, the best fitting model was a continuous normal model.[19] In a subsequent study among the participants in the Fast Track Project, continuous models provided the best fit.[20] They were able to define a two-factor model of externalizing behavior including—(1) ODD + ADHD + CD (2) SUD + Dis-social PD which was later replicated in the national comorbidity survey replication data. The construct of externalizing disorder helps us to conceptualize early onset dependence.[21]

In various studies, individuals having externalizing features showed poorer outcomes including poor treatment retention, greater drug use.[22] There are also treatment implications as focus on substance use alone will not lead to effective outcomes. It is important to target underlying vulnerability, like impulsivity that is acting across various domains.[23] As part of the IMAGE cohort, children with ADHD were followed up over a period of 4 years and the authors conclude that the same is a risk factor for SUD and also disruptive behavior disorders such as conduct disorder.[24] In a cross-sectional Indian study, externalizing disorders were greater in cases with AUDs compared to controls and an association was observed between AUDs and early onset dependence.[25] In a meta-analytic review, children with ADHD were more likely to develop SUD, compared to children without ADHD.[26]

Internalizing disorders are associated with high degree of negative affect and include depressive disorders, anxiety disorders, trauma and stress-related disorders, obsessive-compulsive and related disorders, as well as eating disorders. A second pathway thus exists, where internalizing symptomatology in childhood predicts substance use in adolescents and young

adulthood.[27] In the NESARC study, the rate of SUD among individuals with independent mood and anxiety disorders was 9.35%, which was deemed significant. Similar results were obtained in earlier epidemiological studies such as Epidemiologic Catchment Area study in which among individuals with a mood disorder, 32% had a co-occurring SUD and the National Co-morbidity survey which showed rates up to 7 times in individuals with BPAD compared with individuals with no mood disorder.[28] Behavioral inhibition during infancy is correlated with greater internalizing symptomatology in childhood. These might lead to interpersonal skill deficits and ineffective coping strategies, which predict progression to the use of substances.[29]

Both externalizing and internalizing symptoms can co-occur in children and this may predict greater adult psychopathology as well as problematic substance abuse. Some children with externalizing problems develop internalizing symptoms in preadolescence. Negative experiences such as bullying, victimization, maternal dissatisfaction, and academic difficulties also contribute to the association, possibly through gene-environment interplay.[23]

Personality Disorder

In the NESARC study, associations between personality disorders and alcohol and drug use disorders were overwhelmingly positive and significant. Personality disorders can be subsumed broadly under the two former classes of internalizing and externalizing vulnerabilities. Various cross-sectional studies in borderline personality disorder peg the co-morbid rates of substance abuse between 25 and 70%. The morbidity in the dis-social personality disorder as measured by number and types of substance-related problems and by all treatment variables is considerably greater. Legal and family problems appear to be powerfully associated with antisocial personality disorder (ASPD) and predictive of other problems as well as SUD treatment. Both the conditions may have an underling externalizing diathesis.[30] In a narrative review on the subject, the prevalence of SUD among persons with personality disorders is pegged at 35–73%.[31]

Psychosis

Around half of all patients with schizophrenia are thought to abuse drugs or alcohol and there is evidence that they have poorer outcomes. In individuals with schizophrenia, more than 60% are current smokers.[32] Nicotine may benefit patients by activating nicotinic acetylcholinergic receptors, resulting in increased release of dopamine, and may also reduce deficits relative to dopamine hypofunction in prefrontal cortex, thus leading to some relief in cognitive symptoms. Also, sensory gating deficits leading to auditory hallucinations are transiently normalized with high-dose nicotine.[33] In a cross-sectional study, early onset of psychosis, substance sensitivity, and sensation seeking traits represent vulnerability factors for SUD.[32] Higher scores on behavioral activation and impulsivity can be a shared risk factor for co-occurrence of bipolar disorder and SUD.[34]

The use of substances such as cannabis, inhalants, stimulants, and hallucinogens can result in the individual having psychotic experiences. The relation between cannabis and psychosis has been extensively investigated and the best evidence is for cannabis bringing forward the onset of psychosis in vulnerable individuals and worsening the course of psychosis.[35] Stimulants including cocaine and amphetamines have been found to induce

psychosis in view of their direct action on dopaminergic receptors.[36]

