

Neurobiological and Psychosocial Processes Associated with Depressive and Substance-Related Disorders in Adolescents

Uma Rao* and Li-Ann Chen

Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, TX, USA

Abstract: Adolescents are at heightened risk for the development of both depressive and substance-related disorders. These two disorders frequently co-occur in adolescents and are associated with significant morbidity and mortality. Given the substantial economic and psychosocial burden associated with the comorbid condition, the identification of causal mechanisms associated with their co-occurrence is of great public health importance. Although there is significant understanding of the environmental and neurobiological factors involved in depression and addictive disorders considered separately, the mechanisms underlying the comorbid illness have not been investigated carefully. The purpose of this review is to summarize the extant literature on genetic, environmental and neurobiological processes involved in the etiology of depressive and substance-related disorders in adolescents and adults. It is important to note that the data on common neurobiological systems that link addictive and depressive disorders are primarily from research with adult animals and humans. Given the ongoing maturation of these systems throughout adolescence and early adult life, it is not clear how these neurobiological processes influence the development and progression of both disorders. A better understanding of the pathophysiological mechanisms leading to the onset and course of these disorders during adolescence will be helpful in developing more effective preventive and treatment strategies not only for this population but also for adult patients with early-onset illness.

Keywords: Adolescence, addictive disorder, depression, development, motivation system, neurobiology, psychosocial processes, reward processes.

INTRODUCTION

The prevalence of depression in adolescents is on the rise, and depressive illness during this developmental period is associated with significant impairment in multiple social domains. Also, there is evidence that early depressive episodes persist into adult life along with ongoing psychosocial difficulties [1]. Substance abuse also typically emerges during adolescence, and early-onset of substance abuse is associated with a stable and escalating course into adulthood [2]. The co-occurrence of substance abuse with depression is associated with significant added psychosocial and economic burden [3]. A better understanding of the pathophysiological mechanisms linking these two disorders is critical for developing more effective therapeutic interventions for this disabling illness. Although significant advances have been made with regard to knowledge of the environmental and neurobiological factors involved in depression and substance-related disorders individually, the mechanisms underlying the comorbid illness are not understood well [3, 4]. It is likely that the high prevalence of these disorders occurring together reflects, in part, overlapping genetic, environmental and neurobiological factors. It is also possible that there will be differences in neurobiology based on the temporal course of development of these two disorders; whether depression precedes substance abuse or the reverse. For instance, in the former case, substance use may occur in attempts to improve mood, whereas in the latter it is possible that chronic

substance use leads to neurobiological changes that increase vulnerability for depression.

The purpose of this paper is to summarize research on the epidemiology, clinical course and prognosis of co-occurring depressive and substance-related disorders in adolescents. Information on overlapping genetic, environmental and neurobiological factors also will be described. A few caveats should be considered in interpreting the presented data. Most of the research on the neurobiology of addictive and depressive disorders is based on investigations in adult animals and humans. Because many of these neurobiological systems continue to develop throughout adolescence, the immaturity of some of these systems might play a role in the progression of these disorders [5, 6]. For instance, evidence from animal studies indicates that adolescent substance use may induce stronger effects on the central nervous system than in adults, consequently leading to more severe dependence-related behaviors and problems [6]. Also, it is often difficult to determine whether the observed neurobiological changes in adults preceded the manifested illness, or whether they resulted from repeated drug use and/or multiple depressive episodes. Therefore, an argument will be made for studying developmental influences on these pathophysiological mechanisms as a basis for early treatment and prevention. A better understanding of the developmental differences in neurobiological processes involved in comorbid depression and substance abuse also will be helpful in developing more effective interventions for adult patients with early-onset illness. Evidence suggests that adult patients with juvenile-onset depression show poor response to therapeutic interventions and worse prognosis compared to their counterparts with adult-onset illness [1]. Differential response to treat-

*Address correspondence to this author at the UT Southwestern Medical Center, 5323 Harry Hines Boulevard, Mail Code: 9101, Dallas, TX 75390-9101, USA; Tel: 214-648-5288; Fax: 214-648-5242; E-mail: uma.rao@utsouthwestern.edu

ment also was reported for early- versus late-onset alcoholism [7].

There is an important distinction between experimental/infrequent and regular/problematic substance use. Many youngsters who experiment with addictive substances do not progress to pathological use [8], and experimentation may be associated with no worse [9], or even better [10], outcomes when compared to complete abstinence. Although the mechanisms that drive the progression from experimentation to abuse and dependence are not fully known, it is recognized that each stage might be preceded by unique conditions. Evidence suggests that experimentation with tobacco, alcohol and other drugs is likely to result chiefly from social influences, whereas progression to dependence is more closely tied to internal processes, such as, emotional and/or physiological characteristics [11-14]. This review will focus on levels of substance use that would meet criteria for a diagnosis of abuse or dependence.

