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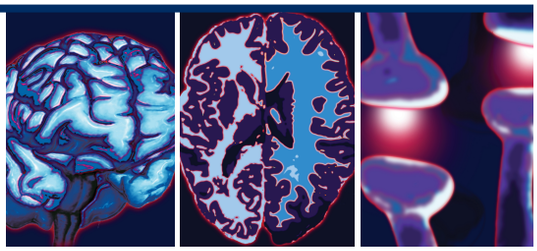

Comorbid addiction in bipolar affective disorder

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Practice points

- Bipolar disorder (BIPD) and addictive disorders (ADDs) are life-long, disabling conditions characterized by periods of remission and relapse.
- Comorbid addiction, including without substance, is found in up to 60% of bipolar subjects according to large epidemiological and clinical studies. BIPD and ADDs increase each other's prevalence and incidence.
- Comorbid BIPD and ADDs exhibit poorer outcomes and social functioning than both disorders considered separately. It also has unique sociodemographic and clinical features in terms of shortened life expectancy, partly due to much higher suicide rates and criminal involvement.
- These correlates are common across a wide range of ADDs, which highlights the interest of studying them as a whole.
- Clinicians should first rely on available guidelines about the respective disorders, although with some caution, as well as general recommendations and specific leads to treat comorbid BIPD and ADDs.
- Future research will need to include comorbid patients in clinical trials as well as experimental studies.

SUMMARY Bipolar disorder is a chronic, disabling, frequent and highly comorbid illness. It is often associated with addictive disorders (ADDs), another chronic and relapsing condition, with a lifetime prevalence three to five times higher than in the general population. However, knowledge is scarce about the possible mechanisms and the optimal treatment of this co-occurrence. Moreover, previous research has focused on separate ADDs, and few incidence data were available at the time. Our objective was, therefore, to evaluate the relevance of regrouping ADDs as classified in the preliminary version of the DSM-V in understanding the comorbidity of bipolar and ADDs. Using a comprehensive review of the existing literature, we report similar correlates across ADDs when comorbid with bipolar

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disorder and the theoretical implications of these findings are discussed. We also identified specific targets for new research in this field, which is urgent given the frequency of this comorbidity.

Bipolar disorder (BIPD) affects up to 4% of the general population, according to studies conducted in the USA [1]. It is a chronic mood disturbance condition characterized by episodes of manic, depressive or mixed polarity [2], with either successive switches or relapses after intervals of remission. Patients with BIPD spend half of their life with symptoms, the majority of which are due to depressive episodes and 15% to mixed or manic episodes (type I) [3]. Moreover, impairment remains during periods of remission due to neuropsychological disturbances in executive function, memory or attention, emotional hyper-reactivity [4,5], physical and psychiatric comorbidities, self-esteem deficits, suicidal ideation, and stigma [6]. Those characteristics have placed BIPD seventh in the WHO classification of disability causes [7], since an individual whose disorder begins at 25 years of age loses a mean of 9 years of life expectancy and 12 years of 'good health' [8].

BIPD is also a highly comorbid condition that is frequently associated with somatic and/or psychiatric disorders, especially anxiety and substance use disorders (SUDs) [6]. Interestingly, the latter share several characteristics with BIPD, including frequent comorbidity with other DSM-IV axis I disorders and a course consisting of relapses after periods of remission, often throughout the patient's lifespan [9], shortening life expectancy by an average of 14 years [10].

A review of studies published between 1970 and 2005 found that 34–60% of individuals with BIPD were affected by at least one SUD across their lifespan [6]. During the last decade, several review papers have been published addressing the issue of 'dual diagnosis' in BIPD; that is, its comorbidity or co-occurrence with SUDs. However, they focused either on illicit drugs and alcohol use disorders [11], nicotine use [12] or gambling disorders [13], thus leaving unexplored common or different aspects that may well be of relevance in managing and understanding BIPD and its comorbid conditions. Moreover, addictive disorders (ADDs) share many clinical and neurobiological characteristics [14,15] and are also highly co-occurring and interrelated [16,17]. Finally, individuals with BIPD have been found to use a wide range of drugs, according to clinical data [18], which prevents exclusion of any substance from study a *priori*. Therefore, in this review we chose to consider gambling disorder along with SUDs as they are regrouped in the revised classification of ADDs proposed in the preliminary version of DSM-V **(Box 1)** [101].

