Allostasis as a conceptual framework linking bipolar disorder and addiction

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INTRODUCTION

Bipolar disorder (BD) is a severe, often chronic condition with lifetime prevalence rates of up to 6.5% for bipolar spectrum disorders in the general population (1). BD patients frequently report co-occurring substance-use disorders (SUDs) and behavioral addictions (1–5). The rates of alcohol and other SUDs are significantly higher in subjects with BD than in the general population (1, 6). The co-occurrence of BD and addiction has important clinical implications (3, 7). Bipolar patients with comorbid conditions present with a more severe course of illness (8), characterized by an overall worse clinical picture (9), poorer treatment outcome (10–12), higher suicidality (13), and mortality (14).

Several studies have aimed to identify the endophenotypic features predisposing to the development of addiction in the general population, as well as in the context of BD. These studies focused on genetic vulnerability, impulsive traits, and decision-making impairment (15–19).

The aim of this paper is to present the possible contribution of the concept of allostasis as a framework linking BD and addiction. We hypothesize that the concepts of allostasis and allostatic load (AL) may contribute to the understanding of the complex relationships between BD and addictive behaviors. Allostasis entails the safeguarding of reward function stability by recruitment of changes in the reward and stress system neurocircuitry (21) and it may help to elucidate neurobiological underpinnings of vulnerability to addiction in BD patients.

METHODS

Computerized database, i.e., PubMed, Psycinfo, Cochrane Library were searched using the following terms: “allostasis,” “AL,” “reward,” “hedonic tone,” “stress system” cross-referenced with “BD,” “addiction,” and “SUDs.” The results of this search are presented in this article, and examined in light of a unifying hypothesis with a potential heuristic value to inform and provide direction to future research in this intriguing area.

RELEVANCE OF ALLOSTASIS IN BD AND ADDICTION FIELD

Bipolar disorders (BDs) and addictions constitute reciprocal risk factors and are best considered under a unitary perspective. The concepts of allostasis and allostatic load (AL) may contribute to the understanding of the complex relationships between BD and addictive behaviors. Allostasis entails the safeguarding of reward function stability by recruitment of changes in the reward and stress system neurocircuitry and it may help to elucidate neurobiological underpinnings of vulnerability to addiction in BD patients. Conceptualizing BD as an illness involving the cumulative build-up of allostatic states, we hypothesize a progressive dysregulation of reward circuits clinically expressed as negative affective states (i.e., anhedonia). Such negative affective states may render BD patients more vulnerable to drug addiction, fostering a very rapid transition from occasional drug use to addiction, through mechanisms of negative reinforcement. The resulting addictive behavior-related ALs, in turn, may contribute to illness progression. This framework could have a heuristic value to enhance research on pathophysiology and treatment of BD and addiction comorbidity.

Keywords: bipolar disorders, addiction vulnerability, allostasis and allostatic load, comorbidity, hedonic tone and anhedonia, dopaminergic system, reward system, CRF/HPA axis and stress system

Abbreviations: AL, allostatic load; BD, bipolar disorder; CRF, corticotropin-releasing factor; GD, gambling disorder; HPA, hypothalamic-pituitary-adrenocortical (axis); SUD, substance-use disorder.
[please refer to the review Kapczinski et al. (24)]. Neurotrophic factors play an important role in maintaining a physiological brain function. They have been shown to be modulated by environmental events in various psychopathological conditions (27), and their role has been confirmed also in pathophysiology and staging of BD (28–31).

These alterations are greater during the acute stages of the disease, but remain sub-threshold even during remission (24). When mediators of allostasis – essential for brain functioning and protection – are driven by mechanisms of homeostatic dysregulation, they act in excess and damage brain tissue (32, 33), which is particularly vulnerable to the harmful effects of the AL [i.e., oxidative stress (34)]. Impairment in the stress response has been acknowledged as a core feature of BD clinical expression, as well as having a central role in the concept of AL (23). Although the exact mechanisms, by which stress exerts its effect on the brain, remain largely unknown, the HPA axis is one of the main stress response systems activated with the objective to maintain stress adaptation for as long as it is necessary (23). The HPA axis is clearly altered in mood disorders, as well as in BD (35–38). Glucocorticoids play an important role in the process whereby the mediators of allostasis interact with neurotransmitter systems and brain peptides resulting in neuroplastic alterations in the hippocampus, amygdala, and prefrontal cortex (39, 40). The role of stress in triggering mood episodes is well established, particularly in the early stages of illness (41, 42). It has been hypothesized that early life stress could affect the endocrine system, producing a stable reprogramming of HPA axis (43), leading to an impairment in brain area involved in emotional processing (44). Alterations in emotional processing involving amygdala circuitry and are related to BD symptoms in several ways. Evidence from amygdala-dependent tasks points to a dysregulation of amygdala-related neurocircuitry in BD patients (45). These alterations render BD patients more prone to trigger AL (23), through a greater stress vulnerability.

**ADDITION**

Drug addiction can be conceptualized as a stress-surfeit disorder (46). It is characterized by the occurrence of an allostatic state in the brain reward system, reflected in a chronic deviation of reward thresholds (46–48). An allostastic state reflects a new balance, a state of chronic deviation of the regulatory system from its normal (homeostatic) operating level to a pathological (allostatic) operating level (47). From a drug addiction perspective, repeated compromised activity in the dopaminergic system and sustained activation of the corticotropin-releasing factor (CRF) system may lead to an AL that contributes significantly to the transition from occasional drug use to drug addiction (49, 50). This model may be applied to pathological gambling as well (51). The transition from occasional controlled drug use to loss of control is endorsed by the emergence of negative affective states, resulting from the abovementioned allostatic dysregulations (i.e., the AL), with a shift from impulsivity to compulsivity and from positive reinforcement to negative reinforcement (49, 52).

Addiction implies dysregulation of the brain reward system (48, 53). Several studies highlighted that negative affective states are a result of the alteration of neurobiological elements central to reward and stress systems (50, 54, 55), in brain areas such as the ventral striatum and the extended amygdala (56, 57). In addition to the reduction of dopaminergic and opioidergic functioning, dysregulation of reward is also mediated by the activation of brain stress systems (i.e., CRF), in the areas of the extended amygdala (57). Stress system alterations have been observed in both the acute and chronic phases of addiction, and seem to play a role in determining reward dysregulation (48, 54). Acute withdrawal raises the threshold for reward, leads to an increase in dysphoric symptoms as well as an increase of CRF levels in the amygdala (49, 58). These changes result from sensitization of the brain stress system in response to the phenomena of abstinence, and persist for a long period of time following cessation of drug intake [protracted withdrawal (59)]. Protracted withdrawal symptoms are related to the compulsivity characterizing addictive disorders, and are factors involved in determining relapse. In addition to CRF, other mediators (norepinephrine, dynorphin, and neuropeptide Y) have been investigated and found to play a role in the transition from impulsivity to compulsivity (58, 60). As a whole, these elements constitute the brain stress system of the extended amygdala, a counter-adaptive system that interacts with the reward system and determine its reduced function (48).