EPIDEMIOLOGY, CLINICAL COURSE AND PROGNOSIS OF COMORBID ADDICTIVE AND DEPRESSIVE DISORDERS IN ADOLESCENTS

Epidemiology

Adolescence is a high risk period for the development of addictive and depressive disorders, with incident rates of each disorder estimated as high as 5% a year [15, 16]. In fact, information obtained from adult community samples indicated that the highest risk period for first episodes of alcohol/drug dependence and major depressive disorder is during mid-to-late adolescence [17, 18]. Several epidemiological studies have shown that depressive illness and substance abuse frequently co-occur (both concurrently and over the lifetime) in adolescents [19]. In a large study of high-school students in Oregon, the lifetime prevalence of unipolar depression among youth with substance-related disorder was 49%, with almost 5-fold increased risk compared to those without substance abuse [20]. In the Methods for the Epidemiology of Child and Adolescent Mental Disorders (MECA) study, the prevalence of concurrent mood disorder (in the past six months) in adolescents with addictive disorder was 32%, with the risk increasing 4-fold compared to their counterparts without the disorder [21]. The high prevalence of comorbidity between addictive and depressive disorders is comparable to the rates in large representative samples of adults in the community [21-23].

Clinical Course and Prognosis

Adolescent depression is often associated with significant psychosocial impairment [24], and this is true of addictive disorders as well [25]. When these two disorders are comorbid, adaptive function is further compromised [26, 27]. The co-occurrence of addictive disorders with depression in adolescents is associated with earlier onset and more severe substance-related problems [28-30], increased frequency of behavioral problems [31, 32], more prolonged and recurrent depressive episodes [31, 33, 34], and more severe impairment in family, school and legal domains [33, 35, 36]. Youth with the comorbid disorder also are at higher risk for suicidal behavior than those without comorbidity [27, 37, 38]. As a result, the comorbid illness is associated with increased utilization of health services and substantially higher treatment

costs compared with those who have depression or substance abuse in isolation [22, 28, 30, 39].

Other important clinical factors, such as treatment response and prognosis, associated with comorbidity have not been studied systematically in adolescents. Nevertheless, the available data suggest that youth with comorbid depression and substance abuse show poor compliance with treatment recommendations, sub-optimal response to therapeutic interventions, and poor prognosis [40-42]. Even among those who show high participation rates, comorbidity is associated with early relapse of substance abuse compared to those with substance abuse in isolation [43-45]. It is important to note, though, that the inadequate response to treatment among comorbid patients may be related to greater clinical severity, exposure to more adverse life situations, limited number of pharmacological agents available for treatment because of heightened concerns about abuse potential, and lack of integrated treatment programs for both disorders [36, 46, 47]. Preliminary evidence from research in adolescents and adults suggests that patients with dual diagnosis can be treated effectively when the intensity of treatment is matched with the complexity of the disorder [48], and both conditions are targeted for treatment [49-52].

CLINICAL AND THEORETICAL MODELS FOR THE ASSOCIATION BETWEEN ADDICTIVE AND DEPRESSIVE DISORDERS

Clinical Aspects

From a clinical perspective, three lines of evidence support the hypothesis that addictive and depressive disorders are linked. Dysphoric or depressive mood is a common feature during withdrawal from several addictive substances, including alcohol, nicotine, opiates and psychostimulants [53, 54]. It is suggested that alterations in reward and motivational processes play a central role in the manifestation of core symptoms of both disorders [55-57]. For example, depressed mood and anhedonia, the core symptoms of major depressive disorder, probably reflect changes in reward and motivational systems of the brain [53, 58]. In a similar vein, the "high", euphoria or elevated mood associated with acute drug administration is believed to result from rapid increases in dopamine (DA) content of the central reward and motivational systems [53, 59].

The second evidence supporting the relationship between addictive and depressive disorders comes from treatment research. Treatment with antidepressant agents reduces substance use in addition to alleviating depressive symptoms [60, 61]. Reduction in drug use in response to antidepressant treatment was demonstrated for several substances, including nicotine [61, 62], alcohol [61, 63], cocaine [61, 64], and opiates [60, 61]. Furthermore, patients with more severe depressive symptoms showed a greater reduction in substance use in response to antidepressant treatment than their counterparts with less severe depressive symptoms [60]. These findings suggest that certain individuals with depression may use addictive drugs in order to help reduce distress; thus, when antidepressant medication is provided to such patients, the need for "self-mediation" with addictive drugs may be diminished or eliminated [57, 65].

Finally, family-genetic studies provide further evidence of linkage between addictive and depressive disorders. Adoption and twin studies demonstrated a common genetic liability between depression and substance abuse [66-68]. Some family studies showed a higher prevalence of addictive disorders in the biological relatives of depressed probands, and particularly in those with early-onset illness [69, 70]. Familial aggregation between depression and substance abuse also was observed in probands with substance-related disorders [14, 71].

Theoretical Models

One mechanism for examining the relationship between addictive and depressive disorders is the temporal sequence in the development of these two conditions, implying that the first disorder, directly or indirectly, predisposes to the latter [72]. It is possible that there will be differences in the neurobiology, clinical course and prognosis of comorbidity depending on the temporal course of its development (i.e., depression followed by substance abuse versus substance abuse followed by depression). Based on longitudinal epidemiological data in pediatric populations, there is stronger evidence for substance use/abuse leading to depressive symptoms/syndrome [19]. A complication in making sense of these results, though, is that many studies with prospective designs had limited time frame for symptom assessment (e.g., in the past 3-6 months) and the time intervals across waves of data collection lasted a few years [19, 73]. In such situations, episodic disorders such as depression, which wax and wane over time, might be missed if the symptoms/episodes did not occur during the specified time frame of the assessment [74].

