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Prevalence of suicide attempts in bipolar disorder: a systematic review and meta-analysis of observational studies

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Abstract

Aims. Bipolar disorder (BD) is a severe psychiatric disorder associated with a high risk of suicide. This meta-analysis examined the prevalence of suicide attempts (SA) in patients with BD and its associated factors.

Methods. A systematic literature search was conducted in the PubMed, PsycINFO, EMBASE and Web of Science databases from their inception to 11 June 2018. The prevalence of SA in BD was synthesised using the random-effects model.

Results. The search identified 3451 articles of which 79 studies with 33 719 subjects met the study entry criteria. The lifetime prevalence of SA was 33.9% (95% CI 31.3–36.6%; $I^2 = 96.4\%$). Subgroup and meta-regression analyses revealed that the lifetime prevalence of SA was positively associated with female gender, BD-I, BD Not Otherwise Specified and rapid cycling BD subtypes, income level and geographic region.

Conclusion. This meta-analysis confirmed that SA is common in BD and identified a number of factors related to SA. Further efforts are necessary to facilitate the identification and prevention of SA in BD. Long-term use of mood stabilisers coupled with psycho-social interventions should be available to BD patients to reduce the risk of suicidal behaviour.

Introduction

Bipolar disorder (BD) is a mood disorder characterised by recurrent depressive and manic/hypomanic episodes (Goodwin and Jamison, 2007), with different subtypes, such as bipolar I (BD-I), bipolar II (BD-II) and BD Not Otherwise Specified (BD-NOS) (American Psychiatric Association, 2013). The lifetime prevalence of BD is estimated to be 2.4% worldwide (Merikangas *et al.*, 2011). Due to its complex and varying clinical presentations, BD is often misdiagnosed for other psychiatric disorders (Berk *et al.*, 2007), such as major depression (Perlis, 2005) and substance abuse disorder (Patel *et al.*, 2015), which results in poor treatment outcomes and increased risk of suicide (Rosa *et al.*, 2010).

Suicide attempt (SA) is an important predictor of completed suicide (Drake *et al.*, 1985; Harkavy-Friedman *et al.*, 1999; Kessler *et al.*, 2005). Compared to the general population, BD patients are at a higher risk of suicide (Nierenberg *et al.*, 2001; Plans *et al.*, 2019). A prospective study found that BD had the highest risk of suicide of all psychiatric diagnoses (Brown *et al.*, 2000). The risk of SA in BD is approximately 30-fold higher than that in the general population (Goodwin and Jamison, 2007), and approximately 0.9% of BD patients attempt suicide every year (Beyer and Weisler, 2016). Further, the combination of BD and history of SA is probably the strongest predictor of completed suicide (Antypa *et al.*, 2013). Approximately 30–50% of BD patients have a lifetime history of SA, of whom 15–20% eventually died by suicide (Baldessarini *et al.*, 2006; Gonda *et al.*, 2012). In a previous study, more lethal methods of SA and suicide were observed in BD patients than in the general population (Simon *et al.*, 2007). Thus, suicide and SA account for a considerable proportion of disease burden in BD (Angst, 2004).

A host of demographic and clinical factors are related to SA in BD, including female gender, single and divorced marital status, history of sexual abuse, younger age of onset, depressive phase, severe depressive symptoms, frequent hospitalisation for depression, BD-I subtype, rapid cycling, comorbid substance abuse and other psychiatric disorders, past history of SA

and suicide in first-degree relatives (Leverich *et al.*, 2003; Hawton *et al.*, 2005; Shabani *et al.*, 2013; Schaffer *et al.*, 2015a, 2015b; Bobo *et al.*, 2018). Epidemiological studies on the prevalence of SA in BD are fraught with methodological limitations resulting in inconsistent findings (Novick *et al.*, 2010; Latalova *et al.*, 2014; Tondo *et al.*, 2016). In previous reviews, relying on only one database (PsycINFO) (Novick *et al.*, 2010) or inclusion of randomised control trials with stringent entry criteria are just two examples of methodological shortcomings that limit the generalisability of the findings (Tondo *et al.*, 2016).

