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Title: Risk factors of substance abuse in bipolar disorder: a systematic review and Meta-analysis

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By considering the debilitating outcome of co-occurrence of bipolar disorder (BPD) and substance abuse, determination of predictive factors of substance use disorders (SUD: abuse or dependence of drugs and/or alcohol) is essential to identify the susceptible patients. The main purpose of this study was to clarify the major predictive risk factors of SUD among adults with BPD by reviewing the relevant literature and using Meta-analysis. We systematically searched electronic databases including PubMed (MEDLINE), EMBASE, OVID, Cochrane, Google Scholar and Scopus for human studies addressing the co-existence of BPD and SUD. All potential published papers up to September 2016 have been reviewed. All the statistical analysis was performed using Comprehensive Meta-analysis version 2. Male gender, number of manic episodes and previous history of suicidality were predictors of SUD in bipolar patients. SUD was not predicted by age, subtype of BPD, hospitalization and co-existence of anxiety disorders or psychotic symptoms. SUD affects many aspects of BPD regarding clinical course, psychopathology, hospitalization, prognosis and treatment responsiveness. Our study demonstrates that male individuals with history of higher manic episodes and suicidality are more susceptible to SUD, thus assignment of more intensive therapeutic interventions to prevent development of SUD should be considered in these patients.

Comment: Exhaustive and much needed review of the literature focusing on risk factors for AUD alongside BD. Meta-analysis component is a methodological strength that makes these findings extremely relevant. I have a few comments regarding the description of the literature search and feedback on the conclusions. These changes will make the findings of this review more convincing and clinically relevant for a broader audience.

-you mentioned in your article that this is a systematic review and meta-analysis. It is not clear to me how you differentiated the two.

-it was mentioned that 2 authors of a meta-analysis abstracted information from studies independently. Please clarify if reviewers searched sources for articles relevant to the meta-analysis and if you calculated interrater reliability

-. It should also be stated whether the reviewers were blinded to the authors and institution of the studies undergoing review. The results from the data abstraction are compared only after completing the review of the articles. Please state any discrepancies between authors and how the discrepancies were resolved.

-Results should be collected only from separate sets of patients, and the authors should be careful to avoid studies that published the same subjects or overlapping groups of subjects that appeared in different studies under duplicate publications. Please mention if you performed this and if not why

-Raw numbers, in addition to risk ratios, should be recorded. Results from intention-to-treat analyses should be reported, when possible. The gold standard of data abstraction in a meta-analysis is to include patient level data from the studies combined in the meta-analysis, which usually requires contacting the authors of the original studies. Obtaining patient level data may reveal differences among the trials that otherwise would not have been detected.

-A quality score for each study included in a metaanalysis may be useful to ensure that better studies receive more weight. More than 20 instruments have been identified for the assessment for quality in both randomized clinical trials as well as meta-analyses of prospective cohort studies. Results can vary by the type of quality instrument, and a sensitivity analysis may need to be performed to determine the impact of the quality score on the results. As with data abstraction, two reviewers should score the quality of the studies using the same quality instrument, and results from the quality assessment should be compared. Agreement among the reviewers should be reported, and differences in quality scores should be reconciled through discussion.

-As with clinical trials, inclusion and exclusion criteria for the studies included in the meta-analysis need to be well defined and established beforehand. The rationale for choosing the criteria should be stated, as it may not be apparent to the reader. Inclusion criteria may be based on study design, sample size, and characteristics of the subject. The number of studies excluded from the meta-analysis and the reasons for the exclusions should also be provided. Please add a flowchart (e.g. PRISMA) addressing this.

-How did you handle missing data?

-How did you handle homogeneity, which is also referred to as the test for heterogeneity, to validate whether the studies were similar and appropriate (ie, homogenous) to combine. Alternatively, did the authors check if the studies included in the analysis for substantial differences among study designs or characteristics of subjects.

- Please provide a table outlining the features of each study, including the characteristics of subjects, study design, sample size, and intervention, including the dose and durations of any drugs. I am mentioning this because substantial differences in the study design or patient populations signify heterogeneity and suggest that the data from the studies should not have been combined.

-how did the authors address publication bias. E.g. did you contact well-known investigators in the field of interest to discover whether they have conducted a negative study that remains unpublished. Can you provide a funnel plot to visually represent the presence of a publication bias in the field.