Although the debate whether substance-related disorder precedes depressive illness, or vice versa, cannot be resolved until such methodological limitations are addressed in future research, there is evidence that depression precedes substance abuse in a subgroup of youngsters with the comorbid condition [75-77]. Although characterizing the temporal development of the two syndromes can be useful from a theoretical perspective, it is more helpful to focus research efforts on the interplay of the co-occurring disorders [78]. For instance, understanding whether substance abuse manifests differently in patients with depression (e.g., whether depressed patients have a heightened sensitivity to addictive substances), or if addictive disorder has an adverse effect on clinical outcomes, has a greater potential for developing more effective interventions [30, 33, 34].

An alternative model for comorbid addictive and depressive disorders is that both clinical conditions have shared risk factors, suggesting that the shared risk factors explain a part of the variance for their association [55-57, 79, 80]. These risk factors can be either genetic, environmental, or a combination of the two [81]. In this model, bidirectional effects can be found between addictive and depressive disorders. For example, through experimentation with nicotine, alcohol or drugs, depressed youth might find a temporary relief of their negative mood which then reinforces further use of these substances, resulting in a more rapid progression to dependence [30, 82-84]. Reciprocally, repeated drug use, possibly through aberrant or excessive neuroadaptations to drug effects, might lead to biochemical changes that induce

additional depressive episodes [33, 34, 85]. Indeed, "depressive mood" during acute nicotine withdrawal is a strong predictor of relapse to smoking [86].

The etiology of depression and substance-related disorders is multi-disciplinary, ranging from molecular and cellular changes, neurobiological alterations, behavioral manifestations, psychological processes, and environmental factors. A description of the various multi-dimensional factors associated with these disorders is beyond the scope of this review, but common genetic, environmental and neurobiological processes involved in these two conditions will be discussed.

GENETIC FACTORS

Evidence from adoption and twin studies has indicated that genetic factors play a prominent role in the vulnerability for both addictive and depressive disorders [14, 87]. Based on epidemiological data, the proportion of variance attributed to genetic factors is between 24% and 58% for depressive illness, and for substance abuse the estimate is over 40% [88]. Genetic influences have been found to vary with age. Shared environmental influences may be more important in younger children, and these influences may be replaced by new genetic and unique environmental influences as children grow older [14, 87]. Modern developments in molecular genetics have intensified the search for genes associated with addictive and depressive disorders. While such efforts clearly hold promise, the power to detect "culprit" genes is limited because these disorders are highly complex with multi-factorial and polygenic origins [89, 90]. It is likely that the discovery of chromosomal regions linked to both disorders will be even more challenging because of the broad clinical phenotypes. Genetic studies of more homogeneous groups (i.e., specific forms of typical comorbid conditions) might define new phenotypes, which then can be used for discovering the specific disorder-related genes.

Research on behavioural genetics initially partitioned population variance into two components, one due to genetic factors and the second due to environmental influences. The implication was that the two were separate, and it was assumed that gene-environment interactions were usually of so little importance that they could be ignored. Theoretical considerations suggested that this was not likely to be true, and empirical findings are now accumulating on the interactions between identified common single genetic variants and environmentally-mediated risks [91]. Indeed, the important role of environmental factors in modulating vulnerability and their interactions with genetic variants has been specifically demonstrated for alcoholism [92, 93], antisocial behavior that is often associated with addictive disorders [94], and for depression [95].

ENVIRONMENTAL FACTORS

There is a significant overlap in the environmental variables associated with addictive disorders and depression [96, 97]. In particular, stress, both acute and chronic, has been linked with both disorders. Because chronic stress is a common element in the environmental variables associated with both depression and substance abuse (e.g., low socioeconomic status, family disruption, and dysfunctional interpersonal relationships), it could account for some of the vari-

ance in their comorbidity [67]. There is also substantial evidence for the contribution of acute stressful experiences in precipitating depressive episodes and relapse in drug abuse [98-100]. Moreover, as described below, disruption of the stress-mediated pathways (e.g., the limbic-hypothalamic-pituitary-adrenal system) has been documented for depression and substance abuse, which might serve as a mediator in increasing vulnerability for the comorbid disorder [3, 57]. Reciprocal influences between stressful life experiences and depression (or externalizing problems) also have been described [99, 101]. In this model, individuals with depression and/or substance abuse contribute to negative life events through their own behavior. This reciprocal relationship in which emotional/behavioral dysregulation predicts stressful situations at a later time, and similarly, previous stressors lead to subsequent symptoms becomes a "vicious cycle", thereby worsening the long-term prognosis.