In order to inform health care policy and frontline mental health professionals in their attempt to reduce suicide risk, it is important to understand the patterns of SA and their related factors. In view of the large number of recently published epidemiological studies of SA in BD (Passos *et al.*, 2016; Baldessarini *et al.*, 2017; Bellivier *et al.*, 2017; Bezerra *et al.*, 2017; Cremaschi *et al.*, 2017; Kattimani *et al.*, 2017; Altamura *et al.*, 2018; Bobo *et al.*, 2018; Duko and Ayano, 2018), this systematic review and meta-analysis explored the prevalence of SA in BD and its associated factors. The main hypothesis of the study was that bipolar patients would have a significantly higher prevalence of SA compared to the general population. In order to make the sample more representative, only epidemiological studies were included in this meta-analysis.

Methods

Search strategy

This meta-analysis followed the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) and MOOSE recommendations (Stroup *et al.*, 2000). The registration number of this protocol in the International Prospective Register of Systematic Reviews (PROSPERO) is CRD42018108290. Two authors (MD and LL) searched the PubMed, PsycINFO, EMBASE and Web of Science databases from their inception through 11 June 2018 using the following search terms: attempted suicide, suicide attempt*, bipolar disorder, manic-depressive disorder, affective disorder, mood disorder, bipolar depression, bipolar affective, hypomania, mania, manic, epidemiology, cross-sectional study, cohort study, observational study, prevalence, rate, percentage, proportion. References of review papers were also searched to identify additional articles. Figure 1 displays the process of the selection of studies for the meta-analysis.

Study selection

Two authors (MD and LL) independently screened the title and abstract of relevant studies and then read their full text for eligibility. Inclusion criteria were: (1) BD diagnosed according to any international or local diagnostic criteria; (2) available meta-analysable data on SA with one or more of the following timeframes: lifetime, 1-year, 1-month, current episode and from illness onset; (3) cross-sectional or cohort studies (only baseline data of cohort studies were analysed); (4) publication in English. Studies were excluded if they (1) were intervention studies or reviews; (2) had very small sample size ($n < 100$) (Walker *et al.*, 2013; Matte *et al.*, 2016) or special populations, such as adolescent or elderly samples; (3) were registry-based studies or extracted data from medical records. If multiple papers were published based on the same dataset, only the study with the largest sample size was analysed. Several papers (such as Carballo *et al.*,

2008; Elizabeth Sublette *et al.*, 2009; Studart *et al.*, 2016) reported overlapping data with the included studies. The corresponding authors were contacted for clarification, but since no reply was received, therefore these studies were excluded. Any uncertainty in the literature search and study selection was resolved by a discussion with a senior researcher (YTX).

Data extraction and quality assessment

Demographic and clinical data were extracted from the included studies covering the first author, publication year, time of survey, study site, sampling method, study design, sample size, mean age, proportion of males, diagnostic criteria of BD, patient source, assessment and timeframe of SA. Data extraction was performed independently by two authors (MD and LL).

Study quality was assessed using the quality assessment instrument for epidemiological studies (Boyle, 1998; Loney *et al.*, 1998); which has the total score ranging from 1 (lowest quality) to 8 (highest quality) points. The eight domains of the instrument are: (1) Target population is clearly defined. (2) Probability or entire population sampling is used. (3) Response rate is $>70\%$. (4) Non-responders are clearly described. (5) Sample is representative of the target population. (6) Data collection methods are standardised. (7) Validated criteria are used to assess the presence of disease. (8) Estimates of prevalence are given with confidence intervals and detailed by subgroup (if applicable). Studies with a total score of 7–8 were considered as high quality, 4–6 as moderate quality and 0–3 as low quality (Yang *et al.*, 2016).

Statistical analysis

Data analyses were performed with the Comprehensive Meta-Analysis (CMA), Version 2.0 (Biostat Inc., Englewood, NJ, USA) and STATA, Version 12.0 (Stata Corporation, College Station, TX, USA). A random-effect model was applied to calculate the overall prevalence and its 95% confidence interval (95% CI). Heterogeneity between studies was assessed with the I^2 statistic. Sensitivity analysis was performed by excluding studies one by one to explore the impact of each study on the overall results. Publication bias was evaluated with funnel plots and the Begg regression asymmetry test. In order to examine the moderating effects caused by demographic and clinical variables on the results, subgroup analyses for categorical variables (rapid cycling, gender, source of patients, income level, region and study design) and meta-regression analyses for continuous variables (per cent of BD subtype, sample size, mean age, illness duration and age of onset) were performed. If the number of studies was <10 , subgroup analyses were conducted for continuous variables, using the median splitting method (Higgins and Green, 2008). All the tests were two-tailed, and $p < 0.05$ was considered significant.

