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Review

Bipolar disorder and gambling disorder comorbidity: Current evidence and implications for pharmacological treatment

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ABSTRACT

Background: The co-occurrence of bipolar disorder (BD) and gambling disorder (GD), though of clinical and public health importance, is still scarcely investigated. Comorbid BD–GD subjects experience a more severe course of illness and poorer treatment outcome, due to a range of clinical and psychosocial factors that collectively impede remission and recovery. The aim of our paper is to review the role of pharmacotherapy in the treatment of comorbid BD–GD, in order to support clinical decisions according to the best available evidence.

Methods: A qualitative systematic review of studies on pharmacological treatment in comorbid BD–GD was performed. A comprehensive literature search of online databases, bibliographies of published articles and gray literature was conducted. Data on efficacy, safety and tolerability were extracted and levels of evidence were assessed. We also provide a brief overview of current epidemiological, neurobiological and clinical findings, with the intention of proposing a dimensional approach to the choice of available drugs.

Results: The only drug with a high level of evidence is lithium. Considering the inclusion of GD in DSM-5 'Substance-related and Addictive Disorders' category, we discuss the use of other drugs with a high level of evidence currently used in BD subjects with co-occurring substance use disorders.

Limitations: Only few clinical trials are available and the population is limited; therefore no conclusive evidence can be inferred.

Conclusions: Further randomized controlled trials are required to evaluate the efficacy of pharmacological treatment strategies in large samples of patients with comorbid BD–GD. Also, attempts should be made to identify other shared clinical and psychopathological domains that are amenable to treatment.

Contents

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1. Introduction

Bipolar disorder (BD) is a severe, often chronic condition with lifetime prevalence rates of up to 6.5% in the general population (Vornik and Brown, 2006). The co-occurrence of other psychiatric disorders in bipolar patients is associated with several indices of illness severity, a low probability of recovery as well as an unfavorable course and outcome (McIntyre et al., 2004). BD patients frequently report co-occurring substance use disorders (SUDs) and behavioral addictions (Di Nicola et al., 2010a; Pettorruso et al., 2014b), including gambling disorder (GD).

GD is characterized by persistent and maladaptive gambling behavior, whereby individuals engage in frequent and repeated episodes of gambling despite serious adverse consequences (Hodgins et al., 2011). GD affects 0.5–1% of adults worldwide; the consequences of this behavioral disturbance often entail severe damage to the lives of patients and their families (Kessler, 2008).

There is strong evidence suggesting that similar predispositions (genetic, environmental and social) influence the development and maintenance of GD and addictive disorders (Potenza, 2008). Also, like SUDs, GD presents the phenomena of tolerance, withdrawal and craving.

The DSM-5 included GD in the diagnostic category of 'Substance-related and Addictive Disorders' (APA, 2013). Pathophysiological models for drug addiction may therefore be relevant to GD as well and GD patients which may benefit from medication used to treat SUDs (Potenza, 2008).

The co-occurrence of BD and GD has important clinical implications. As in BD patients with co-occurring SUDs, BD–GD patients experience a more severe course of illness and poorer treatment outcome, due to a range of clinical and psychosocial factors that collectively impede remission and recovery (Mazza et al., 2009; Kennedy et al., 2010; Mandelli et al., 2012).

2. Epidemiology and risk factors for BD–GD comorbidity

To date, there are relatively few population-based epidemiological studies that report on the prevalence, and associated features, of GD in bipolar patients. With regard to GD sample studies, Lorains et al. (2011) found that GD patients have significantly more axis I disorders than controls, with higher rates of BD (12.6%). Prevalence of GD was significantly higher (6.3%) amongst BD subjects as compared to the general population (2.0%) and major depressed patients (2.5%) (McIntyre et al., 2007). The prevalence of GD in a large sample of individuals with a lifetime history of a mood disorder who were not seeking treatment for GD was 4–5% according to conservative criteria and 10–11% according to liberal criteria. Kennedy et al. (2010) report that liberal GD prevalence estimates are comparable to those obtained for individuals seeking treatment for BD (12.3%). Both conservative and liberal estimates are significantly higher than the estimates reported within the general population, thus indicating that individuals with BD are six times more likely to meet criteria for GD (Cox et al., 2005).

A significant difference in prevalence rates of BD–GD comorbidity was observed between males (19.5%) and females (7.8%) (Kennedy et al., 2010). Alcohol dependence, along with other SUDs, conferred the highest risk for GD in BD patients. BD patients who met criteria for GD had significantly higher levels of somatic anxiety and of clinician-rated depression (Kennedy et al., 2010). These findings have relevant implications for the recognition of BD subjects at a high risk of developing GD.

It has been suggested that mood and anxiety disorders often precede gambling problems (Petry et al., 2005; Kennedy et al., 2010). Also, a recent longitudinal, prospective study found that subjects who reported past-year disordered gambling were significantly more likely to have new onset of axis I psychiatric disorders, including mood disorders (Chou and Afifi, 2011). The relationship between GD and mood disorders is not, however, necessarily causal (Quilty et al., 2011). In pathological gamblers, the co-occurrence of other mental disorders increases the likelihood of treatment-seeking, though it may be the case that GD subjects are more likely to seek treatment for their comorbid disorders rather than for their gambling problems, which thus go undetected (Winters and Kushner, 2003). Opportunistic screening for GD is warranted, particularly in BD patients with comorbid alcohol or substance dependence.

3. Genetic

Familial and illness course characteristics of BD and addictive disorders, as well as shared or similar underlying mechanisms involving impulsivity, reward and behavioral sensitization, suggest potentially important genetic overlap (Swann, 2010; Mandelli et al., 2011). Despite high comorbidity rates between BD and GD, the literature lacks studies specifically investigating common genetic determinants, but preliminary findings hint at the existence of a shared genetic vulnerability for GD and SUDs (Uhl et al., 2008). Comparing data between bipolar and control samples, Johnson et al. (2009) 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 (semaphorin 5A, slit homolog 3, CUB, Sushi domains, neuron navigator 2, cadherin 13) (Johnson et al., 2009). A second group of genes is the family of clock genes, implicated in the regulation of behavioral and physiological periodicity (Swann, 2010).

4. Neuroimaging

Structural imaging studies in patients with comorbid BD–GD found volume reductions in both the dorsal and ventral prefrontal cortex (PFC), which are involved in encoding incentive information used to influence behavioral responses (Wallis and Miller, 2003;