NEUROBIOLOGICAL PROCESSES

Although significant advances have been made with regard to our knowledge on the neurobiology of depression and substance-related disorders individually, to the best of our knowledge, the neurobiology of the comorbid illness has not been investigated. Even from these data, direct comparisons between the neurobiology of these disorders are difficult to make because the two fields of research have taken different approaches to studying the neurobiological processes, and parallel studies of both disorders are very limited. Nevertheless, a synthesis of the literature from both areas suggests significant similarities in neurobiology [3, 4, 57]. In the following sections, the common underlying neurobiological processes involved in addictive and depressive disorders will be discussed. As stated previously, most of the information on the neurobiology of addictive disorders and depression comes from research in adult animals and humans. Indeed, developmental variations have been reported in the areas where empirical data are available [5, 6]. Given the ongoing maturation of these systems throughout adolescence and early adult life, it is not clear how these neurobiological processes influence the development and progression of both disorders in the younger population. An attempt will be made to describe the developmental differences.

The Stress-Response System

The limbic-hypothalamic-pituitary-adrenal (LHPA) system plays a critical role in mediating the effects of stress [102]. Altered LHPA activity is associated with depressive disorder, and recent evidence suggests that normalization of the LHPA system might be the final step necessary for stable remission of depressive episodes [103]. Based on these findings, it has been hypothesized that antidepressant drugs might achieve their action, at least in part, through reduction in LHPA activity [103, 104].

Evidence from preclinical and clinical research suggests that LHPA axis mediates the effects of stress exposure on drug-seeking behavior [105, 106]. For instance, drug administration stimulates corticotropin-releasing factor (CRF) release in the amygdala which, in turn, activates mesocorticolimbic DA pathways that are important in the rewarding properties of addictive drugs [107, 108]. With chronic drug administration, mesocorticolimbic DA pathways induce a compensatory decrease in CRF receptors [109]. Other stud-

ies have indicated that acute withdrawal from addictive substances following chronic administration is associated with elevated LHPA activity [106]. These findings indicate that the LHPA system plays a role in the acute as well as withdrawal effects of addictive drugs.

As described, the LHPA system is involved in both depression and substance abuse. Dysregulation in this system could lead to the comorbid condition in some individuals [55]. We previously reported that depressed adolescents that had increased nocturnal cortisol secretion, a period when the LHPA system is normally quiescent, were at increased risk for developing drug abuse/dependence subsequently compared with their counterparts who had a relatively normal secretory pattern [30, 34]. We also found that, among adolescents who experiment with alcohol and/or drugs, the progression to substance-related disorder was more rapid in the depressed youth compared with non-depressed youngsters [30]. It is possible that the rapid progression to substance abuse in depressed adolescents might result from the drug's effect in reducing LHPA activity. For instance, addictive drugs reduce stress-induced alterations in corticosterone and adrenocorticotropic hormone (ACTH) and attenuate the anxiogenic effect of CRF in animals [110, 111]. In humans, alcohol or cocaine consumption has been shown to reduce plasma ACTH and cortisol responses to corticotropin-releasing hormone (CRH) or to other forms of stress-induction [112, 113]. An alternative route to the comorbidity in which substance dependence precedes depression also can be explained through the mediating effect of LHPA system. As described previously, chronic drug administration leads to altered CRH neurotransmission [106, 109]. The deleterious effects of CRH hypersecretion on mood and cognition have been described extensively [102, 103, 114].

If LHPA activity is involved in the pathophysiology of depression and substance-related disorders, this system could be considered as a potential target of intervention for these disorders. Preliminary data indicate that CRH antagonists might be useful for the treatment of depression [115, 116]. Research in animals suggests that the administration of CRF antagonists or anti-glucocorticoid compounds ameliorates anxiety-related symptoms associated with alcohol/drug withdrawal, and also reduces the self-administration of addictive drugs [117-120]. As described previously, antidepressant drugs are helpful in reducing substance use in addition to alleviating depressive symptoms [60, 61]. One potential mechanism of action of these agents is reduced response to stress and normalization of LHPA activity [103, 121].

In the adolescent studies described above, a substantial proportion of the depressed youth with higher nocturnal cortisol secretion also had comorbid anxiety disorder [30, 34]. In contrast to our finding of an association between elevated cortisol and vulnerability for substance-related disorders, Moss *et al.* observed lower cortisol response to an anticipated stressor in pre-adolescent boys whose biological fathers had substance abuse compared with boys whose fathers did not have an addictive disorder [122]. The lower cortisol response during pre-adolescence was associated with "regular" substance use during adolescence [122]. Antisocial disorders mediated the risk for substance-related problems in the "high-risk" group [123]. Other investigators also found that antisocial behaviors/disorders contributed significant

variance to the association between addictive and depressive disorders, possibly through common genetic and/or environmental factors shared by all three conditions [124]. These findings suggest that there may be two subgroups of depressed youth at risk for developing substance-related disorders, one subgroup with anxiety symptoms and high LHPA function and a second subgroup with conduct symptoms, low LHPA function and high density of substance abuse in family members. It is likely that the two groups would benefit from different treatment strategies; CRH antagonists or anti-glucocorticoid agents may be helpful only in the subset of patients with elevated HPA activity.

Reward and Motivational Systems

NEUROCIRCUITRY AND NEUROPHARMACOLOGY OF THE REWARD-MOTIVATIONAL SYSTEM

Experimental studies in animals and humans indicated that the mesostriatal and mesocorticolimbic DA pathways are involved in processing natural rewards and reward-directed behavior [125]. The mesostriatal-mesocorticolimbic DA system includes reciprocal DA projections from the ventral tegmental area (VTA) in the midbrain into the ventral striatum (NAc and caudate nucleus), the limbic structures (amygdala in particular), and the orbitofrontal cortex [126]. The temporal relationships among exposure to rewards, DA neuronal firing activity and extracellular DA concentrations suggest that DA release in the ventral striatum is involved in forming associations between salient contextual stimuli and internal rewarding events [127].