Results

The search initially identified 3451 articles from the target databases and 12 additional articles from other sources (Fig. 1). Altogether, 79 studies covering 33 719 patients met study entry criteria (online Supplementary Table S1), including 58 cross-sectional and 21 cohort studies published between 1985 and 2018. Twenty, six and four studies employed consecutive, convenience and random sampling, respectively. In terms of diagnosis, 71 and four studies applied the DSM and Research Diagnostic

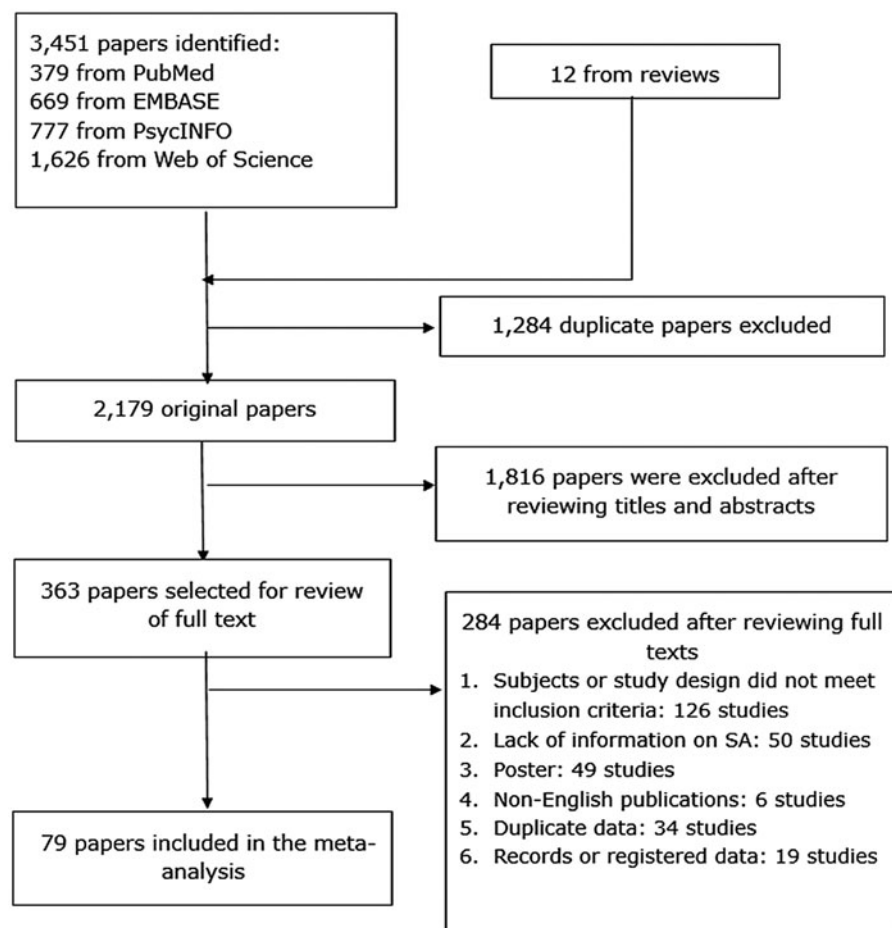


Fig. 1. Flowchart of study selection.

Criteria (RDC) (Spitzer *et al.*, 1978), respectively, and one study each used the ICD, the DSM or/and ICD, DSM or/and RDC, the Affective Disorder Evaluation (ADE) (Sachs *et al.*, 2003). The mean age of the whole sample ranged between 29.0 and 55.8 years, and then proportion of males ranged from 23.3 to 72.1%. Seventy-five of the 79 studies reported lifetime prevalence, three studies reported 1-year prevalence and three reported current episode prevalence of SA. The total score of quality assessment ranged from 4 to 8, with six studies rated as of high quality, and 73 studies as of moderate quality (online Supplementary Table S3).

