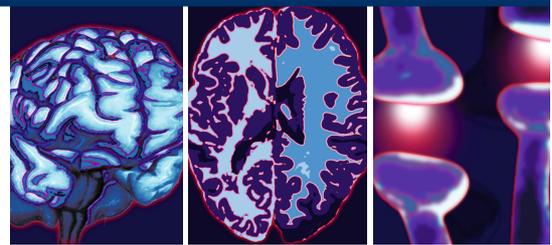


REVIEW



Effects of smoking on health outcomes in bipolar disorder with a special focus on suicidal behavior

Peter Dome*¹, Xenia Gonda¹ & Zoltan Rihmer^{1,2}

Practice points

- The prevalence of smoking is disproportionately high among patients with bipolar disorder (BPD).
- The life expectancy for patients with BPD is decreased in a significant manner compared with individuals from the general population.
- Several results from the general population provide support for the idea that smoking is not only one of the main risk factors for cardiovascular disorders, but is also associated with suicidal behavior.
- Findings from studies investigating the association between smoking and suicidal behavior in patients with BPD are ambiguous.
- The effects of smoking cessation on the course of BPD are almost unknown, however, it seems unlikely that quitting would be associated with the deterioration of symptoms. In addition, beneficial consequences of quitting smoking for physical health are well known. Taking these two premises, promoting smoking cessation is recommended to patients with BPD. Unfortunately, investigations on the safety and efficacy of first-line smoking cessation medications are lacking in this population.

SUMMARY Bipolar disorder (BPD) is a common and devastating mental illness. The life expectancy for patients with BPD is significantly less than for members of the general population. The main causes for excess mortality in bipolar patients are cardiovascular disorders and, to a lesser degree, suicide. Smoking/nicotine dependence is a highly comorbid condition in patients with BPD and it has a well-known role in the etiopathogenesis of cardiovascular disorders and, according to results from the general population, is associated with elevated risk of suicidal behavior. In this literature review, the results of studies on the abovementioned associations and also the effects of comorbid smoking on clinical characteristics of BPD are summarized, with a special focus on suicidal behavior. To identify peer-reviewed research papers and reviews, databases (PubMed and Web of Science) and forward/backward citation searches were used with the following keywords: 'smoking', 'tobacco', 'nicotine', 'suicide' and 'BPD'. Only publications in English were considered.

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Suicidal behavior in general & psychiatric populations

Suicide is the tenth leading cause of death worldwide and is responsible for 1.5% of all death cases; each year approximately 1 million suicide-related deaths occur in the global population [1,201]. In younger cohorts (15–44 years of age), suicide is among the three leading causes of death in some countries [201]. In the last 45 years, global suicide rates have increased by 60%. However, these data should be interpreted with caution owing to changes that occurred in data sources during this period (e.g., the perpetual increase in the number of countries that report their data on suicide rates to the WHO and, partially linked to this issue, the ‘formation’ of ‘new’ countries [e.g., the Baltic States – after the dissolution of the Soviet Union]) [1,2,201]. According to the increasing trend in suicides, 1.5 million suicide death cases per year is expected by the WHO for the year 2020 [3]. Another observable trend is the even more pronounced participation of young cohorts in suicide deaths (the proportion of suicide deaths in subjects aged 45 years and over was 60% in 1950 and only 45% in 2000) [3]. Suicide rates in different countries (regions) are highly different, which may be the consequence of diverse ethnic and sociocultural backgrounds and probably also derived from the between-country differences in the registration and (mis)classification of suicide death cases [1,3].

Suicide attempts – with a lifetime prevalence of 3–5% – are much more frequent than completed suicide. Accordingly, in the general population, suicide attempts are 10–40-times more common than completed suicides and the estimated number of attempted suicides per year is more than 20 million globally [3–6].

According to data from different countries, the lifetime prevalence of suicidal thoughts and wishes is much higher (2.1–25.4%) than prevalences of attempted or completed suicides in the general population [5–8].

