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Review

Alcohol misuse in bipolar disorder. A systematic review and meta-analysis of comorbidity rates

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ABSTRACT

Aims: To assess the comorbidity rates of alcohol use disorders (AUDs) in bipolar disorder (BD) and to explore possible sources of heterogeneity.
Methods: Studies were identified through database searches. Meta-analytic techniques were employed to aggregate data on lifetime comorbidity and to explore possible sources of heterogeneity. Funnel plots were used to detect publication bias.
Results: In clinical studies, AUDs affected more than one in three subjects with BD. Significant heterogeneity was found, which was largely explained by the geographical location of study populations and gender ratio of participants. AUDs affected more than one in five women and two in five men.
Conclusion: AUDs are highly prevalent in BD. Our study revealed a substantial heterogeneity across studies. Further research including control groups is needed. Patients with BD should be assessed for current and previous AUDs.

1. Introduction

Comorbidity has important implications for both research and clinical practice [68]. Nevertheless, important issues about the definition and evaluation of comorbidity remain to be elucidated in psychiatric research [62,69].

From the classic phenomenological work of Emil Kraepelin [36] to contemporary epidemiological studies [50] the comorbidity between alcohol misuse and bipolar disorder (BD) has been reported. Of all DSM-IV axis I disorders, BD has been reported to be the most strongly linked with alcohol or drug abuse [25,41] and compared with other primary psychiatric disorders, mania and hypomania may have one of the highest associations with alcoholism [25,41].

Although considerable research has been devoted to characterizing the link between alcohol related disorders and BD, surprisingly, a preliminary search of MEDLINE, EMBASE and PsychINFO did provide no evidence of any published systematic reviews focusing on the comorbidity between the two disorders.

In this review, we explored the current state of knowledge on the rates of alcohol use disorders (AUDs) in people affected by BD. There are many definitions of alcohol related disorders. Here we included in the definition of AUDs problem drinking (alcohol abuse or harmful use) and addiction (alcoholism or alcohol dependence).

We tested the following hypotheses:

- AUDs are over-represented in people with BD compared to the general population;
- there is an effect of gender on the comorbidity between AUDs and BD, with men having higher comorbidity rates than women. Although it is a common observation in clinical practice that men with BD are over-represented among patients with AUDs comorbidity, evidence from both epidemiological and clinical studies are contrasting;
- methodological differences such as study design, geographical location of the population, diagnostic criteria and instruments of assessment have an effect on comorbidity rates reported in studies. The rates of AUDs in the general population are influenced by cultural [16] and genetic differences [65]. Moreover, diagnostic criteria and research protocol have been implicated as additional sources of variability [53].

2. Methods

Search strategy and reporting are in accordance with the recommendations of the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group [57].

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2.1. Search strategy

An electronic search was conducted in databases MEDLINE, EMBASE, PsychINFO by author A.D.F.

Keywords and Boolean operators employed (set by A.D.F., M.V.D.B. and N.C.) are listed in S1.

No language restrictions were applied to the search. Publications from 1978 to 2013 were retrieved.

The abstracts of the identified studies were independently screened for inclusion in the review by two investigators (A.D.F. and M.V.D.B.).

Bibliographies of eligible articles were checked for possible other relevant studies (ancestor search).

2.2. Inclusion criteria

Studies were selected for inclusion if they met the following criteria:

- disorders defined according to DSM or ICD and RDC criteria;
- for clinical studies, sample size greater than 50 individuals;
- at least 95% of the sample older than 18;
- study employed quantitative research methodology;
- participants not selected on the basis of comorbidity with AUDs (probabilistic sample);
- rates of AUDs in BD participants evaluated and reported;
- study based on original research.

2.3. Data extraction

Data were extracted from full-text articles, with the exception of a single conference abstract [8].

When a sample was reported in more than one paper, data were extracted from the article reporting the largest sample, or from all articles, in case they reported on different variables.