Pooled prevalence of SA

The pooled lifetime prevalence of SA in BD was 33.9% (95% CI 31.3–36.6%; $I^2 = 96.4\%$), 1-year prevalence of SA was 15.0% (95% CI 8.2–21.8%; $I^2 = 85.5\%$) and current episode prevalence of SA was 32.5% (95% CI 20.1–44.8%; $I^2 = 94.6\%$) (Fig. 2). None of the included studies reported 1-month prevalence or prevalence from illness onset.

Sensitivity analysis and publication bias

When sensitivity analysis omitted each study one by one, there was no outlying study that could have significantly changed the lifetime prevalence of SA (online Supplementary Fig. S1). Neither the funnel plot nor Begg's test found significant

publication bias with respect to the lifetime prevalence of SA ($z = 0.76$, $p = 0.44$) (online Supplementary Fig. S2).

Subgroup and meta-regression analyses

The results of subgroup analyses are shown in Table 1. Gender, income level, rapid cycling and region were significantly associated with lifetime prevalence of SA, while study design was significantly associated with its 1-year prevalence. Specifically, the lifetime prevalence of SA in rapid cycling BD (47.0%) was significantly higher than in the non-rapid cycling subtype (30.2%) ($p < 0.001$). Female gender (34.4%) was significantly more prevalent than male gender (26.4%) ($p = 0.002$) in SA in BD. The prevalence of SA in high- (33.7%) and middle-income countries (34.7%) was significantly higher than in low-income countries (12.8%) ($p = 0.003$). The prevalence of SA was highest in the Americas (37.0%) and lowest in Africa (12.8%) ($p = 0.01$). The 1-year prevalence of SA reported in cohort studies (18.2%) was significantly higher than in cross-sectional studies (8.8%) ($p = 0.003$).

In meta-regression analyses, the proportions of BD-I ($B = 0.002$, $z = 3.9$, $p < 0.001$) and BD-NOS ($B = 0.01$, $z = 6.3$, $p < 0.001$) were positively, while sample size ($B = -0.00004$, $z = -3.5$, $p < 0.001$) and the proportion of BD-II ($B = -0.003$, $z = -4.9$, $p < 0.001$) were negatively associated with lifetime prevalence of SA. Mean age ($B = -0.004$, $z = -1.4$, $p = 0.13$), illness duration ($B = -0.004$, $z = -0.8$, $p = 0.40$) and age of onset ($B = -0.004$, $z = -0.7$, $p = 0.46$) were not significantly associated with lifetime prevalence of SA.