It is well known that patients with psychiatric disorders are highly overrepresented among suicide completers, attempters and those individuals who have suicidal thoughts. Accordingly, patients with mood disorders, patients with schizophrenia and patients with alcohol and other substance-use disorders have a 13–26-, 8.5–10.0- and a six-times higher suicide risk than the general population, respectively [9]. Furthermore, replicated studies found that more than 90% of suicide attempters and completers

suffer from at least one, DSM-IV axis-I mental illness, most frequently (approximately 60%) from mood disorders (i.e., major depressive disorder [MDD] and bipolar disorder [BPD]) in high-income countries [10,11]. In low- and middle-income countries, the proportion of those who have a diagnosable psychiatric disorder among suicide completers is lower (60%) [12]. The role of affective disorders in the background of suicide is further supported by the fact that depression is an additional risk factor for suicide in patients with schizophrenia or alcohol-use disorder [9,13,14]. The suicide attempts per completed suicide rate is much lower among patients with major psychiatric disorders (e.g., MDD, BPD and schizophrenia) compared with the general population indicating that psychiatric patients choose more lethal/violent suicide methods [4,15,16].

The great majority (80%) of suicide completers are untreated at time of death and approximately 80% of these individuals have also had contact with the primary care physician within a year of their death [11]. In addition, about 25% of suicide completers commit suicide within 3 months after hospital discharge [9]. The above facts indicate that suicide prevention is possible and easily achievable.

However, since the majority of patients with axis-I psychiatric disorders never take their own lives and also never make an attempt, other suicidal risk factors (personality traits, such as impulsivity and hopelessness; comorbid axis-II disorders; cyclothymic and irritable affective temperaments; stressful life events and permanent adverse life situations) should also play a significant contributory role [9–11,14].

Suicidal thoughts are much more common in patients with major psychiatric disorders compared with members of the general population. Accordingly, suicidal thoughts occur in 79% of depressed phases of BPD and approximately 50% during the course of schizophrenia (25.5% in the prodromal phase of schizophrenia) [17–20]. Alcohol dependence is associated with a 4.6-fold greater risk of suicidal thoughts [21].

Life expectancy for patients with BPD

The life expectancy for patients with BPD is, at least, 10 years less than for individuals of the general population [22,23]. The excess mortality in BPD is attributable to both unnatural causes (suicide and accidental death cases) and general medical conditions (cerebro- and cardiovascular

disorders; respiratory and endocrine disorders). Among all causes of elevated mortality mentioned before, vascular disease is the leading cause [24–26]. Several behavioral factors strongly associated with BPD – for example, unhealthy diet and physical inactivity (both leading to obesity), tobacco smoking and noncompliance with cardiovascular medication – were put forward to explain the elevated cardiovascular mortality in this patient group. Poor access to optimal healthcare/services is also described and may contribute to the undertreatment of somatic disorders among patients with BPD [22,24,27,28]. It is also a possibility that adverse metabolic side effects (e.g., weight gain, dyslipidemia and insulin resistance) of several pharmacological agents for the treatment of BPD contribute to elevated cardiovascular mortality associated with BPD [22,24,26]. Furthermore, some somatic correlates of BPD (e.g., decreased heart rate variability, hypercortisolemia with concomitant insulin resistance and obesity) may also play a role in excess cardiovascular morbidity [29,30]. A third explanation is based on the ‘common root’ hypothesis, which assumes that certain factors (i.e., low levels/consumption of ω -3 fatty acids, inflammation and a common genetic background for the two disorders) may lead to concurrent cardiovascular disease and BPD [31–34].

In summary, cardiovascular mortality and suicide are responsible for the majority of excess death cases in BPD. It is well known that smoking is a paramount risk factor for cardiovascular morbidity and some results (see below) suggest that it is also associated with suicidal behavior.

Suicidal behavior in BPD

The lifetime prevalences of BPD I and II have generally been estimated at 1.0 (0–2.4%) and 1.1% (0.3–4.8%), respectively [35–38]. Similarly, recent studies draw attention to the relevance of episode(s) of subthreshold hypomania (without a consensual definition yet), which is highly frequent among patients whose diagnosis is (unipolar) MDD [39]. The relevance of subthreshold bipolarity in patients with MDD is multiplex. For instance, these patients had a younger age at disease onset, more frequent comorbidity with impulse control, anxiety and substance-use disorders and a higher risk of suicidal behavior compared with individuals with MDD alone. Furthermore, depressive episodes in these patients are less responsive to antidepressants,

and BPD is more frequent among their family members [22,39,40]. In addition, if we consider that approximately 40–50% of patients whose primary diagnosis is (unipolar) MDD, have a lifetime history of subthreshold hypomanic episodes and that several experts facilitate the inclusion of subthreshold hypomania in DSM-5, it is easy to conclude that the prevalence rates of disorders of the newly defined, bipolar spectrum (with the putative inclusion of subthreshold bipolarity) will rise, at the expense of MDD [4,39]. Accordingly, Angst *et al.* found that the lifetime prevalence for a ‘softly defined’ BPD II diagnosis (i.e., MDD with hypomania plus MDD with subthreshold hypomania) is above 8% [40].