Information extracted from original publications is listed in S2. Geographical locations were classified according to:

- the continent where the study was conducted;
- total per capita consumption of pure alcohol, in litres, for the adult population, as reported by the World Health Organization [70];
- patterns of drinking score as calculated by the World Health Organization [70].

In this review, "comorbidity" was defined as the association between BD and AUDs within a given time frame and "co-occurrence" as the cross-sectional association between disorders – i.e. both traits assessed and present at the same time [69].

2.4. Data analyses

Data analyses were conducted using R version 2.13.0 (Copyright 2011 The R Foundation for Statistical Computing, Vienna, Austria).

Meta-analytic techniques were employed to aggregate data on lifetime comorbidity between AUDs and BD.

Firstly, the command "metaprop" was used to calculate the pooled estimates of proportions with the corresponding 95% confidence intervals on the base of the Freeman-Tukey double arcsine transformation. A fixed as well as a random effects model framework was used [21].

The association between gender and AUDs was also evaluated using DerSimonian-Laird estimate (R "metabin" command) for random effect models.

Heterogeneity of combined study results was assessed by Q test and inconsistency statistic (I^2). A P value below 0.10 in the Q test was considered indicative of statistically significant heterogeneity. Values of 25%, 50% and 75% were considered to represent respectively low, medium and high heterogeneity in the I^2 statistic [29]. Since significant heterogeneity was found across studies, only random effects estimates were reported.

Possible sources of heterogeneity were explored using univariate and multivariate random effects meta-regression (R "metafor" package) [64].

Models were fitted using the rma function. For the purpose of a reliable statistical analysis, Freeman-Tukey double arcsine transformed proportions were calculated as outcome measure.

The random-effects models were fitted using the restricted maximum-likelihood estimator and the empirical Bayes estimator.

The effects of the following independent covariates were tested: geographical location of the study, diagnostic tools, diagnostic criteria and sampling methods. Proportion of women and average age at the interview were not included in the model, to avoid "aggregation bias" (i.e., the relationship with patient averages between trials may not be the same as the relationship for patients within trial) [30]. Standard errors of the estimated coefficients were adjusted with the Knapp and Hartung method [35], to account for the uncertainty in the estimate of the amount of (residual) heterogeneity.

To evaluate publication bias, asymmetry in the funnel plots was tested with mixed-effects meta-regression model (R regtest command) using the standard error as the predictor [14].

3. Results

3.1. Search results

The flow chart of the search process is shown in Fig. 1. As a result of the electronic and ancestor researches, 57 research articles and one abstract [8], reporting on 46 original studies, were included in the systematic review. Except for one paper in French [59] and one paper in Flemish [63], all papers were in English.

Studies characteristics are summarised in Table 1.

3.2. Are alcohol use disorders over-represented in people suffering with bipolar disorder compared to the general population?

The majority of epidemiological studies calculated the strength of association with AUDs in BD compared to the general population (Table 2).

3.2.1. Epidemiological studies

Information was extracted from eight epidemiological studies, from ten published papers (table S3a).

Epidemiological studies conducted in Europe [41] and North America [50,25,34,17,20,26] univocally reported that the prevalence of AUDs was significantly increased among participants with BD, regardless the diagnostic criteria (i.e. DSM-III, DSM-III-R, DSM-IV) and the time window (i.e. current, lifetime, other – Table 2) employed. Results were heterogeneous when alcohol abuse (AA) and alcohol dependence (AD) were analysed separately. Only one study reported on the 12 month incidence of AUDs [26]. This study found no differences between BD and the general population and furthermore that participants with bipolar II disorder (BD-II) had a lower risk of AA compared to the general population. Kessler et al. [34] reported a similar finding for lifetime AA incidence in men with mania, despite the fact that this study used different definitions (lifetime prevalence) compared to Grant et al. [26] (12 months incidence) as well as different diagnostic criteria (DSM-III-R versus DSM-IV).