**NEUROBIOLOGICAL ISSUES OF BD-SUD COMORBIDITY**

A complete review of neurobiological features in BD-SUD comorbidity is beyond the purpose of this paper. Familial and illness course characteristics of BD and addictive disorders, as well as shared underlying mechanisms suggest potentially important genetic overlap (19, 61, 62). Preliminary findings hint at the existence of a shared genetic vulnerability for BD and SUDs (15). Johnson et al. (63) found convergent genome-wide association results for BD and SUDs. Products of one group of these genes are likely to play substantial roles in the initial and/or plasticity-related “wiring” of the brain (63). A second group of genes is the family of clock genes, implicated in the regulation of behavioral and physiological periodicity (19). Recently, a significant genetic overlap between candidate genes for both alcoholism and BD was found (64, 65), by using the n-box binding protein knockout mouse, a stress-reactive animal model developed consistently with allostasis and stress-surfeit theory of addiction (46).

To date, no studies have specifically investigated neuroimaging correlates in comorbid BD–SUD patients. Several studies describe putative mechanisms involved in BD vulnerability to addiction. Structural imaging studies in BD patients found volume reductions in prefrontal cortex [PFC (66)], which is involved in encoding incentive information (67). During Iowa gambling task (IGT), BD patients showed abnormalities in the dorsal and ventral PFC, while lateral temporal and polar regions displayed increased activation (68). Jogia et al. (69) confirmed these observations and also reported a greater activation in the anterior cingulate cortex of BD patients performing the IGT and in the insula during the n-back working memory task. Reduced functioning of the dopamine transporter (DAT) has been linked to BD (70–72). Animal models may provide insight into the role of the dopaminergic system in risk-taking behavior. Mice with reduced DAT functioning exhibit a behavioral profile consistent with manic patients and increased risk-taking behavior during a mouse version of the IGT (70). Evidence from these animal model studies and translational
human research in BD subjects (73, 74), allows us to hypothesize that system-related change involving functioning of the dopamine system play a role in impulsive choice, risk-taking behavior, and reward, thus help guiding future studies in BD–SUD subjects.

**ALLOSTATIC DYSREGULATION OF REWARD MIGHT UNDERPIN BIPOLAR VULNERABILITY TO ADDICTION**

Dopaminergic mechanisms are likely to play a key role in the understanding of the pathophysiology of BD and the clinical phenomena of mania and depression have previously been conceptualized in terms of an increase or a decrease in dopaminergic function, respectively (75, 76). Also, converging lines of evidence suggest that dopamine is a key neurotransmitter mediating hedonic allostatics in drug and behavioral addictions (49, 77). From a neurobiological perspective, a central dopaminergic dysfunction has been widely proposed as a neurobiological correlate of anhedonia (78). Different studies suggest anhedonia as a key symptom in addictive disorders, both as part of a withdrawal syndrome and as a relevant factor involved in relapses (51, 59, 79). In addition to dopamine, other neurotransmitters are believed to encode the hedonic experience [endogenous opioids, serotonin (80)], while long-lasting alterations involving cue-induced craving and relapse are thought to result from neuroplastic changes in glutamatergic circuitry (81–83).

Several studies provide support for reward dysregulation accounts in BD (16, 18, 45, 69, 84–95) (Table 1), characterizing neural dynamics underlying inter-temporal reward processing (90). Possibly emotional dysregulation present in BD is related to hypersensitivity to reward-relevant stimuli (93). Impulsive and unsafe decision-making in BD is linked to decreased sensitivity to emotional contexts involving rewards or punishments, possibly reflecting altered appraisal of prospective gains and losses associated with certain behaviors (89). It has been proposed that anhedonia could be mediated by a change in reward sensitivity (78), which has different behavioral consequences involving either stress-related and dopaminergic processes (96). In BD, sustained allostatic states and the consequent cumulative brain damage resulting from increased AL may play a part in the occurrence of negative affective states (i.e., anhedonia) that persist even during periods of remission (84). Counter-adaptive processes, such as opponent process that are part of the normal homeostatic limitation of reward function (55) fail to return within the normal homeostatic range and are hypothesized to repeatedly drive the allostatic state [decreased dopamine and opioid peptide function, increased CRF activity (49)]. This allostatic state is hypothesized to be reflected in a chronic deviation of reward set point that is fueled, not only by dysregulation of reward circuits per se but also by recruitment of brain and hormonal stress responses.

Altered functioning of the HPA axis may hold clues to the nature of the motivational changes accompanying addiction and vulnerability to addiction (97). Pre-existing alterations in frontal–limbic interactions with the HPA may reflect addiction-proneness, as shown in studies of offspring of alcohol- and drug-abusing parents (98). Alterations in the CRF/HPA axis may exert effects on the corticostratal-limbic motivational, learning, and adaptation systems that include mesolimbic dopamine, glutamate, and gamma-aminobutyric acid (GABA) pathways (97), representing the underlying pathophysiology associated with stress-related risk of addiction.

The effects of these allostatic changes in the mesocorticollimbic brain system and in CRF/HPA axis contribute to the underlying pathophysiology associated with stress-related risk of addiction in BD (99). In BD patients, we hypothesize that the hedonic response to an acute drug administration occurs on a pre-existing allostatic dysregulation of the dopamine and CRF system. BD-related allostatic alterations in reward and stress systems thereby constitute vulnerability factors to the development of addiction in subjects exposed to occasional drug use. The failure to self-regulate these systems, determined by the collective contribution of endogenous factors linked to BD and of exogenous substances, results in an AL leading to a facilitated transition to drug addiction.

Dysphoria triggers drug intake, accompanied by an intense activity of the dopaminergic system and followed by a compensatory decrease in the dopaminergic system and increase in the CRF system to re-establish the allostatic set point. Such negative affective states may render BD patients more vulnerable to drug addiction, favoring a very rapid transition from occasional, recreational drug use to compulsive, pathological, drug dependence. The resulting addictive behavior-related ALs, in turn, may contribute to illness progression (Figure 1).

**CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES**

Converging data from addiction and BD studies suggest that these disorders involve similar allostatic processes, and allostasis can contribute to unify these disorders under a unitary perspective. In this context, the concepts of allostasis and AL provide both a pathophysiological model for the understanding of BD–addiction comorbidity and a new perspective for the development of novel therapeutic strategies for the treatment of comorbid patients (100, 101).

Allostatic alterations in brain reward system could render BD patients more vulnerable to drug addiction, favoring a very rapid transition from occasional, recreational drug use to compulsive, pathological, and drug dependence. This framework allows us to explain the high comorbidity rate between these disorders (2), as well as its relevance in early-onset patients (8, 102). Furthermore, it enables us to identify the factors of vulnerability to addiction in inter-episode periods as well (i.e., sub-threshold reward-system dysfunctions) (84). A more accurate monitoring of comorbidity-risk (103), coupled with the inclusion of specific tools for the assessment of hedonic tone, may contribute to early intervention on addiction-vulnerability factors and to initiate primary prophylaxis for substance misuse in youth suffering from BD with high-risk for addiction (104–106).

Currently, accruing evidence suggests that mood alteration episodes increase the risk of substance use (107, 108). Patients with dual disorders are more likely to use substances to self-regulate perceived internal factors (109, 110). SUD comorbidity in BD patients was preceded by greater manic symptoms in the previous period (104), as well as the persistence of depressive symptoms was associated with higher craving and increased risk to develop substance dependence (104, 108). Moreover, in gambling disorder (GD) patients depressive symptoms predicted gambling urges and duration (111). Allostasis framework enables us to extend
| Aim                                           | Methods                                      | Sample                                      | Results                                                                 | Comments                                                                                      | Reference |
|-----------------------------------------------|----------------------------------------------|---------------------------------------------|-------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-----------|
| Trait-related decision-making impairment      | IGT, sensitivity-to-punishment index          | 167 BD (45 mania, 32 depressed, 90 euthymic), 150 HC | Manic, depressed, and euthymic BPs selected significantly more cards from the risky decks than HC. BD preferred decks that yielded infrequent penalties over those yielding frequent penalties. | BD have a trait-related impairment in decision-making that does not vary across illness phase, predicted by high depressive scores | (16)      |
| Decision-making deficits; temporal discounting of reward | Delay discounting task                        | 22 BD, 21 SZ, 30 HC                         | BD and SZ groups discounted delayed rewards more steeply than did the healthy group (even after controlling for current substance use). Working memory or intelligence scores negatively correlated with discounting rate. | BD patients value smaller, immediate rewards more than larger, delayed rewards | (18)      |
| Neural mechanisms related to motivation       | fMRI, probabilistic reversal learning task   | 19 BD, 19 HC, 22 relatives, 22 HC           | Increased activation in response to reward and reward reversal contingencies in the left medial orbitofrontal cortex in BD. Activation of the amygdala in response to reward reversal was increased. | Increased activity of OFC and amygdala, related to heightened sensitivity to reward and deficient prediction error signal | (45)      |
| Functional brain abnormalities during reward and working memory processing | fMRI, IGT, n-back task                        | 36 BD, 37 HC                                | BD showed inefficient engagement within the ventral frontopolar prefrontal cortex with segregation along the medial–lateral dimension for reward and working memory processing, respectively. Greater activation in the anterior cingulate cortex during the IGT and in the insula during the n-back task. | Overactivation in regions involved in emotional arousal is present even in tasks that do not typically engage emotional systems | (69)      |
| Hedonic capacity                              | SHAPS, SANS-An, VAS-HC                       | 107 BD, 86 MDD, 106 HC                     | SHAPS, SANS-An, and VAS scores significantly higher in affective disorder patients. 20.5% of BDs showed significant reduction in hedonic capacity | Reduced hedonic capacity persists irrespective of mood state | (84)      |
| Relationship between SUD and overweight-obesity | Data from CCHS, BMI                           | 36,984 individuals                          | Overweight/obese bipolar individuals had a lower rate of SUD than the normal weight sample (13 vs. 21%). BD + SUD had a lower rate of overweight/obesity when compared with BD non-SUD (39 vs. 54%) | Comorbid addictive disorders may compete for the same brain reward systems | (85)      |
| Neural correlates of reward and decision-making | IGT, RDMUR, ERP-assessed RDGT                | 13 BD, 12 ADHD, 25 HC                      | BD group showed a pattern of enhanced ‘learning by feedback’ and ‘sensitivity to reward magnitude’ regardless of valence. This ERP pattern was associated with mood and inhibitory control. Reduced responses of the cingulate cortex to the valence and magnitude of rewards in BD. | Altered decision-making process in BD with the involvement of cingulate cortex | (88)      |
| Impulsivity                                   | BIS-11, stop signal task, delayed reward task, continuous performance task | 108 BD1 (1-year FU), 48 HC                  | At baseline (manic/mixed state), BD demonstrated significant deficits on all three tasks. Performance on the three behavioral tasks normalized upon switching to depression or developing euthymia. Elevated BIS-11 scores persist across phases of illness. | Impulsivity has both affective-state dependent and trait components in BD. | (87)      |
| Dysfunctional reward processing               | Probabilistic reward task                    | 18 BD, 25 HC                                | BD showed a reduced and delayed acquisition of response bias toward the more frequently rewarded stimulus | Dysfunctional reward learning in situations requiring integration of reinforcement information in BD | (88)      |

