

## Editorial

Bipolar disorder and addictions:  
the elephant in the room

Paul R. A. Stokes, Nicola J. Kalk and Allan H. Young

**Summary**

Addictions are highly prevalent in bipolar disorder and greatly affect clinical outcomes. In this editorial, we review the evidence that addictions are a key challenge in bipolar disorder, examine putative neurobiological mechanisms, and reflect on the limited clinical trial evidence base with suggestions for treatment strategies and further developments.

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give lectures and is on advisory boards for all major pharmaceutical companies with drugs used in affective and related disorders. He was the lead Investigator for Embolden Study (AstraZeneca), BCI Neuroplasticity study and Aripiprazole Mania Study. He has been involved in investigator initiated studies from AstraZeneca, Eli Lilly, Lundbeck and Wyeth. A.H.Y. has been awarded research grants from: National Institute of Mental Health (USA); Canadian Institutes of Health Research (Canada); National Association for Research on Schizophrenia And Depression (USA); Stanley Medical Research Institute (USA); Medical Research Council (UK); Wellcome Trust (UK); Royal College of Physicians (Edinburgh, UK); British Medical Association (UK); UBC-VGH Foundation (Canada); Western Economic Development Council (Canada); Coast Capital Savings Depression Research Fund (Canada); Michael Smith Foundation for Health Research (Canada); National Institute for Health Research (NIHR) (UK).

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Bipolar disorder is one of the most challenging mental health disorders to assess and treat and a key challenge is the very high rates of addiction comorbidities experienced by people with bipolar disorder. The increased prevalence of addictions in bipolar disorder is demonstrated by the recent United States National Epidemiologic Survey on Alcohol and Related Conditions which found that people with bipolar I disorder have a 5.8 times increased lifetime risk of a substance use disorder diagnosis according to DSM-V criteria. This risk was still 2.3 times increased even after adjusting for other psychiatric comorbidities.<sup>1</sup> Studies in the UK reflect the increased risk of addictions in bipolar disorder, with 48% and 44% of people with bipolar disorder experiencing a lifetime history of alcohol and substance misuse respectively.<sup>2</sup> Bipolar disorder has one of the highest rates of cigarette smoking of any mental health disorder and the lowest rate of smoking cessation.<sup>3</sup> Increased rates of behavioural addictions, such as gambling disorder,<sup>4</sup> have also been identified in bipolar disorder and approximately 1 in 10 people with bipolar disorder may have a moderate to severe lifetime risk of problem

gambling.<sup>4</sup> Addiction comorbidity in bipolar disorder is important as it greatly affects clinical outcomes. For example, addiction comorbidity in bipolar disorder is associated with more severe manic episodes, and increased risks of violence, suicide and relapse.<sup>5,6</sup> Despite their greater needs and increased risk, people with bipolar disorder and addiction comorbidity often struggle to access secondary mental health services.<sup>7</sup>

**Why are addictions so prevalent  
in bipolar disorder?**

The association between bipolar disorder and addictions raises the question: why are people with bipolar disorder at increased risk of addictions? There are several potential mechanisms. The first is that people with bipolar disorder 'self-medicate' with alcohol or drugs to alleviate mood episodes. However, only 25% of people with bipolar disorder increase their use of alcohol during a manic episode and most do not change their use during a depressive episode.<sup>8</sup> Indeed, people with bipolar disorder and addiction comorbidities are no different to people with substance use disorder in experiencing increased substance sensitivity or sensation seeking, and in using substances to achieve a sense of euphoria or to alleviate mood and anxiety symptoms irrespective of current mood episode. They also report similar motivations for substance use as the general population.<sup>9</sup>

The second potential mechanism is a shared neurobiology between bipolar disorder and addictions, which means that people with bipolar disorder are at risk of addictions. Indeed, the prospective Zurich cohort study showed that manic symptoms or a diagnosis of bipolar II disorder was associated with a greatly increased risk of developing alcohol or benzodiazepine dependence over 20 years.<sup>10</sup> Certainly there is evidence that young

men who report high rates of hypomanic symptoms, and may be at risk of developing bipolar disorder, experience similar low-level behavioural responses to alcohol as is found in those with a family history of alcohol dependence.<sup>11</sup>

Addiction comorbidities in bipolar disorder are likely to be mediated by the involvement of a number of neurotransmitter systems. Much of the focus of addiction research has been on the dopamine neurotransmitter system and it is likely that vulnerability to addictions in bipolar disorder may be mediated, at least in part, through dopaminergic dysregulation. However, the evidence for this is limited by a lack of studies of the dopamine system in people with bipolar disorder and addiction comorbidity.<sup>12</sup> Anxiety disorders are also highly prevalent in bipolar disorder and so there is also the possibility that people with bipolar disorder use alcohol or other substances to alleviate anxiety symptoms perhaps generated by gamma-aminobutyric acid-A receptor dysregulation previously reported in anxiety disorders.<sup>13</sup>