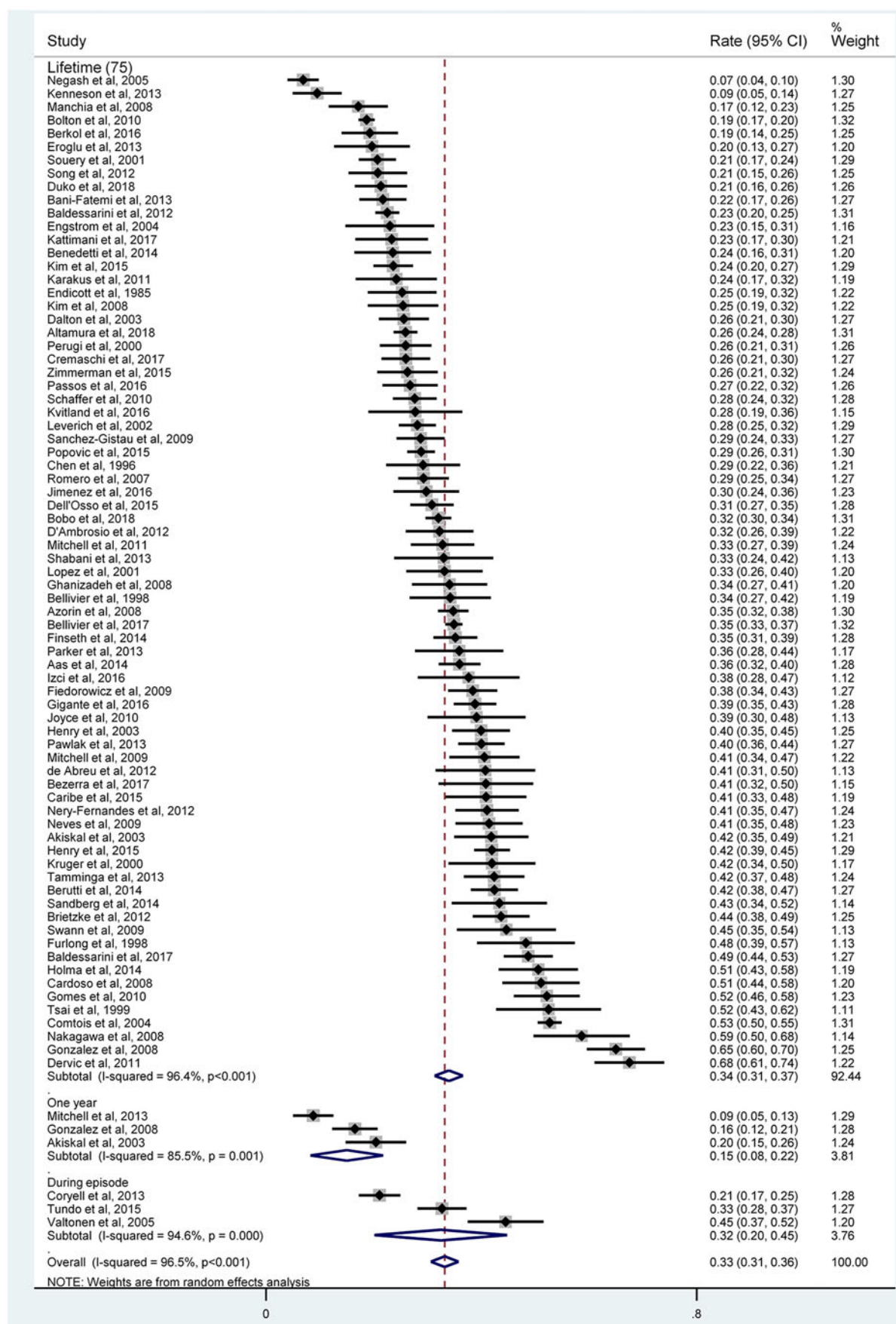


Fig. 2. Forest plot of suicide attempt.

Table 1. Subgroup analyses of SA prevalence in bipolar disorder

Subgroup	Categories (No. of studies)	Patients with SA	Total patients with BD	Prevalence (%)	95% CI (%)	<i>I</i> ² (%)	<i>p</i> values within subgroup ^a	<i>Q</i> (<i>p</i> values across subgroups) ^b
Lifetime prevalence of SA								
	Total (75)	10 790	32 477	33.9	31.3–36.6	96.4	<0.001	
RC/NRC	RC (9)	713	1668	47.0	40.7–53.4	72.9	<0.001	17.83 (<0.001)
	NRC (9)	1521	4900	30.2	25.9–34.9	86.9	<0.001	
Gender	Male (25)	1059	4022	26.4	23.1–30.0	80.1	<0.001	9.21 (0.002)
	Female (25)	1984	5462	34.4	30.7–38.2	83.3	<0.001	
Source of patients	Inpatient (9)	1989	4515	38.3	32.2–44.8	94.3	<0.001	2.08 (0.35)
	Outpatient (26)	2571	7542	33.0	29.6–36.6	91.7	<0.001	
	Mix (17)	2793	8435	34.1	29.9–38.6	89.6	<0.001	
Income	High (52)	8375	24 941	33.7	30.8–36.8	95.6	<0.001	11.61 (0.003)
	Middle (16)	1598	4744	34.7	29.4–40.5	93.3	<0.001	
	Low (2)	78	562	12.8	6.7–23.1	95.5	<0.001	
Region	Africa (2)	78	562	12.8	6.7–23.2	95.5	<0.001	14.56 (0.01)
	The Americas (24)	4317	12 207	37.0	32.4–41.7	97.5	<0.001	
	Eastern Mediterranean (2)	93	276	33.6	19.8–50.9	0	0.85	
	Europe (32)	4627	13 864	32.5	28.8–36.5	90.1	<0.001	
	South-East Asia (1)	35	150	23.3	9.9–45.8	–	–	
	Western Pacific (8)	519	1696	33.0	25.7–41.2	88.3	<0.001	
Study design	Cross-sectional (56)	6883	21 185	32.3	29.4–35.3	95.5	<0.001	1.63 (0.20)
	Cohort (19)	3826	11 292	36.1	31.1–41.6	94.6	<0.001	
One-year prevalence of SA								
	Total (3)	108	710	15.0	8.2–21.8	85.5	<0.001	
Sample size ^c	>217 (1)	49	297	16.5	4.9–42.8	–	–	0.067 (0.796)
	≤217 (2)	59	413	13.7	5.7–29.4	90.7	0.001	
Study design	Cross-sectional (1)	19	217	8.8	5.5–13.6	–	–	8.74 (0.003)
	Cohort (2)	89	493	18.2	14.7–22.3	17.7	0.27	
Prevalence of SA during episode								
	Total (3)	308	1025	32.5	20.1–44.8	94.6	<0.001	
Sample size ^c	<407 (1)	85	191	44.5	25.6–65.2	–	–	2.30 (0.129)
	≥407 (2)	223	834	26.5	16.7–39.3	92.9	<0.001	
Study design	Cross-sectional (1)	133	407	32.7	9.6–68.8	–	–	0.003 (0.95)
	Cohort (2)	175	618	31.6	13.6–57.5	97.0	<0.001	