Addictive substances are believed to exert their reinforcing effects by increasing DA in the nucleus accumbens (NAc) and other limbic regions [125, 128]. Conversely, DA levels are reduced in the NAc and amygdala, among other regions, during periods of withdrawal from these drugs [125]. In addition, DA agonists seem to reestablish drug-seeking behaviors after extinction of that behavior, whereas the use of DA antagonists seems to have the opposite effect [129, 130]. Functional neuroimaging studies examining reward valuation have implicated the orbitofrontal cortex, anterior cingulate, ventral striatum and amygdala [131]. Brain activity changes associated with drug craving in adult patients with substance-related disorders reported alterations in the same neuroanatomical circuits described above [125, 132]. Finally, a direct correlation was found between D₂ receptor number (involved in drug-triggered relapse) and anterior cingulate and orbitofrontal cortex function in addicted persons [133, 134]. However, it is important to note that relapse of addictive behavior is more complex, and DA antagonists do not exert therapeutic effects under all circumstances. Non-dopamine mechanisms also contribute to relapse in addicted persons [130].

The role of DA in depression also has been recognized [135, 136]. The best evidence for the involvement of DA in depression is provided by preclinical pharmacological studies. For example, chronic antidepressant treatment increases extracellular DA levels in the striatum [58, 137]. Increased functional sensitivity of the NAc to direct and indirect DA agonists provides additional support [58, 130]. Consistent with the hypothesis of reduced mesostriatal-mesocorticolimbic DA function, magnetic resonance imaging and post-mortem studies in adult depressed patients

showed reduced volumes in the caudate and NAc regions, as well as reductions in the gray matter and glial cells in the amygdala and orbitofrontal cortex [138]. Moreover, functional neuroimaging studies revealed metabolic changes in the caudate nucleus, amygdala, anterior cingulate and orbitofrontal cortex [138, 139]. The direction and regional localization of blood flow changes were variable across studies, however, and were attributed to symptom severity, clinical profile, medication status, treatment history and longitudinal clinical course.

Taken together, these data suggest that mesostriatal-mesocorticolimbic DA system, a crucial pathway for processing rewards, is altered in depression and substance-related disorders. The evidence for association between DA and addictive disorders is very strong. Although the data support a DAergic deficit in at least some types of depression, the importance of such a deficit as a mediator of depressive illness is unclear. Furthermore, even though almost all addictive substances increase DA in the NAc, this does not explain why the comorbidity with depression is higher for certain types of drugs. It is possible that social factors have an influence on the strength of association between depression and different types of drugs [4]. For example, the greater availability of nicotine as compared to the illegal drugs may explain, in part, the high prevalence of nicotine dependence in depressed patients [140]. It is also likely, however, that the unique pharmacological properties of nicotine (by virtue of its antidepressant effects) contribute to the comorbidity [141-143].

In contrast to DA, which is an appetitive/stimulatory part of the motivational-reward system, serotonin or 5-hydroxytryptamine (5-HT) encodes suppressive/inhibitory behaviors. For instance, following 5 days of 3, 4-Methylenedioxymethamphetamine (MDMA) administration, which is toxic for 5-HT axonal projections, reward-related learning was impaired in rats [144]. Unlike control rats, MDMA-administered rats performed conditioned behaviors for over a week in the absence of cue for action [144]. Other studies found a correlation between impulsive or aggressive behavior (both of which are associated with substance abuse) and lower 5-HT turnover [145-147], and increases in 5-HT activity correlated with reduced aggression and impulsivity in both animals and humans [147, 148].

5-HT receptors are abundant in central DAergic terminal regions, including the ventral striatum [149-152]. A central 5-HT deficit is thought to be involved in the pathogenesis of substance-related disorders by modulating motivational behavior, neuroadaptive processes, and resulting emotional disturbance [153, 154]. It is speculated that 5-HT neurons dampen the effects mediated by mesolimbic DA, and pharmacological manipulations that increase extracellular 5-HT can attenuate emotional, locomotor and reinforcing properties of addictive substances [154-156]. The therapeutic effect of clinically proven antidepressants (many of which affect 5-HT function) in treating drug addiction was described previously [60, 61].

Several lines of evidence suggest that serotonergic (5-HT) alterations are involved in depression. For example, reduction in the central 5-HT activity, as reflected by measures of 5-hydroxyindoleacetic acid (a major 5-HT metabolite) in the cerebrospinal fluid, platelet 5-HT uptake and neu-

roendocrine responses to 5-HT challenges, has been demonstrated in numerous studies [157-160]. Also, tryptophan depletion induces dysphoric mood and affects cognitive performance in healthy volunteers, remitted depressed patients, and in individuals at high risk for depression [161-163]. The therapeutic action of a variety of antidepressant drugs, including tricyclic agents, selective serotonin re-uptake inhibitors, monoamine oxidase inhibitors and atypical antidepressant compounds, involves adaptations in 5-HT function through both presynaptic and postsynaptic mechanisms [164,165]. Finally, genetic polymorphisms of the 5-HT transporter, tryptophan hydroxylase and 5-HT receptor have been shown to influence individual variations in vulnerability to mood disorders as well as differences in therapeutic response to antidepressant treatment [166-169].