There are somewhat conflicting results concerning the risks of completed suicides and suicide attempts when comparing patients with different types of major affective disorders (i.e., unipolar MDD, BPD I and II) [1,4,10,15,35,40–45]. Although some studies found that patients with MDD have a higher risk of suicidal behavior than those with BPD [4,42,46–48], other studies concluded that BPD confers a higher risk of suicidal behavior than MDD [4,15,40,43]. It is worth mentioning that criticisms regarding their methodology have been applied to some of the studies that found that MDD is a stronger risk factor for suicidal behavior than BPD. According to these critics, they overestimate the risk of unipolar depression and underestimate it for BPD [4,49]. The finding that patients with MDD and subthreshold hypomania have higher risks for suicide attempts than patients with MDD, but without subthreshold hypomania, also suggests that bipolarity – even if it is present to a subthreshold degree – confers an additional risk of suicidality over the risk associated with ‘pure’ MDD [40]. Regarding the comparison of suicide risk between BPD I and II, it is worth mentioning that the risk of suicide attempts is similar in these patient groups (or perhaps slightly higher in BPD I), but patients with BPD II more frequently choose highly violent methods; consequently, BPD II poses a higher risk of completed suicide than BPD I [15,35,40,41,45]. Despite the uncertainties regarding suicide risk between different subtypes of affective disorders discussed above, it is well established that patients with affective disorders, as a whole, have a markedly elevated risk of suicidal behavior compared with members of the general population, and even to subjects with other axis-I disorders (the latter observation is more pronounced in males)

[9,43,50–52]. Accordingly, the rate of completed suicide is 25–90-times higher among patients with BPD than the corresponding rate of the general population, and both the lifetime prevalences for suicide attempts (25–60%) and deaths (4–20%) highly exceed the same figures of the general population [4,41]. Several risk factors for suicidal behavior were identified in patients with BPD, such as Caucasian ethnicity, current depression or mixed episode depression, being unmarried, comorbid substance-use disorders and rapid cycling. However, with regards to some of these factors, results are not entirely unambiguous [4,53–56]. On the other hand, adequate therapy for BPD may have protective effects against elevated suicidality [4,57,58].

Associations between smoking & suicidal behavior in the general population

Several studies with different methodological approaches (prospective, retrospective, cross-sectional, individual-based and ecologic) have investigated the association of smoking with the risk of different forms of suicidal behavior (thoughts, attempts and completed suicide) in the general population [59].

Three individual-based prospective studies with large samples (50,000 US men, 300,000 US army male personnel and 121,700 nurses) showed that smoking is associated with the elevated risk of completed suicide [60–62]. Some sociodemographic factors (but not the presence of depression or a previous suicide attempt – two major risk factors for suicide) were adjusted in two of these investigations [60,61]; the third study was not controlled for any possible confounding variable [62]. A large-scale prospective study also found a positive association between baseline smoking and completed suicide after adjusting for some confounders (i.e., alcohol-drinking habits, living with spouse, self-reported stress and physical activity) in a sample of Japanese men, however, the study did not control for psychiatric diagnoses [63]. Results of a recent cohort study in a sample representing the adult southern German general population confirmed the positive association between smoking and completed suicide (but the only confounding variable included in the analyses was alcohol consumption). Furthermore, results also suggest an additive interaction effect between smoking and drinking on completed suicide (namely the biggest increase in suicide risk was observable among smokers with risky alcohol use) [64].