BD, bipolar disorder; NOS, Not Otherwise Specified; NRC, non-rapid cycling; RC, rapid cycling; SA, suicide attempt.

^aTest of heterogeneity within subgroups.^bTest of prevalence of SA across subgroups.^cMedian splitting method was used.Bold values = $p < 0.05$.

Discussion

In this meta-analysis, the lifetime prevalence of SA in BD (33.9%; 95% CI 31.3–36.6%) was significantly higher than in the general population (0.8%; 95% CI 0.7–0.9%) (Bernal *et al.*, 2007; Cao

et al., 2015) and in schizophrenia (14.6%; 95% CI 9.1–22.8%), but was only slightly higher than the figures found in major depression (31%; 95% CI 27–34%) (Howe *et al.*, 2014; Dong *et al.*, 2017, 2018). The higher risk of SA in BD compared to major depression relates to the differences in clinical profile

between both disorders (Szadoczk *et al.*, 2000). Impulsivity, a trait of BD (Tondo and Baldessarini, 2005), is associated with both SA and suicide (Swann *et al.*, 2005). In addition, several key factors contributing to SA, e.g. mixed state and depressive phase, are part of BD (Oquendo *et al.*, 2000; Schaffer *et al.*, 2015a). However, the difference between BD and depression with regard to lifetime prevalence of SA did not reach a significant level (33.9%, 95% CI 31.3–36.6% *v.* 31%, 95% CI 27–34%) in a meta-analysis (Dong *et al.*, 2018). Another review of 24 studies (Novick *et al.*, 2010) reported the lifetime prevalence of SA (36.3% in BD-I and 32.4% in BD-II). However, in the Novick *et al.* review, only the PsycINFO database was searched yielding only 439 relevant hits and the prevalence estimates of SA in different timeframes were not reported. In contrast, the current meta-analysis more comprehensively covered the literature and examined the prevalence of SA in different timeframes. Novick *et al.* analysed randomised control trials with stringent entry criteria, which could lead to selection bias, while this meta-analysis included observational studies, thereby increasing the representativeness of the study sample. Furthermore, more sophisticated analyses including subgroup and sensitivity analyses were carried out in the present study.

The lifetime prevalence of SA was higher in females than in males, which is also found in previous studies (Tondo *et al.*, 2003, 2016). The possible reasons include relatively more frequent depressive episodes (Schneck *et al.*, 2004), rapid cycling BD (Cruz *et al.*, 2008) and history of childhood physical and sexual abuse (Stefanello *et al.*, 2008) in female patients. Male BD patients are more likely to resort to more lethal methods of suicide (Pompili *et al.*, 2009). Previous findings comparing the SA rate between BD-I and BD-II have been inconsistent. Higher SA rates in BD-I (Oquendo *et al.*, 2010; Antypa *et al.*, 2013; Bobo *et al.*, 2018) and in BD-II (Song *et al.*, 2012; Holma *et al.*, 2014) were reported, while other studies did not find significant differences between the two subtypes (Novick *et al.*, 2010; Tondo *et al.*, 2016). In the current meta-analysis, both BD-I and BD-NOS were positively associated while BD-II was negatively associated with lifetime prevalence of SA, which is similar to the findings of some (Angst *et al.*, 2005; Popovic *et al.*, 2015; Altamura *et al.*, 2018), but not all (Angst *et al.*, 2005; Neves *et al.*, 2009; Pawlak *et al.*, 2013) studies. The close association between the depressive phase and SA may be a reason for the diverse SA rates in different BD types (Schaffer *et al.*, 2015a). SA is more likely to occur during mixed states and depressive episodes in BD-I, and during depressive episodes in BD-II (Tondo *et al.*, 1999). Poorer insight and treatment adherence due to more frequent psychotic symptoms in BD-I (van der Werf-Elderling *et al.*, 2011; Depp *et al.*, 2014; Silva *et al.*, 2015) can lead to an increased risk of SA.