ANOTHER NEW DIMENSION: BEHAVIORAL ADDICTIONS

In a seminal paper in 1990, Isaac Marks introduced the concept of behavioral addiction.[37] Thereafter, research in this field has seen a boom, with its accompanying controversies and methodological flaws. As discussed earlier, gambling disorder is included in the SUD section in both DSM-5 and ICD-11, whereas gaming disorder is classified as an addictive behavior in the latter.[8,14] This is part of a growing understanding of addiction as the result of neuroadaptations related to dysregulation of neurotransmitters, structural functional changes in circuitry which may be precipitated by an exogeneous chemical or a repetitive behavior. There is an unusually high rate of co-occurrence between gambling disorder and SUD; around 50% of participants with gambling disorder report substance abuse, and up to 63% of individuals seeking treatment for gambling disorder screen positive for lifetime substance use disorder. Evidence from neuroimaging suggests a shared circuitry for gambling disorder and SUD **(Table 1)**.[38]

The essential feature of behavioral addictions is the failure to resist an impulse, drive, or temptation to perform an act that is harmful to the person, or to others. Behavioral and substance addictions have many similarities in natural history, phenomenology, and adverse consequences. However, there exist several controversies regarding behavioral addiction research.[39]

Disorders on the Fence

DSM-5 did not include hypersexual disorders as an addictive behavior based on the objection that there was no accepted definition about frequency of normative sexual behavior. Kleptomania was classified under the chapter on Disruptive, Impulse control and Conduct Disorders, though some features as impulse dyscontrol, such as the need for immediate

TABLE 1: Differences between ICD-11 and DSM-5.

DSM-5	*ICD-11*
Dimensional	Categorical
Criteria divided into 4 larger groups with equal importance across criteria	Behavioral criteria are given predominance
Traditional 9 class of substances	• Additionally separate classification for synthetic cathinones, synthetic cannabinoids, MDMA and associated substances, Ketamine and Phencyclidine are classified separate from hallucinogens • Harmful pattern of use on non-psychoactive substances also coded in this session
Internet Gaming Disorder is classified under conditions for further study	Internet Gaming Disorder is classified under Addictive Disorders
Defines use of substances in physically hazardous situations	• Defines Single episode of Harmful use, Harm to others • Hazardous use is classified in the session on Factors influencing health status

gratification and personality profiles are similar to SUD. Moreover, some cases of kleptomania show response to high doses of naltrexone, an opioid antagonist. These lead to the question that whether there are differing profiles of the same disorder and whether classifying them by ignoring these differences helps in treatment. Similarly, a group of trichotillomania patients with positive family history of the same disorder respond to naltrexone, whereas most patients do not.[40,41] There are not enough studies that which lend evidence that candidate disorders considered in DSM-5, i.e., sexual addiction, excessive buying, and stealing share sociodemographic and clinical features, neurobiology, and treatment response with SUD.[41] Moreover, in the current scenario where there are no satisfactory animal models to support research, behavioral addiction is also a major drawback.[42]

ETIOLOGICAL UNDERSTANDING

A vast amount of literature has accumulated explaining the biological underpinnings of addiction.

Neurodevelopmental Disorders

Addiction spectrum disorders also are co-morbid with neurodevelopmental disorders such as autism. Similarities in neurobiology, such as improper functioning of the HPA axis and developmental dysregulation of the limbic and cortico-striatal loops, have been described. Substances can facilitate social engagement.[43] In individuals with intellectual disability, the prevalence of SUD is lower. However, when present, it is more problematic due to lack of evidence-based interventions and due to the difficulty in handling the positive reinforcement the substance provides.[44]