Bronisch *et al.*, in their longitudinal study (with a 4-year follow-up period), investigated the temporal relationship between smoking and suicidality in a randomly chosen sample of adolescents and young adult residents of Munich [65]. The authors found that nicotine dependence at baseline was strongly associated with previous suicide thoughts and suicide attempts [65]. During the follow-up period, increased risks for the new onset of suicide thoughts and/or attempts – even after controlling for DSM-IV-based mood disorders – were positively associated with prior occasional and regular smoking. By contrast, pre-existing suicidal thoughts or attempts (assessed at baseline) were not associated with an elevated risk of the first onset of smoking during the follow-up period [65]. Similarly, Breslau *et al.* also reported that the association between smoking and increased risk of suicidality is present even after adjustment for psychiatric disorders [66]. In their longitudinal study conducted in a general population sample, the positive association between current daily cigarette smoking, but not past daily smoking, and increased risk of subsequent suicidal thoughts or attempts held, even when potential confounders (i.e., prior suicidal behavior, current or past major depression and current or past substance abuse) were taken into consideration [66]. Tanskanen *et al.* found, by analyzing follow-up data of an adult sample chosen randomly from the Finnish population register, that there is a dose-dependent association between smoking and elevated risk of completed suicide, even after adjusting for several confounding factors, including symptoms of depressed mood and anxiety [67]. By using data of the northern Finland 1966 Birth Cohort Study (an unselected general population birth cohort), Riala *et al.* found, after controlling for psychiatric disorders and sociodemographic factors, that smoking is associated with suicide attempts [68]. A recent cross-sectional study by Yaworski *et al.*, using data of the National Epidemiological Survey on Alcohol and Related Conditions with a representative sample to the noninstitutionalized adult US population, found that nicotine dependence is associated with suicide attempts, independent of a wide range of psychiatric disorders and sociodemographic factors, as well as physical disease; however, an important limitation of this study is that results are confined to a nicotine-dependent population, which does not unequivocally correspond to the smoker population [69].

At the same time, in contradiction with some of the above results [65–69], a few studies found that while smoking is associated with a higher risk of suicide, after introducing new confounding variables (e.g., mental disorders, ‘low emotional control’ or low levels of parental attachment) into the statistical analysis or using more sophisticated statistical methods in the processing of data, the positive association between smoking and suicidal behavior vanished [70–73].

The majority of studies found a dose-dependent association between cigarette smoking and suicidal behavior; suicidal behavior was more frequent among heavy smokers than among light smokers [60,61,63,65,67,70,72,74–76].

Several studies found that the association between smoking and suicide risk is different between genders. However, results are contradictory: some of them suggest that the association is stronger among males [74,76,77], while others suggest that the association is stronger among females [68,78].

Intriguingly, the results of the few postmortem studies investigating the association between nicotine consumption and suicide are in partial contradiction, both to the above results and with each other. Accordingly, Launiainen *et al.* found in a young adult sample that the proportion of those who died by suicide in the nicotine user group did not significantly differ from the proportion of suicide completers in the nicotine nonuser group [79]. Similarly, Moriya *et al.* found that among suicide completers the proportion of smokers is larger than the proportion of smokers in the nonsuicide group [80]. Furthermore, they found that levels of nicotine and cotinine in the blood and urine were higher among smokers who committed suicide compared with smokers who died of nonsuicide-related causes. Accordingly, a psychological autopsy study with a sample of suicide completers and a control group matched for age, gender and general practice also found that current smoking is associated with an elevated risk of suicide [81].

Possible explanations for the positive association between smoking & suicidal behavior

Hereinafter, possible etiological links that may explain the positive association between smoking and suicide are discussed. As mentioned in the section ‘Suicidal behavior in general & psychiatric populations’ the majority of suicide victims and attempters suffered from mood

disorders (mainly an episode of major depression) [10]. Accordingly, during the discussion below MDD will be considered as a ‘proxy’ for suicide.