INFLUENCE OF DEVELOPMENT ON REWARD-MOTIVATIONAL SYSTEM AND IMPLICATIONS FOR MOOD AND SUBSTANCE-RELATED DISORDERS IN ADOLESCENTS

Adolescence is a critical developmental period for the maturation of neurobiological processes that underlie higher cognitive functions, as well as emotional and social behavior. The neurobehavioral systems that sub-serve these skills include inferior, orbital and dorsolateral portions of the prefrontal cortex (PFC) with rich interconnections to several limbic structures. The PFC matures later than other regions, and its development is paralleled by increased abilities in abstract reasoning, attentional shifting, processing speed and response inhibition. Simultaneously, changes in emotional capacity, including improvements in affective modulation and discrimination of emotional cues, also occur during adolescence [170-173].

In addition to structural and functional changes in the central nervous system during adolescence, dramatic alterations occur in virtually all neurotransmitter systems. Most relevant to the development of mood and substance-related disorders are the changes experienced in DA and 5-HT systems [173-176]. Research in animals and humans has shown that synaptic pruning of DA receptors occurs in the NAc during adolescence [177, 178]. In contrast to the changes in the NAc, DA receptors in the PFC do not demonstrate significant pruning until late adolescence [178, 179], and DA inputs to the PFC in non-human primates peak during adolescence [173, 180]. Furthermore, increased DA synthesis has been observed in the striatum and PFC in adolescent rats [181]. Finally, DA systems in the adolescent rat display significant regenerative plasticity following neurotoxin administration [182]. In conclusion, these studies suggest a functional increase in mesostriatal DA activity during adolescence, although the region and timing of these increases seem to differ across species [173, 174, 176].

The nature of 5-HT alterations during adolescence is not as well established. 5-HT turnover in the NAc is up to four times lower in adolescent rats than in younger or older rats [183], and 5-HT_{1A} receptor binding appears to decrease most dramatically during adolescence in human males [184]. DA input to the PFC is up to 3 times greater than 5-HT input [185], and concentrations of DA precursor in the PFC are much greater than those of 5-HT precursor in pubertal rhesus monkeys [186]. Finally, there is evidence that younger pu-

bertal rats already undergo significant 5-HT synaptic pruning in the basal forebrain [187]. Taken together, these data suggest that there is an imbalance of DA and 5-HT neurotransmission during adolescence, with DA levels close to a functional maximum and relatively lower levels of 5-HT. Experimentation with addictive substances and mood regulation are certainly the product of many influences, one of which is likely to be this imbalance in reward-motivational processes.

In addition to the developmental changes in DA and 5-HT systems during adolescence, alterations occur in gamma-aminobutyric acid (GABA) and glutamate inputs to the NAc and PFC, among others [173, 180]. PFC appears to be crucial for the regulation of motivationally-driven behaviors [188, 189] through a glutaminergic feedback loop with the NAc [190, 191]. PFC dysfunction has been associated with impulsiveness and affect dysregulation [192-195], as well as increased vulnerability for addictive disorders [196] and depression [139]. Diminished PFC input to the subcortical structures could disrupt the motivational loop, and persistent dysfunction could impair the neuroplastic shaping of the motivational circuit, leading to mood dysregulation and/or substance abuse [197, 198]. GABA also likely regulates emotional and motivationally-driven responses through projections from the central amygdala to the VTA, and through connections from the NAc core and ventral pallidum [196, 199].

Activation of the motivational circuit appears to differ between adolescent and adult humans. In a task in which participants could either win or avoid losing money, reduced activation in the striatum and amygdala was observed during anticipation of a gain in adolescents, relative to young adults [200]. This implies differences in the ability of adolescents to use information to regulate motivational behavior as compared to adults. Ernst and collaborators compared the neural responses of adolescents and adults on a gambling task [201]. Adolescents had greater activation of the NAc in response to positive outcomes than adults. Adolescents also showed reduced activation of the amygdala in response to negative outcomes compared to adults. These data suggest that adolescents process rewarding stimuli better than inhibitory feedback. The integration of diverse neural structures is crucial for the regulation of motivated drives [202], and adolescents likely are not equipped to exert maximal control over their appetitive urges. Thus, it appears that a heightened ratio of the stimulatory relative to the suppressive aspects of motivation may be normal for the adolescent phase of development [188]. This imbalance may explain, partly, the impulsivity/risk-taking behavior and experimentation with addictive substances seen in many adolescents [6, 173, 174, 176]. Immaturity of the neuronal circuits sub-serving affect regulation and interpersonal relationships can likely explain the increased vulnerability to depression also during this developmental period [170, 172, 175].