Endophenotypes

Gottesman and Gould defined endophenotypes as "measurable components unseen by the unaided eye along the pathways between disease and distal genotype. Specific endophenotypes for alcohol include subjective response to alcohol and event-related potentials and neurobiological correlates.[45] Significant findings are present related to P3. There was reduced amplitude of P3 with a delayed latency after the stimuli. This has been demonstrated with alcohol, opioid, and cocaine use.[46] Interestingly, similar reductions in P3 amplitude are seen in people with at risk mental states for psychosis.[47] Lower response to alcohol was described by Schuckit, who demonstrated that a lower sensitivity to modest dose of alcohol is associated with a significant increase in the risk of future alcoholism, perhaps through increasing the chances that a person will drink more heavily and more often.[48] Impulsivity measured through delayed reward discounting and executive function deficits have also been seen in SUD replicated in many studies.[45]

Neurobiological Correlates

The mesolimbic dopaminergic system is a neural circuit involving the nucleus accumbens (located in the ventral striatum), which receives dopaminergic inputs from the ventral tegmental area. This neural circuit is a common neural pathway of reward. The incentive sensitization model posits that addiction is caused primarily by drug-induced sensitization in the brain mesolimbic systems that attribute incentive salience to reward-associated stimuli. Critical for craving and relapse is the process of associative learning, whereby environmental stimuli repeatedly paired with drug

consumption acquire incentive-motivational value, evoking expectation of drug availability and memories of past drug euphoria.[49] Conditioned responses to such stimuli can activate brain reward mechanisms. Drugs hijack this system and render natural rewards (such as food, sex) unrewarding.[50] If rendered hypersensitive, these systems cause pathological need for drugs. Substance use disorders are characterized by disturbances in three major neurocircuits which occur as recurring cycles: (1) basal ganglia-driven binge/intoxication stage where neutral stimuli gain incentive salience and habit formation is promoted, (2) extended amygdala-driven withdrawal/negative affect stage where opponent processes reduce brain reward function and increase stress mediated through corticotrophin releasing hormone and dynorphin, (3) prefrontal cortex-driven preoccupation/anticipation stage where executive function deficits through dysregulation of glutamatergic, dopaminergic, and GABAergic projections in the prefrontal cortex with heightened sensitivity to drug induced cues. All the three major circuits can act in conjunction to drive the substance abuse.[51]

Genetics

The heritability estimates of SUD vary from 45 to 80%, being least for alcohol and tobacco and most for stimulant use disorders.[52] Study of genetic underpinnings of addiction has progressed from early candidate gene studies to more recent genome-wide association studies (GWAS). OPRM1, DRD2, DRD4, BDNF, and SLC6A4 are associated with two or more SUDs.[53] Polymorphisms in ALDH2 and ADH1B influence progression to alcohol dependence and medical complications due to alcohol use.[54,55] In GWAS studies, a functional missense polymorphism at nicotinic acetylcholine CHRNA5–CHRNA3–CHRNB4 locus which has been consistently shown to be associated as a risk variant for nicotine dependence.[56] More recently, two large GWAS done in individuals of American and European ancestry found 18 and 29 genome-wide significant loci including ADH1B and 1C, DRD2 which have also been implicated in candidate gene studies. In the latter study, problematic alcohol use was correlated with genetic trait of SUD, depressive disorder and schizophrenia.[57,58] Similarly, GWAS in opioid use disorder implicated OPRM1 as a risk locus. As with alcohol, there was correlation with other SUDs, severe mental illness and chronic pain.[59,60] In GWAS of cannabis use disorder, FOX P2 has been implicated, that has in turn been related to externalizing disorders and educational attainment. Another interesting locus was that of CHRNA2, seen both in smoking and schizophrenia.[61,62] All these recent findings indicate the complex nature of addiction and its link to environmental risk factors and other psychiatric disorders. Epigenetic models of addiction allow a better understanding and synthesis of environmental effects on innate biology.[63]

Early Onset Dependence

In a large proportion of individuals, addiction starts in adolescence and progresses with age. Early onset dependence (<25 years of age) does support the evidence that addiction spectrum disorders may have neurodevelopmental origins. The externalizing and internalizing diathesis are pathways of this process which progresses from infancy.