There are at least three different explanations for the positive association that is consistently found between smoking and suicidal behavior [82]. The ‘common cause’ hypothesis suggests that smoking is a noncausal marker of an elevated risk of suicidal behavior (i.e., both smoking and suicidal behavior have common risk factors [e.g., mental disorders] or both smoking and mental disorders have common [e.g., genetic] roots) [82,83]. In concordance with this hypothesis, high levels of impulsivity, which is more frequent among smokers than among nonsmokers and also associated with decreased success of quitting, is a well-known risk factor for suicidal behavior. However, it should be noted that it is not entirely clear whether impulsivity is a risk factor for smoking initiation or maintenance, or the opposite is true, or both [1,9,84,85]. The ‘mediation’ hypothesis states that smoking is a physical/psychological toxin that first leads to mental disorders and subsequently to an elevated risk of suicide. This theory is supported by epidemiological studies that report that smoking at baseline is associated with an elevated risk of onset of depression [59,86–90]. In addition, a recent study demonstrated that an early onset of smoking is associated with a shorter time interval between the onset of smoking and the onset of affective/anxiety disorders, which suggests – in accordance with results of animal studies – that the neurotoxic effects of nicotine is more pronounced in the developing nervous system [91]. One version of the mediation theory postulates that smoking leads to physical illness(es) and then these physical disorder(s) increases the risk of suicide. Interestingly, subjects suffering from some kind of pulmonary disease (i.e., bronchial asthma and chronic obstructive pulmonary disease) have an increased risk of affective and anxiety disorders [59]. While tobacco smoking elevates the risk of development and/or negatively influences the course of these disorders, the positive association between smoking and the risk of psychiatric disorders and suicide may also partially be explained by tobacco smoke-evoked lung damage. Another version of the mediation hypothesis is based on the recently recognized relationship between hypoxia and elevated suicide risk. As smoking leads to a decreased oxygen supply to the tissues, this may

partially explain its association with the elevated risk of suicide [92].

The 'self-medication' hypothesis views smoking as a form of self-medication in the case of an already existing mental disorder (which is a risk factor for suicide) [59,82,93]. This theory is underpinned by epidemiological studies that report that MDD (and other mood disorders) confers an elevated risk of the initiation/progression of smoking or for smoking relapse in abstinent former smokers [59,89,94–99], and by neuropharmacological studies that found that both the agonists (e.g., nicotine) and the antagonists (e.g., mecamylamine) of nicotinic acetylcholine receptors have antidepressant effects. In addition, in line with the self-medication theory, cigarette smoke contains ingredients with monoamine oxidase inhibitor activity (it is well known, monoamine oxidase inhibitors have antidepressant effects) [59].

The self-medication hypothesis is strongly weakened (and, consequently, the mediation hypothesis is strengthened) by two facts. First, although some previous investigations found that smoking cessation confers an elevated risk of the initiation of a major depressive episode (for discussion of these studies, see the 'Introduction' section of Torres *et al.* [100]) and does not alter the risk of suicidal behavior [101], several recent studies have demonstrated that the risk of suicidal behavior and/or the severity of depressive symptoms after smoking cessation are lower – or at least not higher – than before cessation (i.e., former smokers have a decreased risk of suicidal behavior and/or have milder depressive symptoms than current smokers) [60,63,66,69,75,87,90,93,100,102–110]. Although, results discussed above suggest that smoking cessation is associated with a decreased suicide risk in the long term, tribute should be paid to the lively debate on the possible suicide/depression provoking effects of some cessation agents – mainly varenicline and less for bupropion [111]. In addition, Shahab and West found – in consonance with the above view – that levels of self-reported life satisfaction/enjoyment are lower in current smokers than in former smokers (who abstained from smoking for at least a year) [112]. Second, four recent studies demonstrated that regular exposure of nonsmoking individuals to second-hand smoke is associated with an elevated risk of depression/psychological distress. This suggests that cigarette smoke has depressive rather than antidepressant effects [113–116].

Smoking & its association with suicidal behavior in unselected psychiatric patients

The smoking rates of patient groups suffering from various psychiatric disorders (e.g., schizophrenia or schizoaffective disorder, affective disorders, substance-use disorders and ADHD) are significantly higher than the smoking rates of the general population. Only a few psychiatric disorders, such as obsessive–compulsive disorder, the catatonic subtype of schizophrenia and autism spectrum disorders, are associated with lower rates of smoking than the corresponding rate in the general population [59,117,118]. Intriguingly, individuals with a lifetime history of 'subthreshold' psychiatric disorders (i.e., syndromes that only partially fulfill the DSM or International Classification of Diseases [ICD] diagnostic criteria of a given disorder) may have intermediate smoking prevalences between patients with DSM/ICD-based psychiatric diagnoses and those without history of any ('subthreshold' or DSM/ICD-based) psychiatric diagnoses [119]. A key finding of the National Epidemiological Survey on Alcohol and Related Conditions study is that 7.1% of the overall population, who have both a mental health disorder and are nicotine dependent, consume 34.2% of all cigarettes smoked in the USA. Furthermore, individuals with a current psychiatric disorder (with or without nicotine dependence) make up 30% of the population and consume 46% of all cigarettes smoked in the USA [120]. Moreover, large-scale studies (National Comorbidity Survey and National Health Interview Survey), with samples representative of the general population, uniformly found that the smoking rate among those individuals who have more than one psychiatric diagnosis is higher compared with those who have only one psychiatric diagnosis [117,118]. Furthermore, these studies also found lower smoking cessation rates among subjects with any psychiatric diagnosis when compared with the general population [117,118].