Of note, caffeine (for removal) and internet (for inclusion) use disorders are currently recommended for further study. To date, impulse control and eating disorders are classified in other sections of DSM-V.

Moreover, results from prospective data of the second waves of both the National Comorbidity Survey Replication (NCS-R) and the NESARC were not available at the time of previous reviews on dual diagnosis, yet they can bring new insight into the possible mechanisms or direction of the comorbidity.

Therefore, we performed a comprehensive review of the literature on comorbid BIPD and ADDs (BIPADD) with a twofold objective: review available data about the comorbidity between BIPD and ADDs considered as a whole and evaluate whether such a broad vision of addictive comorbidity is relevant in terms of epidemiology, course of illness and therapeutics, and how it may help us understand comorbid addiction in BIPD.

Our main hypothesis was that ADDs would be associated with similar correlates when co-occurring with BIPD.

Finally, although there are clinical and scientific reasons for systematically documenting subsyndromal hypomanic presentations in the assessment and diagnosis of mood disorders, we did not consider subthreshold bipolarity, which still raises important diagnostic and therapeutic challenges [19], especially in cases of concurrent substance use. To keep up with the notion of dual diagnosis, we did not consider nonpathological substance use or gambling, except for discussion purposes.

Epidemiology of comorbid BIPD & ADDs in the general population

The prevalence of comorbid addiction in BIPD has been estimated by several general population surveys mostly conducted in the USA **(Table 1)**. BIPD mainly occurred before the onset of all ADDs.

Incidence data

A study based on the second wave of the NCS study aimed at identifying mental disorders at risk for later SUDs [20]. The odds ratios for the 10-year incidence of SUDs for BIPD versus non-BIPD subjects estimated by multiple regression were 3.1 (95% CI: 1.9–5.1) for nicotine, 3.6 (95% CI: 1.1–11.4) for alcohol and 5.1 (95% CI: 1.8–14.7) for illicit drug dependence. Based on ages of onset recorded in the NCS-R, retrospective assessment of disorders' sequence of onset showed that BIPD predicted the onset of disordered gambling, which was 9.1-times (2.4–33.9) more frequent than in non-BIPD respondents [21]. Conversely, in the NESARC sample the incidence of SUD among baseline BIPD respondents was not significantly changed 3 years later at re-interview in the fully adjusted model, except for alcohol abuse (odds ratio = 2.8; 95% CI: 1.01–7.92) [22].

In the case of a first-occurring ADDs, data from the NESARC reassessment at 3 years found that BIPD incidence was 2.4-fold that of the general population (95% CI: 1.39–4.16) in those with baseline alcohol dependence [22], and that the incidence of mood disorders in general was 2.37-fold higher in pathological gamblers (95% CI: 1.03–5.48) [23]. Accordingly, BIPD incidence among individuals with non-medical prescription use was 2.61 (95% CI: 2.03–3.36; $p < 0.0001$) times higher than for nonusers [24].

Box 1. Substance use and addictive disorders in the proposed revision of the DSM classification.

- Alcohol-related disorders
- Caffeine-related disorders
- Cannabis-related disorders
- Hallucinogen-related disorders
- Inhalant-related disorders
- Opioid-related disorders
- Sedative-/hypnotic-related disorders
- Stimulant-related disorders
- Tobacco-related disorders
- Unknown substance disorders
- Gambling disorders

The latter results are, however, limited by the rarity of sedative and opioid use at baseline in the NESARC sample.

Correlates of specific ADDs when associated with BIPD: available evidence

The main finding that could justify the use of a broad vision of addictive comorbidity in BIPD would be the high similarity of specific correlates of ADDs when associated with BIPD. These correlates are listed in **Table 2**. We separated them into different categories only for presentation purposes

Data for ADDs other than alcohol and tobacco use disorders were scarce, reflecting their respective prevalence. Of note are the

Table 1. Lifetime prevalence of bipolar disorder and addictive disorder, and their reciprocal odds ratios in US nationwide surveys.