(Continued)
| Aim | Methods | Sample | Results | Comments | Reference |
|-----|---------|--------|---------|----------|-----------|
| **Risky decision-making (rewards vs punishments)** | Risky decision-making task | 20 BD-2, DF, 20 HC | The BD participants overestimated the number of bad outcomes arising out of positively framed dilemmas. Risky choice in BD is associated with reduced sensitivity to emotional contexts that highlight rewards or punishments. | In BD, altered valuations of prospective gains and losses associated with behavioral options. | (89) |
| **Neural correlates of hypersensitivity to immediate reward** | (1) Two choice impulsivity paradigm (2) Delay discounting task, EEG | 1) 32 subjects 2) 32 subjects | (1) The hypomania-prone group made significantly more immediate choices than the control group. (2) The hypomania-prone group evidenced greater differentiation between delayed and immediate outcomes in early attention-sensitive (N1) and later reward-sensitive (feedback-related negativity) components. | Provide support for reward dysregulation accounts of BD, characterizing neural dynamics underlying inter-temporal reward processing. | (90) |
| **Substance sensitivity and sensation seeking** | SCID-I, SCI-SUBS | 57 BD1-SUD, 47 BD1, 35 SUD, 50 HC | BD + SUD and SUD have higher scores on self-medication, substance sensitivity and sensation seeking. No differences in reasons for substance use between BD + SUD and SUD (improving mood; relieving tension; alleviating boredom; achieving/maintaining euphoria; increasing energy). | In BD patients, substance sensitivity and sensation seeking traits are possible factors associated with SUD development | (91) |
| **Reward sensitivity and positive affect** | RPA; RRI; BQL-BD | 90 BD1, 72 HC | The majority of BD-1 reported avoiding at least one rewarding activity as a means of preventing mania. Lower quality of life related to dampening positive emotions. | People with BD-1 report avoiding rewarding activities and dampening positive emotion | (92) |
| **Neural correlates of hypersensitivity to reward** | fMRI, anticipation and outcome reward task | 21 BD1, 20 HC | BD displayed greater ventral striatal and right-sided OFC (BA 11) activity during anticipation, but not outcome, of monetary reward. BD also displayed elevated left-lateral OFC (BA 47) activity during reward anticipation. | Elevated ventral striatal and OFC activity during reward anticipation as a mechanism underlying predisposition to hypo/mania in response to reward-relevant cues. | (93) |
| **Sensitivity to positive and negative feedback** | Learning task (positive/negative feedback) | 23 BD1, 19 MD, 19 HC | The quality of the last affective episode was the only significant predictor. BD1 patients who last experienced a manic episode learned well from positive but not negative feedback, whereas BD1 patients who last experienced a depressive episode showed the opposite pattern. | Differences in response to positive and negative consequences carrying over into the euthymic state are related to the polarity of the preceding episode. | (94) |
| **Motivational aspects of decision-making in relation to reward and punishment** | IGT | 28 BD (14 acute and 14 remitted), 25 HC | Acute BD were characterized by the tendency to make erratic choices. Low choice consistency improved the prediction of acute BD beyond that provided by cognitive functioning and self-report measures of personality and temperament. | Low choice consistency in BD patients. | (95) |

BD, bipolar disorder; SZ, schizophrenia; HC, healthy controls; SUD, substance-use disorder; SCID-I, structured clinical interview for DSM-IV axis I disorders; SCI-SUBS, structured clinical interview for the spectrum of substance use; DF, drug-free; SHAPS, Snaith–Hamilton pleasure scale; SANS-An, scale for the assessment of negative symptoms, subscale for anhedonia/asociality; VAS-HC, visual analog scale for hedonic capacity; BIS-11, Barratt Impulsiveness Scale; RPA, responses to positive affect measure, BQL-BD, brief quality of life in bipolar disorder scale; RRI, reward responses inventory; IGT, Iowa gambling task; RDMUR, task of rational decision-making under risk; RDGT, rapid-decision gambling task; ERR, event-related potentials; fMRI, functional magnetic resonance imaging; EEG, electroencephalography; CCHS, Canadian Community Health Survey-Mental Health and Well-Being; OFC, orbitofrontal cortex; BA, Brodmann area; FU, follow-up.
the self-medication theory (112) beyond the established clinical domains, increasing the understanding of the interactions between BD symptoms and substance use. For instance, euthymic bipolar patients are more likely to experience cognitive impairment (deficits in measures of executive functions, verbal learning, immediate and delayed verbal memory, abstraction, sustained attention) (113). Cannabis abuse seems to positively affect cognitive function in a BD sample (114), and it may represent an attempt to counterbalance these alterations, even though causing an increased risk of rapid cycling and an earlier onset of manic episodes (114, 115).

Practitioners should be particularly vigilant in monitoring for substance misuse early after the onset of mood disorders, as well as they should be aware of personality traits related to the risk of addiction, in particular antisocial and schizotypal personality disorder (11, 116). The existence of additional risk factors [i.e., ADHD (117)] for the development of a BD-SUD comorbidity is controversial (105, 118). Combined with a specific role of traumatic stress as independent vulnerability factor (99, 119), these elements contribute to the build-up of a cumulative AL. Clinicians can therefore incorporate specific therapy approaches for dual disorders (120–122) to target adherence weaknesses (123) and to enhance the effects of existing treatments.

Given the notion that exposure to stress or drugs leads to enduring changes in gene expression or activation of transcription factors, determining long-term neuroadaptation of brain functions, a promising field of future research could involve the detection and reward-system alterations, determining long-term neuroadaptation of brain functions, a promising field of future research could involve the detection of negative affective states mediating the switch from impulsivity to compulsivity in bipolar patients. Cumulative effects of mood episodes and substance use on stress system have been hypothesized.

Future studies aimed at assessing brain AL in patients with BD and addiction comorbidity may help to shed light on the complex interactions underlying neurobiological vulnerability to these disorders and to improve their treatment options. Early effective treatment strategies specifically devised for comorbid patients (104, 125) could prevent, or possibly reverse, some of the neurobiological abnormalities and indicators of AL, thus potentially leading to numerous benefits for these patients.