In the subgroup analyses, the lifetime rate of SA in rapid cycling BD (47.0%) was significantly higher than in non-rapid cycling BD (34.4%). Rapid cycling is a major risk factor of SA in BD (MacKinnon *et al.*, 2005), which is attributed to the younger age of onset, more illness severity, longer illness duration, poorer outcomes and higher risk of disability in rapid cycling BD (Kupka *et al.*, 2005; Mackin, 2005; Schneck *et al.*, 2008; Gigante *et al.*, 2016). The lifetime rate of SA was significantly higher in high- and middle-income countries compared to low-income countries, and also higher in the Americas, Western Pacific and Europe than in Africa and South-East Asia. The discrepancy in SA rate across regions could be partly due to differences in health care services, ethnicity, and economic and sociocultural factors (Westman *et al.*, 2003; Karch *et al.*, 2006). Westman *et al.* (2003) have found that

the place of birth and socioeconomic status were significantly associated with the risk of SA. The risk of suicide and associated factors were different between Caucasian and African Americans (Kung *et al.*, 1998). Studies of suicide in BD in low- and middle-income countries are few and far between, which can result in biased comparisons.

The sample size was negatively correlated to the lifetime prevalence of SA. Results of studies with small sample size are less reliable (Dong *et al.*, 2017). The higher 1-year prevalence of SA was found at baseline of cohort studies than in cross-sectional studies, while there was no group difference between lifetime and current episode prevalence between the two types of studies. Again, it is likely that the low number of cohort and cross-sectional studies resulted in unstable results.

The results of this meta-analysis should be interpreted with caution because of several methodological limitations. First, relevant factors related to SA, such as pharmacotherapy, comorbidities, illness severity and the actual mood state of BD, were not reported in most studies, hence their moderating effects on SA could not be explored. Second, publication bias of the 1-year and current episode prevalence of SA could not be assessed as the number of studies was <10 (Wan *et al.*, 2013). In addition, the pooled current episode and 1-year SA prevalence estimates and the SA-moderating effects of the region and low-income countries were examined in a small number of studies, therefore the findings are only preliminary. Third, most studies were conducted in the Americas and Europe, making the generalisability of findings limited. Fourth, although subgroup analyses have been performed, heterogeneity could not be avoided as it is a common pitfall in the meta-analysis of epidemiological studies (Winsper *et al.*, 2013; Long *et al.*, 2014; Rotenstein *et al.*, 2016). The heterogeneity in the current meta-analysis was probably due to the systematic differences between included studies, such as diverse study aims and inclusion/exclusion criteria. Fifth, there may be recall bias in the assessment of SA. Finally, the number of studies that reported data on the current episode and 1-year prevalence was less than those that examined lifetime prevalence that could have influenced the results to an uncertain degree.

In conclusion, the meta-analysis found that the prevalence of SA in BD is higher than the figures reported in schizophrenia and in the general population. Given the major impacts of SA on BD, more mental health resources should be allocated and effective measures should be undertaken to reduce the risk of SA in this population. Identifying the risk factors of SA (e.g. rapid cycling type and female gender as found in this study) and the long-term use of mood stabilisers coupled with psychosocial interventions could reduce the risk of suicidal behaviour (Rihmer, 2008), e.g. long-term treatment with lithium reduced SA by 10% and completed suicide by 20% (Benard *et al.*, 2016).

Supplementary material. The supplementary material for this article can be found at <https://doi.org/10.1017/S2045796019000593>.

Data. All the data supporting the findings of this meta-analysis have been provided in Tables, Figures and Supplemental Tables and Figures.

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Conflict of interest. None.

Ethical standards. N/A.

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