Regional brain morphology has a temporal variance. It follows a caudal-to-rostral pattern, with maturation occurring in the occipital and sensorimotor cortices and

striatum earlier, followed by the prefrontal cortex and association cortices, which are among the last to reach maturation. Parallel to the temporal lag of gray matter decline, frontotemporal white matter tracts seem to mature at a later stage. In externalizing disorders, there is a delay in brain maturation, as myelination in the white matter tracts occurs later.[64]

In people with late-onset dependence to substances, evaluation must focus on the presence of underlying axis I diagnosis such as mood disorder, any recent loss, use of substances is generally restricted to a single class.[65]

Psychological Theories

Various psychological models have been posited to explain the variation across SUDs. Khantzian's self-medication hypothesis posits that individuals select various substances based on their ability to regulate different emotional states, whether they be painful or happy.[66]

Behavioral models discussed earlier posit that certain environmental cues acquire incentive motivational value when coupled with drug use. One of the prominent models postulated is by Marlatt and Gordon on factors leading to relapse. This model centers on high-risk situations and the individual's ability to handle the same. There are numerous intrapersonal factors such as self-efficacy, craving, motivation, negative mood states, outcome expectancies and coping and interpersonal factors, such as social support, which interact to cause relapse. Individuals have varying combinations of the above factors that determine further progress of substance use.[67] Cognitive behavioral models explore how individuals make seemingly irrelevant decisions that lead onto the aforementioned high-risk situations and lapse. Every client may hold a unique set of cognitions and environmental cues that drive his substance use.[68]

Recent psychological research has focused on relation of temperament with initiation and progression of SUD. Various models of temperament have been described. One of the commonly used models is the temperament character inventory, devised by Cloninger. His work showed that the dimension of novelty seeking predicts early onset substance abuse and criminality and discriminates individuals with alcohol use disorder with dis-social traits from their non-dis-social counterparts.[69] In a subsequent study, Cloninger's theory could predict problematic substance abuse. Youth with high novelty seeking and low persistence found substances more reinforcing and hence interventions could be focused at primary prevention in this risk group.[70]

Environmental Factors

The variation in the onset and course and outcome is mediated by a number of environmental factors. These can include prenatal features such as maternal stress, presence of a medical co-morbidity during pregnancy, preterm labor, any history of asphyxia at the time of delivery. Postnatal factors include nutrition, adverse childhood experiences, parenting, peer groups, availability of substances all of which interact with the underlying genetic and temperamental antecedents leading onto onset and progression of substance abuse. Similarly, in a person whom dependence has been established, recovery is similarly driven by factors discussed under psychological theories making the journey through addiction unique for every individual that we come across.[71]

Addiction is a complex interaction between various environmental and

genetic factors. Individuals with SUD have a higher propensity to be in environments with substance use by selecting them preferentially. The environment mediates the development of problematic substance use in a genetically vulnerable individual. This is illustrated by role of peer influence in substance use. Conversely regimented environments reduce risk for substance use.

Epigenetic models of addiction allow a better understanding and synthesis of environmental effects on innate biology

Thus, it is important to expand the notion of SUDs as a heterogenous group of disorders, intimately related to other psychiatric disorders, psychopathological conditions and temperaments. Interventions therefore need to take into considerations the entire accompanying spectrum for a meaningful and comprehensive recovery to occur.

CONCLUSION

In the above discussion it is clear that addiction does not imply a unitary process. It is a culmination of various risk factors which are genetic and environmental in origin. There are some underlying similarities with respect to neurobiology, neuropsychological profiles such as executive function deficits and temperamental vulnerabilities such as the externalising syndrome. Substances can have accompanying polymorphisms in genes that directly increase vulnerability to addiction or act indirectly on the intermediary pathways. Environment through epigenetic changes play a role in the progression to a disorder. Once dependence develops, recovery depends on the cognitive profiles and environmental conduciveness to promote change and maintain the same. The phenotypes expressed through this complex interaction vary from abstainers to dependence. Varying severity of substance use needs different treatment strategies as use of substances lead to several neuroadaptations leading to downstream effects and diverse consequences.

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ISBN 978-93-7202-050-2