The Nicotinic-Cholinergic System

The theory that cholinergic systems are involved in depression has existed for a long time [203]. Strong evidence supports the presence of exaggerated responses (including behavioral, sleep and neuroendocrine) to cholinergic agents in patients with affective disorders relative to controls [204]. For example, physostigmine, an indirect cholinergic agonist,

increases heart rate and blood pressure and produces symptoms of dysphoria, irritability, anxiety and depression when administered to normal volunteers. When physostigmine was administered to patients with depression, symptoms of negative affect were more pronounced [205]. Reduced latency to rapid eye movement (REM) sleep and cortisol hypersecretion are consistent findings associated with depression, and depressed patients show shortening of REM latency and cortisol secretion to a greater extent in response to the administration of cholinergic agonists [206]. Cholinergic hypersensitivity also may be a marker of genetic predisposition to mood disorders, with unaffected relatives of depressed patients demonstrating exaggerated behavioral, sleep and neuroendocrine responses to cholinergic agonists [204].

The cholinergic hypersensitivity theory in depression was postulated when more was known about muscarinic than nicotinic receptors (nAChRs). While much more is known now about nAChR pharmacology, few attempts have been made to explain the role of nAChRs in the inter-relationships between cholinergic systems and mood disorders [143]. The nAChRs are expressed throughout the nervous system, and they not only exist on neuronal cell bodies and dendrites but also are located on axon terminals and are involved in multiple neurotransmitter release, including acetylcholine, DA, 5-HT, GABA, glutamate and norepinephrine [207, 208]. It is known now that the neuroendocrine effects of physostigmine are mediated primarily through the activation of nAChRs, and not muscarinic receptors [209, 210]. In addition, studies characterizing the effects of smoking on mood in normal smokers suggest that while mood improves immediately after smoking, mood impairments (including dysphoria and irritability) occur between smoking episodes [211], and the depressive mood predicts relapse of smoking behavior [86]. This repetitive cycle of shifting mood suggests a role for nAChRs, and may explain partly the high comorbidity between depression and nicotine dependence in both adolescents and adults [140, 212, 213].

In experimental studies, discontinuation of continuous nicotine infusion produces withdrawal signs, and these withdrawal signs also can be precipitated by mecamylamine, a non-competitive nAChR antagonist, showing evidence of nicotine dependence [214, 215]. The Flinders Sensitive Line (FSL) rat has been used as an animal model of depression [216]. These animals are selectively bred for their hyperresponsiveness to cholinergic stimulation, and they demonstrate depression-related behaviors and physiology [216]. FSL rats showed evidence of increased neuronal nAChR expression [217]. Interestingly, the increased nAChR binding observed following chronic nicotine administration was less marked in FSL animals than in control animals, suggesting a potential mechanism of nicotine dependence associated with depression. A study in humans demonstrated higher frequency of the non-functional variant (characterized by 2 base-pair deletion in exon 6) of the partially duplicated $\alpha 7$ -nAChR gene in patients with depression than in controls [218].

Putative associations among depression, tobacco smoking and nAChR function are best understood through the mechanisms of antidepressant drug actions [219, 220]. Bupropion, an atypical antidepressant agent, has been found to be effective in reducing tobacco smoking in broad groups

of patients, also including persons with depression [61, 221]. Experimental studies have shown that bupropion blocks the activation of nAChRs by nicotine with some degree of selectivity, with the highest potency at $\alpha 3\beta 2$ sites [219, 220]. The functional blockade of the nAChRs was non-competitive, and given the relative selectivity of bupropion at inhibiting $\alpha 3\beta 2$ receptors which are implicated in nicotine-induced DA release from midbrain DA neurons (and thereby enhance its rewarding properties), the therapeutic efficacy of bupropion is partly explained. In addition to bupropion, other antidepressant drugs have been tested for their efficacy in promoting smoking cessation but only nortriptyline was shown to have significant beneficial effect [222]. Although many of these agents lacking therapeutic effect (e.g., selective serotonin reuptake inhibitors) also inhibit nAChRs at therapeutic concentrations [208, 219], one possible explanation for the discrepancy in clinical efficacy is that different nAChR subtypes are involved in mood regulation and nicotine dependence. It is likely that most antidepressant drugs affect the nAChR subtypes involved in modulating mood but only a few also affect nAChR subtypes involved in nicotine dependence [208, 219].

The Opioid System

Although abuse of opioid agents is not a new phenomenon, recently, there has been a marked increase in the use of opioid medications in the United States, and an even greater increase in problems associated with their use [223]. For instance, recent epidemiological surveys of youth in the United States indicated that opioid analgesics were among the most frequently abused illicit drugs among Secondary School Students, second only to marijuana [224]. In addition to the social policy measures of reducing access of these drugs to youngsters, it is critical to understand the effects of acute and chronic opioid administration on the developing brain. Data in adults indicate that depression frequently co-occurs with opiate addiction and that the presence of depressive illness influences treatment outcome and long-term prognosis of these patients, positively in some circumstances [225]. A better understanding of the underlying mechanisms linking their comorbidity might be helpful in developing effective interventions for this alarming problem.