Survey	Classification/ diagnostic tool	Sample size (n)	Age (years)	Lifetime prevalence of BIPD in the GP; % (SE)	Lifetime prevalence of ADDs in the GP; % (SE)	Lifetime prevalence of ADDs among BIPD respondents; % (SE)	Odds ratio of ADDs among BIPD respondents versus GP (95% CI)	Ref.
ECA	DSM III-R NIMH DIS-III-R	20,291	18+	1 (0.2)	Drug dependence among 18–44 year olds: 5.1	BIPD-I: Any SUD but nicotine: 60.7 (7.9) AUD: 46.2 (5.6) DUD: 40.7 (11.1)	Any SUD but nicotine: 6	[79]
NESARC	DSM IV-TR AUDADIS-IV	43,093	18+	3.3 (0.13)	AUD: 30.3 DUD: 10.3 (0.3) ND: 12.8 (0.8) GD: .42 (NA)	AUD: 58 (1.64) DUD: 37.5 (1.73) ND: 44.4 (1.92) GD: BIPD-I: 2.92 (0.61); BIPD-II: 0.85 (0.26)	AUD: 3.5 (3.0–4.1) DUD: 4.8 (4.1–5.6) ND: 3.4 (2.9–4.0) GD: BPID-I: 8.3 (3.8–17.7); BPID-II: 2.9 (0.9–7.1)	[76,80]
NCS-R	DSM IV-TR WMH CIDI	9282	18+	2.1 (0.2)	14.6 (0.6) GD: 0.6 (0.1)	Any SUD but nicotine: BPID-I: 60.3 (4.2); BPID-II: 40.4 (3.7) GD (all BPID): 17 (7.1)	Any SUD but nicotine: BPID-I: 8.8 (5.9–13.1); BPID-II: 3.9 (2.7–5.7) GD (all BPID): 4.6 (1.5–14.2)	[1,21]

ADD: Addictive disorder; AUD: Alcohol use disorder; AUDADIS-IV: Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV; BIPD: Bipolar disorder; DUD: Drug use disorder; ECA: Epidemiologic Catchment Area; GD: Gambling disorder; GP: General population; NCS-R: National Comorbidity Survey Replication; ND: Nicotine dependence; NESARC: National Epidemiologic Survey on Alcohol and Related Conditions; NIMH DIS-III-R: National Institute of Mental Health Diagnostic Interview Schedule, Version III, Revised; SE: Standard error; SUD: Substance use disorder; WMH CIDI: WHO's Composite International Diagnostic Interview.

Table 2. Correlates of comorbid addictive disorders in bipolar disorder.

Addictive disorder	Correlates in BIPADD vs BIPD subjects													
	Prevalence ratio in the general population	M:F ratio	BIPD subtype	Age at onset of BIPD	Psychiatric family history		Induced episodes	Reasons for use	Other psychiatric comorbidity	Treatment response	Episode severity	Mortality	Suicide attempts	Impulsivity	Ref.
					ADDs	BIPD									
Tobacco	↑	↑		↓					↑	↓	↑	↑	↑	↑	[12,71,81]
Sedative/hypnotic	↑	↑					D	SM	↑				↑		[82,83]
Alcohol use disorders	↑	↑	I > II			↓	D	SM, E	↑		↑	↑	↑	↑	[30,71,76,84–89]
Other Substance use disorders	↑	↑	I > II	↓	↑	↓	D, M, Mx	SM, E	↑	↓	↑	↑	↑	↑	[11,30,71,73,76,85,87,89]
Gambling	↑	↑			↑		D	E	↑					↑	[13,21]

Data were drawn from epidemiological and clinical studies. Blanks indicate that no specific data were available.
↑: Increase in BIPADD compared with BIPD; ↓: Decrease in BIPADD compared with BIPD; ADD: Addictive disorder; BIPADD: Comorbid bipolar disorder and addictive disorder; BIPD: Bipolar disorder; D: Depression; E: Euphoria; M: Mania; M:F: Male:female; Mx: Mixed; SM: Self-medication.

possible mood disturbances associated with the use of caffeine [25] and the relatively high rates of hallucinogen use in populations of BIPD patients [18,26]. Overall, the correlates of BIPADD were found to be consistent across the nine other categories of ADDs.