REFERENCES

1. Vornik LA, Brown ES. Management of comorbid bipolar disorder and substance abuse. J Clin Psychiatry (2006) 67(Suppl 7):24–30.
2. Grant BF, Stinson FS, Hasin DS, Dawson DA, Chou SP, Ruan WJ, et al. Prevalence, correlates, and comorbidity of bipolar I disorder and axis I and II disorders: results from the National Epidemiologic Survey on alcohol and related conditions. J Clin Psychiatry (2005) 66(10):1205–15. doi:10.4088/JCP.v66n1001
3. Altamura AC. Bipolar spectrum and drug addiction. J Affect Disord (2007) 99(1–3):285. doi:10.1016/j.jad.2006.09.005
4. Di Nicola M, Tedeschi D, Mazza M, Martinotti G, Harnic D, Catalano V, et al. Behavioural addictions in bipolar disorder patients: role of impulsivity and personality dimensions. J Affect Disord (2010) 125(1–3):82–8. doi:10.1016/j.jad.2009.12.016
5. Pettorruso M, Di Nicola M, De Risio L, Fasano A, Martinotti G, Conte G, et al. Punding behavior in bipolar disorder type I: A case report. J Neuropsychiatry Clin Neurosci (2014) 26(4):E8–9. doi:10.1176/jnp.neuropsychi.13090217
6. Regier DA, Farmer ME, Rae DS, Locke BF, Keith SJ, Judd LL, et al. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the epidemiologic catchment area (ECA) study. JAMA (1990) 264(19):2511–8. doi:10.1001/jama.1990.03450190043026
7. Fagioli A, Furgiome R, Macci R, Cuomo A, Morana B, Dell’Osso MC, et al. Prevalence, chronicity, burden and borders of bipolar disorder. J Affect Disord (2013) 148(2–3):161–9. doi:10.1016/j.jad.2013.02.001
8. Tsai HC, Lu MK, Yang YK, Huang MC, Yeh TL, Chen WJ, et al. Empirically derived subgroups of bipolar I patients with different comorbidity patterns of anxiety and substance use disorders in Han Chinese population. J Affect Disord (2012) 136(1–2):81–9. doi:10.1016/j.jad.2011.08.015
9. Faye MA, Saloum EM. Bipolar disorder and comorbid alcoholism: prevalence rate and treatment considerations. Bipolar Res (2006) 8(6):677–85. doi:10.1111/j.1399-5618.2006.00370.x
10. Mazza M, Mandelli L, Di Nicola M, Harnic D, Catalano V, Tedeschi D, et al. Clinical features, response to treatment and functional outcome of bipolar disorder patients with and without co-occurring substance use disorder: 1-year follow-up. J Affect Disord (2009) 115(1–2):27–35. doi:10.1016/j.jad.2008.08.019
11. Mandelli L, Mazza M, Di Nicola M, Zaninotto L, Harnic D, Catalano V, et al. Role of substance abuse comorbidity and personality on the outcome of
depression in bipolar disorder: harm avoidance influences medium-term treatment outcome. *Psychopathology* (2012) 45(3):174–8. doi:10.1515/9000303364

McIntyre RS, Nguyen HT, Soczyńska JK, Lorenczo MT, Woldeyohannes HO, Konaraki JZ. Medical and substance-related comorbidity in bipolar disorder: translational research and treatment opportunities. *Dialogues Clin Neurosci* (2008) 10(2):203–13.

Carrà G, Bartoli F, Crocpresso C, Brady KT, Clerici M. Attempted suicide in people with co-occurring bipolar and substance use disorders: systematic review and meta-analysis. *J Affect Disord* (2014) 167:125–35. doi:10.1016/j.jad.2014.05.066

Yoon YH, Chen CM, Yi HY, Moss HB. Effect of co-morbid alcohol and drug use disorders on premature death among unipolar and bipolar disorder decedents in the United States, 1999 to 2006. *Compr Psychiatry* (2011) 52(5):453–64. doi:10.1016/j.comppsych.2010.10.005

Ahn WY, Rass O, Fridberg DJ, Bishara AJ, Forsyth JK, Breier A, et al. Temporal discounting of rewards in patients with bipolar disorder and schizophrenia. *J Abnorm Psychol* (2011) 120(4):911–21. doi:10.1037/a0023333

Swaab DF, Kriaa E, Mackin P, Young AH. Hypothalamo-pituitary-adrenal axis and bipolar disorder. *Psychiatr Clin North Am* (2005) 28(2):469–80. doi:10.1016/j.psc.2005.01.005

Watson S, Gallagher P, Ritchie JC, Ferrier IN, Young AH. Hypothalamo-pituitary-adrenal axis function in patients with bipolar disorder. *Br J Psychiatry* (2004) 184:496–502. doi:10.1192/bjp.184.6.496

McEwen BS. Structural plasticity of the adult brain: how animal models help us understand brain changes in depression and systemic disorders related to depression. *Dialogues Clin Neurosci* (2004) 6(2):19–33.

McEwen BS. Central effects of stress hormones in health and disease: understanding the protective and damaging effects of stress and stress mediators. *Eur J Pharmacol* (2008) 583(2–3):174–85. doi:10.1016/j.ejphar.2007.11.071

Alman S, Haeri S, Cohen LJ, Ten A, Barron E, Galynker II, et al. Predictors of relapse in bipolar disorder: a review. *J Psychiatr Pract* (2006) 12(5):269–82. doi:10.1097/00131746-200609000-00002

Horesh N, Aptar A, Zalsman G, Timing, quantity and quality of stressful life events in childhood and preceding the first episode of bipolar disorder. *J Affect Disord* (2011) 134(1–3):434–7. doi:10.1016/j.jad.2011.05.034

Lai MG, Huang LT. Effects of early life stress on neuroendocrine and neurobehavioral function and implications. *Pediatr Neonatol* (2011) 52(3):122–9. doi:10.1016/j.pedn.2011.03.008

Baker LM, Williams LM, Korgaonkar MS, Cohen RA, Heaps JM, Paul RH. Impact of early vs. late childhood early life stress on brain morphometrics. *Brain Imaging Behav* (2011) 5(2):196–203. doi:10.1007/s11682-012-9215-y

Lippe T, King AV, Riedschel M, Strohmaier J, Hemerici M, Gass A, et al. Increased medial orbitofrontal and amygdala activation: evidence for a systems-level endophenotype of bipolar I disorder. *Am J Psychiatry* (2012) 169(3):316–25. doi:10.1176/appi.ajp.2011.11050711

Koob GF, Buck CL, Cohen A, Edwards S, Park PE, Schlosburg JE, et al. Addiction as a stress surfeit disorder. *Neuropharmacology* (2014) 76(1–3):370–82. doi:10.1016/j.neuropharm.2013.05.024

Koob GF. Addiction: a reward deficit and stress surfeit disorder. *Front Psychiatry* (2013) 4:372. doi:10.3389/fpsyt.2013.00372

Koob G, Le Moal M, Koob GF. Allostasis and addiction: role of the dopamine and corticotropin-releasing factor systems. *Physiol Behav* (2012) 106(1–2):58–64. doi:10.1016/j.physbeh.2011.11.004

Koob G. Kreek MI. Stress, dysregulation of drug reward pathways, and the transition to drug dependence. *Am J Psychiatry* (2007) 164(8):1499–509. doi:10.1176/appi.ajp.2007.05053050

Pettorossi M, Martinotti G, Fasano A, Loria G, Di Nicola M, De Riso L, et al. Anhedonia in Parkinson’s disease patients with and without pathological gambling: a case-control study. *Psychiatry Res* (2014) 215(2):448–52. doi:10.1016/j.psychres.2013.12.013

Koob GF. Neurobiological substrates for the dark side of compulsive addiction. *Neuropharmacology* (2009) 56(Suppl 1):18–31. doi:10.1016/j.neuropharm.2008.07.004

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53. Gilpin NW. Brain reward and stress systems in addiction. *Front Psychiatry* (2014) 5:79. doi:10.3389/fspyt.2014.00079