In addition to the results of the investigations discussed in the section 'Associations between smoking & suicidal behavior in the general population', which were conducted in nonclinical populations, the cross-sectional investigations by Malone *et al.* [121], Rihmer *et al.* [122] and Tanskanen *et al.* [123] showed that smoking is also associated with an elevated risk of suicide attempts in unselected adult psychiatric patient populations. This relationship was also observed

among unselected adolescent psychiatric patients [124,125]. Furthermore, a follow-up study among adolescents admitted with psychosis – with one of the following primary diagnoses: schizophrenia, schizoaffective disorder, affective disorders and substance abuse – found that smoking during the follow-up period was positively associated with suicide attempts [126].

Smoking & BPD

Large-scale studies with samples representative of the general population of the USA (National Comorbidity Survey and National Health Interview Survey) and Australia (Survey of Mental Health and Wellbeing) found that the current/lifetime smoking prevalences in patients with BPD are much higher and, accordingly, cessation rates are much lower than corresponding rates of the general population [28,117,118,127]. Furthermore, results of several studies from different countries conducted in clinical populations confirmed that the smoking rate of patients with BPD is much higher than that of the general population (for discussion of these studies see [28,59,128]). In addition, results of these studies, together with the findings of the abovementioned large-scale general population studies [117,118,127], also suggest that BPD is one of the axis-I disorders with the highest prevalence of smoking. Even if it is present in a subthreshold manner, bipolarity further increases the already elevated risk of smoking associated with ‘pure’ MDD [129].

The temporal sequence of the initiation of smoking and the onset of BPD is unclear: Gonzalez-Pinto *et al.* [130], Prochaska *et al.* [131] and Kreinin *et al.* [132] found that the onset of smoking precedes the onset of BPD in most cases, but the results of Goldstein *et al.* [133] did not confirm this result. Similarly, the majority [132,134–137], but not all studies [133,138] found that smoking is associated with an earlier onset of BPD.

There are also mixed results on whether or not smoking is associated with clinical features and the course of BPD. Accordingly, some investigators found that smoking is associated with rapid cycling, more (and more serious) affective episodes, elevated risk of psychotic episodes or more time spent in hospital, while others did not find such associations [28,59,132,133,136–140]. In this regard, the most uniform finding is that smoking is associated with an elevated risk of concomitant substance-use disorder(s) in patients with BPD [130,132–134,136–140].

According to the scarce data available, smoking cessation is not associated with the onset/worsening of symptoms of either depression or mania [28,139]. Patients with BPD wish to stop smoking at a similar rate (70%) to smokers of the general population [131]. However, to date, only two randomized, double-blind, placebo-controlled pilot studies (with remarkably low numbers of recruited subjects; $n = 5$ in both studies) evaluated the efficacy/safety of first-line cessation aid medications (bupropion and varenicline) in BPD [141]. Furthermore, several case reports described that varenicline treatment may provoke mania in subjects with or without a history of mood disorders [142–146]. In addition, it is also a possibility that the other first-line cessation agent, bupropion – primarily an antidepressant – may provoke (hypo)mania in patients with BPD [28,128].

The exact mechanism(s) responsible for the unexpectedly high smoking rate in patients with BPD are still unclear, although several possible explanations have been raised [28,59,147,148].

Smoking & suicidal behavior in patients with BPD

Previously in sections ‘Suicidal behavior in BPD’ and ‘Smoking & BPD’, the astonishingly high risk of suicidal behavior, as well as elevated smoking rates associated with mood disorders in general and with BPD in particular have been discussed. The question arises whether smoking is associated with suicidal behavior in the population of patients with BPD, similar to the situation observed in the general population (discussed in section ‘Associations between smoking & suicidal behavior in the general population’). Hereinafter, the results of studies that have dealt with this issue are discussed.