### Treatment approaches

How to do we best treat people with bipolar disorder and comorbid addictions? The first step is to ensure that comorbid addictions are adequately identified in people with bipolar disorder. National Institute for Health and Care Excellence guidelines recommend that all patients who disclose substance use are asked about quantity, frequency and pattern of use, route of administration and duration of current level of use.<sup>14</sup> It is also important to establish whether criteria for substance dependence are met as this will greatly influence clinical management.<sup>14</sup> We would suggest that a history of behavioural addictions such as gambling, sexual and shopping addictions is also taken. Frequent reassessment of substance use and behavioural addictions is recommended especially following a change in mental state.<sup>15</sup> Once addiction comorbidity has been identified, the intensity of intervention will depend on the severity of the problem identified and resources available locally, but joint working with expert addictions services is recommended to achieve the best outcomes.<sup>7</sup> It is important to note that addiction services are rarely commissioned to provide psychiatric care and so secondary care mental health services should lead treatment and people with bipolar disorder should not be excluded from these services because of addiction comorbidity.<sup>7</sup> Clinicians should also develop care plans that consider the potential for greater mood instability, higher risks of self-harm and poorer medication adherence found in people with bipolar disorder with addictions comorbidities.

### Pharmacological management

The pharmacological management of bipolar disorder with addiction comorbidities is complicated by a lack of good-quality, placebo-controlled, randomised control trials (RCTs). This may partly be due to pharmaceutical industry sponsored trials excluding people with bipolar disorder and comorbid addictions. The evidence that does exist is based on a relatively small number of RCTs which typically assess the effects of interventions in less than 30 participants over a 12-week period. Several RCTs have investigated the effects of mood stabilisers on substance use and mood scores. Although we are not aware of any studies that have examined the effect of lithium in people with bipolar disorder and alcohol dependence, a large multicentre trial of lithium in alcohol-dependent people with a history of depression found no improvement in alcohol consumption or mood scores.<sup>16</sup> Another study found that sodium valproate in addition to lithium

and psychosocial interventions improved alcohol consumption but not mood scores in people with bipolar disorder and alcohol dependence.<sup>17</sup> Turning to bipolar disorder with substance use disorder comorbidity, a large trial that compared the effectiveness of lithium and valproate compared with lithium alone failed due to lack of adherence and non-response to acute treatment.<sup>18</sup> Lamotrigine has been found to improve the amount spent on cocaine but not mood scores in people with bipolar disorder and cocaine dependence<sup>19</sup> and, in a small RCT, lithium has been found to be effective in reducing gambling behaviour and mood instability in pathological gamblers with bipolar disorder.<sup>20</sup>

There are surprisingly few studies of the effectiveness of antipsychotic medication in people with bipolar disorder and comorbid addictions. Those studies that are available have examined the effectiveness of adding quetiapine to mood stabilisers for alcohol use disorder comorbidity and have shown that it is largely ineffective in improving either alcohol consumption or mood measures.<sup>21,22</sup>

Two small pilot RCTs have investigated the effectiveness of adjunctive acamprosate or naltrexone in alcohol-dependent people with bipolar disorder. Neither found improvements in alcohol consumption or mood scores,<sup>23,24</sup> although naltrexone was associated at a trend significance level with fewer drinking days and lower craving scores, and both medications were safe, well-tolerated and did not destabilise mood. Naltrexone is recommended by the British Association for Psychopharmacology treatment guidelines to help people with bipolar disorder to reduce their alcohol consumption and acamprosate is then recommended if naltrexone has not been effective in supporting abstinence.<sup>15</sup>

### Limitations

There are several limitations which constrain our understanding of addiction comorbidity in bipolar disorder and how best to provide treatment. Most of the prevalence data originate from high-income countries, particularly the USA, and there is a real need for comorbidity prevalence data from low- and middle-income countries. Given the importance of addictions in bipolar disorder, there are also surprisingly few studies which have investigated neurobiological mechanisms which mediate addictions comorbidity. There have also been few well-powered RCTs which have investigated the effectiveness of pharmacological treatments for bipolar disorder with addiction comorbidity and the lack of an evidence base is a real challenge in determining best treatment practice.

### Conclusions

Addictions are highly prevalent in bipolar disorder and affect clinical outcomes and risk profiles. The reasons why people with bipolar disorder are at high risk of addiction remain unknown and require further investigation but may be mediated by shared neurobiological mechanisms. Treating addictions in bipolar disorder requires an inclusive, comprehensive approach which supports the identification of addiction comorbidity in bipolar disorder and the development of care plans to minimise risks. There is an urgent need for well-powered placebo-controlled RCTs in this area and, as addictions are so prevalent in bipolar disorder, we suggest that excluding people with bipolar disorder with a history of addictions from clinical trials significantly limits the generalisability of findings to the 'real life' bipolar disorder population.

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