54. Koob GF. A role for brain stress systems in addiction. *Neuron* (2008) 59(1):11–34. doi:10.1016/j.neuron.2008.06.012

55. Koob GF, Le Moal M. Addiction and the brain antireward system. *Annu Rev Psychol* (2008) 59:29–53. doi:10.1146/annurev.psych.59.103006.093548

56. Koob GF. Hedonic homeostatic dysregulation as a driver of drug-seeking behavior. *Drug Discov Today Dis Models* (2008) 5(4):207–15. doi:10.1016/j.ddmod.2009.04.002

57. Koob GF. Neuroadaptative mechanisms of addiction: studies on the extended amygdala. *Eur Neuropsychopharmacol* (2003) 13(6):442–52. doi:10.1016/j.euro.2003.08.005

58. Koob GF. The role of CRF and CRF-related peptides in the side effects of addiction. *Brain Res* (2010) 1314(3–4):14. doi:10.1016/j.brainres.2009.11.008

59. Martiretti G, Nicola MD, Reina D, Andreoli S, Pocà F, Cunniff A, et al. Alcohol protracted withdrawal syndrome: the role of anhedonia. *Subst Use Misuse* (2008) 43(3–4):271–84. doi:10.1080/10826080701202429

60. Valdez GR, Koob GF. Allotaxis and dysregulation of and neuropeptide Y systems: implications for the development of alcoholism. *Pharmacol Biochem Behav* (2004) 79(4):671–89. doi:10.1016/j.pbb.2004.09.020

61. Carmino N, Peralta JM, Almasy L, Contreras J, Pacheco A, Escamilla MA, et al. Shared genetic factors influence risk for bipolar disorder and alcohol use disorders. *Eur Psychiatry* (2014) 29(5):282–7. doi:10.1016/j.eurpsy.2013.10.001

62. Mandelli L, Mazzu M, Marangoni C, Di Nicola M, Martirini G, Tavani D, et al. Preliminary analysis of genes involved in inflammatory, oxidative processes and CA2+ signaling in bipolar disorder and comorbidity for substance use disorder. *Clin Neuropharmacol* (2011) 34(6):347–53.

63. Johnson C, Drgon T, McMahon FJ, Uhl GR. Convergent genome-wide association study for bipolar disorder suggests a role for anhedonia. *Bipolar Disord* (2009) 11:11–34. doi:10.1111/j.1399-5618.2009.00760.x

64. Petruzzo M, De Risio L, Martinotti G, Di Nicola M, Ruggieri F, Conte G, et al. Targeting the glutamatergic system to treat pathological gambling: current evidence and future perspectives. *Biomed Res Int* (2014) 2014:970986. doi:10.1155/2014/970986

65. Pettorossi M, Martirini G, Nicola D, Monofrì M, Di Giannantonio MC, Conte G, et al. Amantadine in the treatment of pathological gambling: a case report. *Front Psychiatry* (2012) 3:102. doi:10.3389/fspyt.2012.00102

66. Franceschi M, Petroni A, Burt C, Francioli P, Di Virgilio G, Persico A, et al. People with bipolar I disorder report avoiding rewarding activities and dampening positive emotion. *Bipolar Disord* (2013) 15(3):282–7. doi:10.1111/bip.12070

67. Haldane M, Frangou S. New insights help define the pathophysiology of bipolar disorder. *Am J Med Genet B Neuropsychiatr Genet* (2011) 155B(4):850–77. doi:10.1002/ajmg.b.31087

68. Wallis JD, Miller EK. Neuronal activity in primate dorsolateral and orbital prefrontal cortex during performance of a reward preference task. *J Neurosci* (2003) 18(7):2069–81. doi:10.1016/j.jnsc.2003.02.022.x

69. Younis A, Cetkovic M, Petroni A, Urquina H, Baer S, Gonzalez-Gadea ML, et al. The neural basis of decision-making and reward processing in adults with euthymic bipolar disorder or attention-deficit/hyperactivity disorder (ADHD). *PLoS One* (2012) 7(5):e37306. doi:10.1371/journal.pone.0037306

70. Strakowski SM, Fleck DE, DelBello MP, Adler CM, Shear PK, Kendler KS, et al. Impulsivity across the course of bipolar disorder. *Bipolar Disord* (2010) 12(3):285–97. doi:10.1111/j.1399-5618.2010.00806.x

71. Pizzagalli DA, Goetz E, Ostacher M, Iosifescu DV, Perlis RH. Euthymic patients averse to reward: neuropsychological evidence for competing addictions. *J Clin Psychiatry* (2007) 68(9):1352–7. doi:10.4088/JCP.06M0905

72. Ibanez A, Cvetkovich M, Petroni A, Urquina H, Baer S, Gonzalez-Gadea ML, et al. Neural correlates of decision-making and reward processing in euthymic bipolar disorder patients and healthy controls. *J Psychiatr Res* (2013) 47(8):1088–103. doi:10.1016/j.jpsychires.2013.06.003

73. Pettorossi M, Di Nicola M, Monofrì M, Onofrì M, Di Giannantonio MC, Conte G, et al. Targeting the glutamatergic system to treat pathological gambling: current evidence and future perspectives. *Biomed Res Int* (2014) 2014:970986. doi:10.1155/2014/970986

74. van Enkhuizen J, Henry BL, Minassian A, Perry W, Millegaard-Timot M, Higa K, et al. Reduced dopamine transporter functioning increases high-risk reward-prediction consistent with bipolar disorder. *Neuropsychopharmacology* (2014) 39(3):3112–22. doi:10.1038/npp.2014.170

75. Berk M, Dodd S, Kauer-Sant’anna M, Malhi GS, Bourin M, Kapczinski F, et al. Dopamine dysregulation syndrome: implications for a dopamine hypothesis of bipolar disorder. *Acta Psychiatr Scand Suppl* (2007) 434:41–9. doi:10.1111/j.1600-0447.2007.01058.x

76. Cousins DA, Butts K, Young AH. The role of dopamine in bipolar disorder. *Bipolar Disord* (2009) 11(6):787–806. doi:10.1111/j.1399-5618.2009.00760.x

77. Diana M. The dopamine hypothesis of drug addiction and its potential therapeutic value. *Front Psychiatry* (2011) 2:64. doi:10.3389/fspyt.2011.00064

78. Der-Avakian A, Markou A. The neurobiology of anhedonia and other reward-related deficits. *Trends Neurosci* (2012) 35(1):68–77. doi:10.1016/j.tins.2011.11.005