Galfalvy *et al.* investigated patients with BPD admitted due to a depressive episode in a follow-up study [149]. At the time of admission the proportion of smokers was higher in subjects with a past history of suicide attempts than in subjects without a past history of suicide attempts (50 and 40.7%, respectively); however, the difference did not reach a level of significance. Furthermore, smoking was not a significant predictor of suicide attempts during the 2-year follow-up period [149]. Smoking was also not associated with a history of suicide attempts in another study [55]. In a prospective study with a 2-year follow-up, Marangell *et al.* demonstrated that the proportion of smokers was higher in

subjects who attempted or completed suicide over the follow-up period compared with those who did not (40.4 vs 29.6%) [150]. However, in the final regression model, smoking was not a significant predictor of suicidal behavior [150]. Another study with an 18-month follow-up period also found that smoking did not predict suicide attempts among patients with BPD [151]. Similarly, Oquendo *et al.* reported that the smoking rate of inpatients with BPD with a history of suicide attempts, did not differ significantly from those who had no history of suicide attempts (76 vs 50%; $p = 0.16$) [152]. Neither smoking at baseline nor smoking during the follow-up period were associated with suicide attempts in a prospective study of first-episode patients with BPD I (median follow-up: 122 weeks) [139]. However, Neves *et al.* found a significantly higher frequency of smoking in BPD patients with a history of suicide attempts compared with those without a history of suicide attempts (63 vs 43%) [153], although smoking was not proven to be an independent risk factor for suicidal behavior according to the results of the regression model. Similarly, Slama *et al.* found that the proportion of smokers was significantly higher in BPD patients with a history of suicide attempts compared with those without a history of suicide attempts (73.6 vs 60.3%), but in the final regression model, smoking was no longer associated with suicide attempts [154]. Dodd *et al.* did not find a significant difference in suicidal behavior between daily smokers and nonsmokers in a sample of patients with either BPD or bipolar-type schizoaffective disorder [140]. In addition, Kreinin *et al.* also concluded that there is no association between smoking and suicide attempts in patients with BPD [132].

In contrast with the above findings, several studies reported that smoking is associated with an elevated risk of suicidality in patients with BPD. For instance, in a cross-sectional study Waxmonsky *et al.* found that patients who had a history of attempted suicide were 1.8-times more likely to be smokers [134]. Another cross-sectional study demonstrated that smoking may be independently associated with a history of suicide attempts, and this association is stronger among heavy smokers than in nonheavy smokers [133]. In a retrospective study, Ostacher *et al.* also found that a lifetime history of smoking was significantly related to elevated rates of previous suicide attempts, even after adjusting for some

potential confounders. Later, the same research group confirmed this finding in a prospective study [135,137]. A study by Baethge *et al.* found that smokers were almost twice as likely to exhibit suicidal behaviors as nonsmokers (27.5 vs 15.6%) [136]. In addition, results of their multiple logistic regression model suggest that smoking is independently associated with elevated risk of suicidality [136].

Conclusion & future perspective

The prevalence of smoking in patients with BPD is remarkably higher than corresponding rates in the general population and in patients with other axis-I psychiatric disorders.

However, while the great majority of studies found that smoking is (independently) associated with an elevated risk of suicidal behavior in the general population, results on this association among patients with BPD are far from clear. Several possible factors may account for this discrepancy. For example, sample sizes for studies conducted in the general population are typically much larger than those conducted in patients with BPD. Accordingly, it is possible that studies in clinical samples are unable to detect the small effect of smoking on suicide risk in a statistically significant manner.

Although the effect of smoking on the different clinical features (including suicidal behavior) and the course of BPD are not yet entirely known, according to the scarce data available, smoking cessation is not associated with onset/worsening of symptoms of either depression or mania. Considering this and the beneficial effects of smoking cessation on general (somatic) health, it is clear that it is highly recommended to promote smoking cessation in patients with BPD. The lack of investigations on efficacy and safety of first-line medications for smoking cessation in this patient population is the main obstacle to evidence-based pharmacologically supported smoking cessation in patients with BPD.

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