■ Additional & detailed data

BIPADD patients exhibit poorer psychosocial functioning than those without ADDs. Data from the STEP-BD trial showed that patients with BIPD who experience sustained remission from a SUD fared better than patients with a current SUD, but still worse than subjects with no history of SUD [27]. It seems that global functioning might better reflect the impact of SUDs on the course of BIPD than symptomatic status [28].

Cardiovascular diseases associated with metabolic syndrome [29] and smoking [12] are probably involved in the overall excessive mortality observed in BIPD patients with SUDs [30]. They could also cause excessive mortality in cases of comorbid BIPD and gambling disorder, with which they are very often associated; although this has not been addressed to date. In a specifically designed study, BIPD outpatients with a comorbid SUD (including smoking) had prevalence ratios for at least one medical disorder of 1.11 ($p = 0.003$ and 0.002, respectively) compared with those without a SUD [31].

BIPD has a balanced sex ratio in all general population surveys, whereas men are much more likely to suffer from ADDs than women, as found in the general population [16,32,33]. However, a clinical study including 267 BIPD outpatients [34] found that the odds ratios for alcohol dependence compared with the general population were 7.35 (95% CI: 3.32–16.26) for women and 2.77 (95% CI: 1.59–4.81) for men.

Finally, Comorbid SUDs are associated with more criminal arrests in cases of acute mania compared with noncomorbid BIPD subjects. The increase in risk was found to be greater for women than men [35].

■ Treatment issues

There is, to date, no official guideline for the treatment of BIPADD, partly because the condition is often an exclusion criterion in pharmacological trials for such patients. We found general recommendations for the treatment of comorbid ADDs with other psychiatric disorders (dual diagnosis). There is a consensus

on the need for integrated treatment of both disorders [36], especially targeted at therapeutic education and medication adherence, which is greatly impaired in BIPADD [37]. This can be achieved through concurrent treatment programs, possibly hospitalization [38], ideally by the same providers.

First, we will review strategies that have been specifically assessed in BIPADD. Second, we will review those available for ADDs that could also be of some interest in the BIPADD condition, with a focus on their expected effect on mood states.

Strategies specifically assessed in BIPADD

The Canadian Network for Mood and Anxiety Treatments association recently published a systematic review of available data on pharmacological and nonpharmacological options for comorbid mood disorders and SUDs [39]. The authors established four levels of evidence, depending on the number of randomized controlled trials (RCTs) available for a given strategy. These levels resulted in three levels of treatment choice based on the strength of available evidence, as well as study sample size, potential side effects and substance/medication interactions. The paucity of available evidence unfortunately prevented the authors from constructing a full decisional algorithm for treatment choice; therefore, they established recommendations rather than guidelines. Data were completed with evidence from the review by Vornik *et al.* [40] and other specific papers when necessary.

Among the few medications that have been specifically tested in BIPADD, divalproex was found to be effective for cannabis and cocaine use disorders associated with BIPD as an adjunctive medication to lithium on the basis of one double-blind RCT. Divalproex has also been shown to reduce cannabis use in a study designed for assessment in BIPADDs [41]. Adding naltrexone was suggested as the first-choice medication in bipolar patients with comorbid alcohol use disorder, with divalproex and disulfiram as a second-line option, and topiramate or gabapentin as a third choice.

The antipsychotics risperidone and quetiapine, as well as lamotrigine and citicoline, may be used as a second-choice option for cocaine and amphetamine dependence, alone or as an add-on therapy. Lamotrigine as an add-on therapy was supported by a recent RCT [42].