79. Hatrigkaioumou DS, Martirini G, Giannantonio MD, Janiri L. Anhedonia and substance dependence: clinical correlates and treatment options. *Front Psychiatry* (2011) 2:101. doi:10.3389/fspyt.2011.00100

80. Kirby LG, Zeeb FD, Winstanley CA. Contributions of serotonin in addiction vulnerability. *Neuropsychopharmacology* (2011) 61(3):421–32. doi:10.1038/neuro.2011.03.022

81. Van den Oever MC, Spiker S, Mith AB. The synaptic pathology of drug addiction. *Adv Exp Med Biol* (2012) 790:469–91. doi:10.1007/978-3-7091-0932-8_21

82. Pettorossi M, De Risio L, Martinotti G, Di Nicola M, Ruggieri F, Conte G, et al. Brain Imaging Epilepsy Patients with Bipolar Disorder: Preliminary Evidence for Imaging Change. *J Clin Psychiatry* (2007) 68:1352–7. doi:10.4088/JCP.06M0905

83. Petruzzo M, Martinotti G, Di Nicola M, Onofri M, Di Giannantonio MC, Conte G, et al. A New Neuroimaging Approach to Bipolar Disorder: Preliminary Evidence for Imaging Changes in Bipolar Disorder Patients. *J Clin Psychiatry* (2007) 68:1352–7. doi:10.4088/JCP.06M0905

84. Chandler RA, Wakeley J, Goodwin GM, Rogers RD. Altered risk-aversion and risk-seeking behavior in bipolar disorder. *Biol Psychiatry* (2009) 66:849–40. doi:10.1016/j.biopsych.2009.05.011

85. Mason L, O’Sullivan N, Blackburn M, Bentall R, El-Deredy W. I want it now! Waiting to win: elevated striatal and orbitofrontal cortical activity during reward anticipation in euthymic bipolar disorder adults. *Bipolar Disord* (2012) 14(5):249–60. doi:10.1111/j.1399-5618.2012.01012.x
94. Linke I, Sonnekes C, Wessa M. Sensitivity to positive and negative feedback in euthymic patients with bipolar I disorder: the last episode makes the difference. Bipolar Disord (2011) 13(7–8):638–50. doi:10.1111/j.1939-5618.2011.00956.x

95. Yechiam E, Hayden EP, Bodkins M, O’Donnell BL, Hetrick WP. Decision making in bipolar disorder: a cognitive modeling approach. Psychiatry Res (2008) 161(2):42–52. doi:10.1016/j.psychres.2007.07.001

96. Pizzagalli DA. Depression, stress, and anhedonia: toward a synthesis and integrated model. Am J Clin Psychol (2014) 18:393–422. doi:10.1097/01.ajcp.0000458715.28058.6b

97. Sinha R. Chronic stress, drug use, and vulnerability to addiction. Am J Acad Sci (2008) 1141:105–30. doi:10.1096/annals.1411.030

98. Lovallo WR. Cortisol secretion patterns in addiction and addiction risk. Int J Psychophysiol (2006) 59(3):195–202. doi:10.1016/j.ijpsycho.2005.10.007

99. Lijffijt M, Hu K, Swann AC. Stress modulates illness-course of substance use disorders: a translational review. Front Psychiatry (2014) 5:83. doi:10.3389/fpsyt.2014.00083

100. Levy YZ, Levy DJ, Barto AG, Meyer JS. A computational hypothesis for allostatic: delineation of substance dependence, conventional therapies, and alternative treatments. Front Psychiatry (2013) 4:1467. doi:10.3389/fpsyt.2013.00147

101. Post RM, Kalivas PM. Bipolar disorder and substance misuse: pathological and therapeutic implications of their comorbidity and cross-sensitisation. Br J Psychiatry (2013) 203(3):172–6. doi:10.1192/bjp.bp.112.116855

102. Azorin JM, Bellivier F, Kadajian A, Adida M, Belzeaux R, Fakra E, et al. Characteristics and profiles of bipolar I patients according to age-at-onset: findings from an admixture analysis. J Affect Disord (2013) 150(3):993–1000. doi:10.1016/j.jad.2013.05.026

103. Pope MA, Joher R, Mallia AK. Diagnostic stability of first-episode psychotic disorders and persistence of comorbid psychiatric disorders over 1 year. Can J Psychiatry (2013) 58(10):588–94.

104. Goldstein BI, Strober M, Axelsson D, Goldstein TR, Gill MK, Hower H, et al. Predictors of first-onset substance use disorders across the prospective course of bipolar spectrum disorders in adolescents. J Am Acad Child Adolesc Psychiatry (2013) 52(10):1026–37. doi:10.1016/j.jaac.2013.07.009

105. Kenneson A, Funderburk JS, Maisto SA. Risk factors for substance use disorders in people with childhood and adolescent-onset bipolar disorder: opportunities for prevention. Compr Psychiatry (2013) 54(5):439–46. doi:10.1016/j.comppsych.2012.12.008

106. Duffy A, Horrocks J, Milun R, Doucette S, Persson G, Grof P. Adolescent substance use disorder during the early stages of bipolar disorder: a prospective high-risk study. J Affect Disord (2012) 142(1–3):57–64. doi:10.1016/j.jad.2012.04.010

107. Do KE, Mezuk B. Comorbidity between hypomania and substance use disorders. J Affect Disord (2015) 155(3):974–80. doi:10.1016/j.jad.2015.05.023

108. Priscianardo J, De Santis SM, Chizzaro C, Brown DG, Brady KT, Tollever BK. Impact of depressive symptoms on future alcohol use in patients with co-occurring bipolar disorder and alcohol dependence: a prospective analysis in an 8-week randomized controlled trial of acamprosate. Alcohol Clin Exp Res (2012) 36(3):490–6. doi:10.1111/j.1530-0277.2011.01645.x

109. Saddichha S, Prakash R, Sinha BN, Khess CR. Perceived reasons for and continuity of substance abuse among patients with psychosis. Prim Care Compr Psychiatry (2013) 12(5):e1–7. doi:10.4088/PCC.09m00926gry

110. Pettinati HM, O’Brien CP, Dundon WD. Current status of co-occurring mood and substance use disorders: an exploratory study. J Affect Disord (2013) 144(3):279–83. doi:10.1016/j.jad.2012.10.008

111. Khantzian EJ. The self-medication hypothesis of addictive disorders: focus on alcohol dependence in major depressive disorder: a major depressive disorder. Eur Arch Psychiatry Clin Neurosci (2014) 264(5):391–400. doi:10.1007/s00406-013-0456-6