Several lines of evidence implicate the opioid system in the neurobiology of depression and in the therapeutic effects of antidepressant drugs [226]. For example, μ -opioid receptors are distributed densely in the brain regions implicated in response to stressors and emotionally salient stimuli, both of which are involved in the pathophysiology of depression [227-229]. Moreover, altered endogenous neurotransmission of μ -opioid receptors was observed in patients with depression [230]. In a prospective investigation of patients with pain-related conditions, baseline symptoms of distress (also including depressive mood) predicted continued pain and disability over three years [231]. Additionally, μ -opioid receptor agonist drugs (e.g., oxycodone, oxymorphone) have been shown to improve mood in patients with refractory depression [232]. Heroin dependent patients with depression showed a better response to treatment with buprenorphine (a partial agonist at μ -opioid and antagonist at κ -opioid receptors) compared with their counterparts with other psychiatric comorbidity or to individuals with pure heroin addiction [233]. Research in animals has indicated that chronic antide-

pressant treatment displays anti-nociceptive and antidepressant effects [234]. Chronic antidepressant treatment also induces adaptations in the density of opiate receptors in the cortical, limbic and thalamic regions of the brain [226, 234]. Since these structures are part of the neuroanatomical circuit involved in depression, and because opioid receptors are also localized on 5-HT neurons in the dorsal raphe nucleus [234, 235], these neuroadaptations might participate in the modulation of monoaminergic neurotransmission and simultaneously alleviate depressive symptoms and reduce drug use [61, 225].

SUMMARY AND FUTURE DIRECTIONS

Common genetic, environmental and neurobiological factors that potentially mediate/moderate the relationship between addictive and depressive disorders were described. A review of the various risk mechanisms involved in these conditions must, by necessity, be selective in its approach and regretfully omit important advances in the field. The specific number, combination, or weighting of these or other risk factors for predicting depression or substance abuse is not known yet. No one risk factor is either necessary or sufficient; rather the interaction among several risk factors may be involved in the development and maintenance of these disorders [91].

The information on neurobiology of addictive and depressive disorders is based on neurobiological studies of these disorders individually, and there are no empirical data on how these factors interact to increase vulnerability for the comorbid illness or how these processes change over time as a consequence of the comorbid illness. Before we wrestle with the complexities of how co-occurring addictive and depressive disorders interact neurobiologically, we need to recognize how the study of addictive drugs may yield important insights into depression [78]. For example, cellular targets for almost all drugs of abuse have been identified [236]. Neural systems for reward, craving and addiction also have been identified [125]. A large number of drug-induced changes at the molecular and cellular levels have been characterized in these brain areas, and rapid progress is being made in relating individual changes to specific behavioral abnormalities in animal models of addiction [199]. Moreover, neurobiological studies related to substance abuse have provided complex cognitive concepts that are relevant for depression, such as the identification of hedonic circuits, and the importance of context [237]. Furthermore, advances have been made in discovering allelic variants of genes that are likely to provide the heritable components of addiction vulnerability in humans [238]. Because research on depressive disorder has not yet yielded consistent cellular or systems level pathophysiological changes, investigators can exploit the insights from the findings on addictive disorders to understand the enigmas of depressive illness [78]. Simultaneously, as the genetic studies of depression move forward, it is possible to discover important molecular candidates for the vulnerability to substance abuse. The challenge to map the shared and interacting neurobiology of addictive and depressive disorders is enormous but the recent advances in molecular biology and neuroimaging techniques also offer tremendous opportunities.

In interpreting the data on the neurobiology of addictive and depressive disorders, it is also important to note that the available information comes primarily from adult samples

and research in adolescent cohorts is limited. From these findings, it is often difficult to determine whether the observed neurobiological changes preceded the manifested condition(s), and thereby serve as vulnerability markers, or whether they resulted from repeated drug use and/or multiple depressive episodes [198, 239]. Future research should involve adolescent populations and longitudinal study designs. Because adolescence is a high-risk period for developing both disorders, this developmental period offers a unique opportunity to delineate the pre-morbid markers from illness-related sequelae within a relatively short period of time, and without many of the potentially confounding variables that might occur in adults as a result of chronic drug use and recurrent depressive episodes. Moreover, it will be possible to clarify the temporal sequence in the onset of these disorders. A systematic examination of the inter-relationships among addictive disorder(s), depression and neurobiological markers will aid in the development of evidence-based algorithms for the diagnosis and treatment of individual patients with these disorders. Effective intervention early in the course of illness will be helpful in preventing recurrent episodes, and in improving the long-term prognosis of these disabling illnesses. Furthermore, insights on the developmental differences in neurobiology might be useful for developing more effective treatments for adult patients with early-onset illness.

Key Learning Objectives:

1. Readers will learn about the prevalence and clinical significance of comorbid depression and substance-related disorders in adolescents.
2. Readers will gain an understanding of the common pathophysiological mechanisms that link these two disorders.
3. Readers will gain some insights into the developmental differences in neurobiological processes involved in addictive and depressive disorders.

Future Research Directions:

1. Future studies should focus on the interaction of specific risk factors involved in addictive and depressive disorders that increase vulnerability for the comorbid illness or how these processes change over time as a consequence of the comorbid illness.
2. In order to better understand the neurobiology of addictive and depressive disorders in youth, emphasis should be placed on direct studies of adolescent populations, both in animals and humans.
3. Future research also should focus on developmental studies, examining developmental continuities and discontinuities in the trajectory of these disorders from adolescence to adult life.

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