There was no other first- or second-choice treatment option and only one inconclusive study has assessed medication for polysubstance use in BIPD.

Strategies used in ADDs: potential harms & benefits in the case of comorbid BIPD

Agents used as mood stabilizers

Preliminary data (case report and open trials) have suggested that aripiprazole might be useful in comorbid patients with cocaine dependence [43].

Among the numerous GABAergic agents that have been tested in cocaine use disorders, topiramate has shown some efficacy in reducing craving in a subset of subjects in an open-label study [44].

Both lithium and valproate, but not topiramate, have been shown to be effective for non-BIPD pathological gamblers in single- and double-blind RCTs [45–47].

Finally, clozapine is sometimes used in treatment-resistant BIPD, and has shown reductions in SUDs [48] in that population as well as in schizophrenic patients.

Other agents

A very recent control trial of acamprosate in BIPADD failed to demonstrate superiority over placebo [49]. There is no reason for particular caution about its use among BIPD patients, except regarding digestive side effects in cases of concurrent lithium therapy.

Buprenorphine and methadone are the first-choice maintenance treatment for opioid dependence. Although little is known about their particular usefulness in cases of comorbid BIPD, they tend to regulate opiate-dependent patients' moods as well as reducing opiate use [50]. Pharmacokinetics interactions are seen with methadone if associated with carbamazepine, as well as most selective serotonin reuptake inhibitors and venlafaxine [51]. Such combinations warrant therapeutic drug monitoring to ensure safety and/or efficacy.

Baclofen has received growing interest for treating alcohol [52] and cocaine [53] use disorders. It should be used with great caution in the case of BIPD given the possible induction of depressive states at high doses, but also elevated mood at low regimens, especially as it did not demonstrate any superiority over placebo in controlled trials.

Pilot studies and preclinical data have shown that *N*-acetyl cysteine, which has

glutamate-regulating properties, might be a promising strategy in cocaine, nicotine and gambling disorders [54,55]. It was also efficient and well tolerated in significantly reducing cannabis use among adolescents in a recent RCT [56].

Finally, an important issue is the diagnosis and treatment of comorbid ADHD, frequently associated with BIPADD. Comorbid ADHD in BIPADD patients could be very difficult to diagnose. However, in these situations, methylphenidate is very likely to improve both ADHD (in particular with regard to residual symptom and relapse prevention) and the comorbid addiction, especially for psychostimulants including cocaine [13]. Caution is needed regarding the risk of medication abuse.

Available data for comorbid BIPD & nicotine dependence

A pilot study has specifically assessed nicotine dependence (ND) treatment with bupropion among five patients with stabilized BIPD, two of them receiving placebo [57]. Only one was still taking bupropion at the end of the trial. None of the bupropion-treated subjects experienced mood disturbance, with one who confirmed quitting at end point. Varenicline, another antidepressant-like compound approved for ND, should be used even more cautiously since several cases of varenicline-induced manic symptoms have been reported among BIPD patients [58], in addition to the US FDA warning about suicidality.

Other concerns are the 40% lower rates of successful treatment of ND in acutely depressed unipolar subjects and the risk of withdrawal-precipitated depression and/or suicidal thoughts [59]. However, an online survey on retrospective and current smoking outcomes for 685 BIPD subjects found that of the 13% who were 'ex-smokers', 46% had used specific medication and 54% reported no worsening of their mood symptoms when quitting [60]. No specific data were available regarding the methods they used. Nicotine replacement therapy has yet to be tested in subjects with comorbid BIPD and ND [12].

Psychosocial treatment

None of the psychosocial interventions reviewed in the paper by Beaulieu *et al.* could reach level one (meta-analysis or at least two RCTs) of evidence [39]. Cognitive behavioral therapy was not found superior to usual management, unless part of a more integrated therapy specifically designed for individuals with dual diagnosis [39], as designed by Weiss *et al.* [61]. More generally, assertive community therapy also seemed efficient in reducing substance use and mood disturbances in BIPADD patients. Motivational therapy, one of the bases of management of individuals with SUDs and contingency management, which has shown efficacy in stimulant use disorders, did not show evidence of better outcomes than usual care for BIPADD.