112. Prisciandaro JJ, DeSantis SM, Chiuzan C, Brown DG, Brady KT, Tolliver BK. Impact of depressive symptoms on future alcohol use in patients with co-occurring bipolar disorder and alcohol dependence: a prospective analysis in an 8-week randomized controlled trial of acamprosate. Alcohol Clin Exp Res (2012) 36(3):490–6. doi:10.1111/j.1530-0277.2011.01645.x

113. Blythe MC, Lowndes L, Pintor P, Le Foll B. The relationship between depression and substance use disorders: an exploratory study. J Affect Disord (2013) 144(3):279–83. doi:10.1016/j.jad.2012.10.008

114. Quello SB, Brady KT, Sonne SC. Mood disorders and substance use disorders: a complex comorbidity. Sci Pract Perspect (2005) 31:13–21. doi:10.1151/spp.05313

115. Kempton AM, Perrett ID, Kavanagh AM, Siddle J. The importance of early intervention for substance misuse in people with co-occurring substance use disorders: a qualitative study. J Affect Disord (2012) 138(3):314–9. doi:10.1016/j.jad.2012.05.010

116. Marston HM, Martin FD, Papp M, Gold L, Wong EH, Shahid M. Attenuation of chronic mild stress-induced ‘anhedonia’ by asenapine is not associated with place preference in a conditioned place preference assay. Neurosci Biobehav Rev (2013) 37(3):381–90. doi:10.1016/j.neubiorev.2013.02.003

117. Langas MA, Malt UF, Oijpoldsmao S. Independent versus substance-induced major depressive disorders in first-admission patients with substance use disorders: an exploratory study. J Affect Disord (2013) 144(3):279–83. doi:10.1016/j.jad.2012.10.008

118. Quello SB, Brady KT, Sonne SC. Mood disorders and substance use disorders: a complex comorbidity. Sci Pract Perspect (2005) 31:13–21. doi:10.1151/spp.05313

119. Le Foll B, Khess CR. Perceived reasons for and continuity of substance abuse among patients with psychosis. Prim Care Compr Psychiatry (2013) 12(5):e1–7. doi:10.4088/PCC.09m00926gry

120. Pettinati HM, O’Brien CP, Dundon WD. Current status of co-occurring mood and substance use disorders: a new therapeutic target. Am J Psychiatry (2013) 170(1):23–30. doi:10.1176/appi.ajp.2012.100112

121. Marchese G, Scheggia S, Secci ME, De Montis MG, Gabarbara C. Anhedonic activity of long-term lithium treatment in rats exposed to repeated unavoidable stress. Int J Neuropsychopharmacol (2013) 16(7):1617–21. doi:10.1017/S1465117213000354

122. Orsetti M, Canonicci PL, Dellarole A, Colella L, Di Bisio E, Ghi P. Quetiapine prevents anhedonia induced by acute or chronic stress. Neuropsychopharma- cology (2007) 32(8):1785–90. doi:10.1016/j.neuropharm.2007.04.008

123. Marston HM, Martin FD, Papp M, Gold L, Wong EH, Shahid MM. Attenuation of chronic mild stress-induced ‘anhedonia’ by asenapine is not associated with place preference in a conditioned place preference assay. J Neuropsychopharmacol (2011) 35(10):1388–98. doi:10.1038/jnnp.2011.107

124. Mazza M, Squillaciotti MR, Pecora RD, Janiari L, Bria P. Effect of aripiprazole on self-reported anhedonia in bipolar depressed patients. Psychiatriy Res (2009) 165(1–2):193–6. doi:10.1016/j.psychres.2008.05.003

125. Pettorriso et al. Allostasis, bipolar disorder, and addiction
135. Martinotti G, Andreoli S, Di Nicola M, Di Giannantonio M, Sarchiapone M, Janiri L. Quetiapine decreases alcohol consumption, craving, and psychiatric symptoms in dually diagnosed alcoholics. *Hum Psychopharmacol* (2008) 23(5):417–24. doi:10.1002/hup.944

136. Prisciandaro JJ, Brown DG, Brady KT, Tolliver BK. Comorbid anxiety disorders and baseline medication regimens predict clinical outcomes in individuals with co-occurring bipolar disorder and alcohol dependence: results of a randomized controlled trial. *Psychiatry Res* (2011) 188(3):361–5. doi:10.1016/j.psychres.2011.04.030

137. Di Nicola M, Martinotti G, Mazza M, Tedeschi D, Pozzi G, Janiri L. Quetiapine as add-on treatment for bipolar I disorder with comorbid compulsive buying and physical exercise addiction. *Prog Neuropsychopharmacol Biol Psychiatry* (2010) 34(4):713–4. doi:10.1016/j.pnpbp.2010.03.013

138. Janiri L, Martinotti G, Di Nicola M, Aripiprazole for relapse prevention and craving in alcohol-dependent subjects: results from a pilot study. *J Clin Psychopharmacol* (2007) 27(5):519–20. doi:10.1097/JCP.0b013e31815c841

139. Di Nicola M, De Risio L, Pettorruso M, Caselli G, De Crescenzo F, Swierkowsz-Lenart K, et al. Bipolar disorder and gambling disorder comorbidity: current evidence and implications for pharmacological treatment. *J Affect Disord* (2014) 167:285–98. doi:10.1016/j.jad.2014.06.023

140. Beaulieu S, Saury S, Sareen J, Tremblay J, Schütz CG, McIntyre RS, et al. The Canadian network for mood and anxiety treatments (CANMAT) task force recommendations for the management of patients with mood disorders and comorbid substance use disorders. *Ann Clin Psychiatry* (2012) 24(1):38–55.

141. Sani G, Kotzalidis GD, Vohringer P,ucci D, Simonetti A, Manfredi G, et al. Effectiveness of short-term olanzapine in patients with bipolar I disorder, with or without comorbidity with substance use disorder. *J Clin Psychopharmacol* (2013) 33(2):231–5. doi:10.1097/JCP.0b013e318287019c

142. Machado-Vieira R, Ibrahim L, Henter ID, Zarate CA Jr. Novel glutamatergic agents for major depressive disorder and bipolar disorder. *Pharmacol Biochem Behav* (2012) 100(4):678–87. doi:10.1016/j.pbb.2011.09.010

143. Olive MF, Cleva RM, Kalivas PW, Malcolm R. Glutamatergic medications for the treatment of drug and behavioral addictions. *Pharmacol Biochem Behav* (2012) 100(4):801–10. doi:10.1016/j.pbb.2011.04.015

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