Psychological treatments, such as cognitive behavioral therapy and contingency management, have been shown to be very helpful in gambling disorder [62] and ND [12], but still have to be tested specifically in comorbid BIPD.

Conclusion

To our knowledge, this is the first review on comorbid addiction in BIPD that regarded ADDs as a whole, including ND and gambling disorder. With the most up-to-date data, we reported how prevalent BIPADD is and how associated ADDs worsen the course of BIPD. Moreover, BIPADD patients tend to poorly respond to available treatments, and no specific guideline is available to help improve this. Much evidence was found to support the study of ADDs as a whole in the situation of comorbidity with BIPD.

The epidemiological data gathered on BIPADD were overall convergent across different countries and samples from general and clinical populations. Assessment methodology of ADDs was good to excellent across the studies reviewed, except for benzodiazepine use disorders. Thus, the latter were categorized as 'non-medical' or 'excessive' use, which may reflect the difficulty of assessing these disorders [63]. Furthermore, results from epidemiological studies must be interpreted bearing in mind the limits of current diagnostic tools and criteria, and their use in the general population. Their sensitivity and specificity are not only low to average in the case of comorbid psychiatric disorders, especially ADDs, but also at the far ends of the BIPD severity range. This is particularly important given the higher severity, often unusual age of onset and multiple psychiatric comorbidities associated with BIPADD. Finally, several ADDs, such as heroin dependence or gambling disorder, are fairly rare in the general population [64], which can cause issues in statistical interpretation. Accordingly, laws and country-dependent regulations dramatically change the availability

of addictive substances, as well as the ability to gamble, thus introducing a confounding factor in the observed prevalence of ADDs, even though the willingness to use illegal substances might itself reflect a risk factor for ADDs.

As a result, data on sociodemographic or clinical correlates of some ADDs were scarce and even nationwide studies were unable to study relevant subgroups of individuals. This raises the issue of diagnostic tools when assessing complex comorbidity patterns, for which specific instruments such as the Psychiatric Research Interview for Substance and Mental Disorders might be more relevant. This may also explain discrepancies in the rates of BIPD observed in clinical samples of patients with illicit drug use disorders compared with the general population [26,65]. Accordingly, recent versus past history of ADDs could have differential effects on BIPD outcomes and subjects' recall abilities, thus introducing bias in prevalence measures. Finally, the interpretation of results from studies comparing BIPADD with noncomorbid subjects is also subject to caution given the superior drop-out rates observed in this population [66].

Unfortunately, no clear recommendation has emerged from therapeutic trials, apart from general advice about the need for integrated care and the use of potentially effective or at least nonharmful medications. If a poorer response to usual mood stabilizers in BIPADD patients seems to be established, we found some discrepancies regarding the natural course of BIPD in cases of ADDs. In this context, it is surprising that lithium was helpful in several comorbid conditions; however, although it may simply be the most extensively studied yet. Potential confounding factors in treatment response might also be the low medication adherence of patients with ADDs, which is very often found in studies on BIPD [37], and the reduction in the plasma levels of several antipsychotics [67] associated with tobacco smoking.

Clinicians should be aware of the epidemiological and clinical characteristics when assessing ADD patients, in which mood disorders are particularly hard to identify. There is indeed a substantial risk of missing BIPD by attributing mood symptoms to the effects of a substance, or to its withdrawal. However, overdiagnosis is also possible given the high affective instability caused by a substance and its associated conditions such as polysubstance use, full-syndrome addiction, as well as other psychiatric comorbidities. This might be particularly true for stimulant use or gambling disorders. For example, a study that used retrospective chart review showed that only a third of the 85 diagnoses of BIPD among cocaine users were confirmed [68]. Such patients' clinical presentations are often atypical and justify thorough assessment of mood symptoms and addictive behaviors in order to carefully detect BIPDs, for example, using timeline follow-back methods. Another key issue might be to prevent ADDs in youth recently diagnosed with BIPD, who are often already using addictive substances [69]. Knowing that SUDs seem to be persistent, even when a comorbid psychiatric disorder is remitted [70], treatment of BIPD before the development of addictive comorbidity is essential in adolescents and young adults.

Overall, BIPD exhibits a wide and unique set of addictive comorbidity with quite similar correlates, very different from that of major depressive or anxiety disorders. In turn, ADDs seem to constitute a specific entity to study in BIPD when looking at epidemiological (prevalence ratios and rates, and life expectancy), neuropsychological (impulsivity [71]) and neurobiological (sensitivity to reward [72]) data available for both disorders. BIPD has a higher prevalence of SUDs than any other psychiatric illness [11]. Anxiety disorders, the other most commonly observed comorbidity in BIPD [6], do not share the same number of plausible common pathways, but their association with addictive [11,13] and medical [31] comorbidity in BIPD warrants further investigation.

The distinction between primary and secondary development of ADDs in BIPD may matter in terms of pathophysiology or illness course, knowing that ADDs usually begin after BIPD onset [6,21]. In a thoroughly selected clinical sample of BIPD patients assessed after their first hospitalization, comorbid alcohol or cannabis use disorders appeared to worsen the course of BIPD only if they occurred after the onset of the mood disorder [73]. Using NCS-R data, Glantz *et al.* demonstrated that SUD incidence was not changed after treatment of a prior mental disorder, using statistical projections where such treatment would always result in 100% success [70]. These results weaken the 'self-medication' theory commonly hypothesized as an explanation for the high rates of comorbid SUDs in psychiatric disorders. The pathophysiology of BIPADD seems to rely upon a complex genetic and environmental vulnerability and there is

a growing body of evidence for shared genetic [74] and neuropsychological profiles [75] in both ADDs and BIPD. Moreover, vulnerability to stress and emotional dysregulation seem to offer plausible pathways to explain both high rates of comorbidity and the impact of ADDs on the course of BIPD (and *vice versa*), as well as the particular comorbidity observed in epidemiological and clinical studies between BIPADD and anxiety disorders, which might independently increase SUD incidence in BIPD patients, as well as personality disorders from DSM-IV cluster B, known as 'emotionally labile' [76]. Enhanced emotional reactivity in BIPADD versus BIPD patients was suggested clinically in the retrospective chart review of 335 outpatients with BIPD by Manwani *et al.*, who reported that antidepressant-induced (hypo)mania was 5.06-times (95% CI: 1.31–19.64; $p < 0.05$) more likely in cases with a history of SUD [77]. A history of SUD might also increase direct switches from depression to elevated mood states without antidepressant therapy [78].

Given the complexity of addressing mechanisms underlying the comorbidity of BIPD and ADDs, it is highly probable that different explanations combine differentially over the lifetime of BIPD patients, partly depending on their mood state or the dominant polarity of their disorder. Since ADDs and BIPD increase the likelihood of developing the other disorder when one is present, they probably share a large amount of vulnerability. That shared vulnerability is probably partly innate, but seems to be enhanced by stressors such as substance use or other environmental adversity. Thus, the holistic view of addictive comorbidity patterns that was used in this review may help in understanding the trajectory of comorbid BIPADD patients, with different consumptions being able to trigger others (e.g., gambling and alcohol), therefore, leading to the onset of a new disorder, which in turn enhances the subject's vulnerability.

Future perspective

Research on comorbid addiction in BIPD has gathered enough data to now focus on specific aspects. From available data, researchers need to focus more specifically on nicotine and prescription drug use disorders, gambling disorder, neuropsychological endophenotypes and treatment issues, especially the correlates of response to usual mood stabilizers, such as lithium in BIPADD, or their ability to prevent development of ADDs in noncomorbid patients, notably in the young. To do so, studies will need to compare BIPADD subjects to those with only one disorder, thereby stopping to consider comorbidity as an exclusion criterion and trying to assess ADDs as a whole. Future studies may also investigate patterns of BIPD associated with specific drugs (alcohol, psychostimulants, opiates and polyconsumption).

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