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BIPOLAR DISORDER AND ALCOHOL: DOUBLE TROUBLE OR JUST CO-OCCURRENCE?

Jan van Zaane

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INTRODUCTION AND OUTLINE OF THESIS

INTRODUCTION

Already in 1913, Emil Kraepelin, the well known German psychiatrist, wrote:

> *"Alkoholismus kommt bei männlichen Kranken in etwa ¼ der Fälle vor, ist aber als Folge der in der Erregung begegangenen Ausschweifungen, nicht als Ursache zu betrachten[1]"*
>
> *["Alcoholism occurs among male patients in about a quarter of the cases, but it is to be regarded as the consequence of debaucheries committed in excitement, not as a cause[2]"]*

Kraepelin was impressed by the negative effects of alcohol in patients and in the general population. In his opinion there was no mental illness that did not worsen by alcohol consumption.[3] However, as a moderate drinker he also noticed some positive effects on his own mood.[4] He wondered, therefore, if alcohol would be useful to improve mental health reason. After several months of abstinence he decided that there was no reason to use alcohol, other than improving one's mood.[3] Due to his observations on manic patients, his abstinence trial, and possibly the fact that his father had alcohol problems, he decided alcohol was not only bad for psychiatric patients but also for the general population. In 1895 he became a teetotaler to set an example for his fellow citizens.[3] He was a co-founder of the Society of Abstinent Physicians and joined the Society against the Misuse of Alcoholic Drinks.

Could Kraepelin's observation about the relationship between alcoholism and bipolar disorder (BD) have been biased by his "war on alcohol"? Possibly.

In any case, after his publication in 1913, it took more than sixty years before epidemiological studies proved him right by showing that patients with BD had a lifetime prevalence of about 50% of substance use disorders (SUD), including alcohol dependence.[5-9] Since then it became apparent that BD and SUD are "co-travelers".

EPIDEMIOLOGY

There have been several epidemiological and some clinical studies on the comorbidity of bipolar disorders and SUD (including alcohol use disorders [AUD]).

General population studies

In the US Epidemiologic Catchment Area Study[5] in the early 1980s (20.291 respondents, 18 years and older, Diagnostic Interview Schedule [DIS][10]) it was shown that bipolar I and II patients had a lifetime prevalence of SUDs amounting to 61% (OR: 7.9) and 48% (OR: 4.7), respectively with alcohol being the most commonly abused substance.

The results of the US National Comorbidity Survey[6] in the early 1990s (8.098 respondents between 15 and 54 years, Composite International Diagnostic Interview [CIDI][11]) confirmed the relation between BD and alcohol use disorders (AUD) and other SUDs. People with a bipolar disorder were almost ten-fold (OR: 9.7) as likely to have a lifetime diagnosis of alcohol dependence and eight times (OR: 8.4) more likely to have a lifetime diagnosis of another substance dependence compared to the rest of the general population without a bipolar disorder. Moreover, approximately 50% of the people with a bipolar disorder and

comorbid alcohol abuse reported problems with at least one other substance. The first edition of Netherlands Mental Health Survey and Incidence Study performed in 1996 (NEMESIS, 7.076 respondents between 18 and 64 years, CIDI, 12-month prevalence) confirmed that drugs and alcohol dependence are strongly comorbid with BD (OR of 25.7 and 3.4 for drug and alcohol dependence, respectively) compared to the rest of the general population.[7,12]

In the more recent (2001-2002) US National Epidemiological Survey on Alcohol and Related Conditions (NESARC, 43.093 respondents, ≥18 years, Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV version [AUDADIS-IV][13] mania was strongly related to any drug dependence (OR: 13.9) and alcohol dependence (OR: 5.7).[14]

Clinical studies

A study that should be mentioned is the study of McElroy et al[15], performed in the US, Germany and the Netherlands. In this study, 288 bipolar I and II outpatients from the Stanley Foundation Bipolar Outcome Network[16] were evaluated. Sixty five percent (N=187) of the patients had at least one co-morbid lifetime axis I disorder (DSM-IV). Forty two percent (N=78) had a lifetime SUD. There was no difference in SUD comorbidity between the patients with bipolar I and bipolar II disorder.

The effect of comorbid substance use disorders on bipolar disorders

In the last two decades the negative effects of comorbid SUD (including AUD) on course and outcome of BD have been well documented in several

studies[9,17], showing that BD with comorbid SUD is associated with an earlier age of onset[18-21] but in other studies also with a later age at onset[22-24], a higher number of symptomatic episodes[25], longer symptomatic episodes[26], more symptoms during inter-episode intervals[27,28], a higher probability of syndromal recurrence[23,29], more mixed episodes[30], a higher number of total mood-related symptoms and manic symptoms at presentation[31], more hospitalizations[6,32], more suicidality[33], decreased treatment adherence[27,28], and poorer response to treatment[26,34] compared to BD without comorbid SUD. However, the results of these studies are difficult to interpret due to the retrospective design of these studies (with a serious risk of recall bias) and findings are difficult to compare due to the variation in patient populations, diagnostic assessments, criteria and definitions of episodes and thresholds.

The effect of alcohol consumption on bipolar disorders

Much less is known about the effect of (moderate) alcohol consumption on the course and outcome of BD. To the best of our knowledge, only five retrospective and five prospective studies examined the effect of alcohol use on the course and outcome of BD. The five prospective studies[29,35-38] and one of the retrospective studies[39] mainly looked at previous and/or current AUD without further specification of the actual amount of alcohol intake. The other four (retrospective) studies[31,32,39,40] (also) looked at the actual amount of alcohol intake. However, frequency and quantity of alcohol consumption in these studies were assessed in different ways making it rather difficult to compare the findings. All ten studies had serious methodological limitations. In the five retrospective

studies, recall bias may have influenced the reliability and validity of the data, whereas in the five prospective studies only a very spaced follow-up was performed. In addition only use/abuse of alcohol in general was assessed and almost never the actual amount of alcohol intake. As a consequence, almost no data are currently available about the effect of moderate alcohol consumption on the (prospective) course and outcome of BD.

Comorbidity of bipolar disorders and substance use disorders

In this thesis the terms comorbidity and co-occurrence will be used interchangeably due to the overlap of their definitions. Comorbidity refers to 'any distinct additional entity that has existed or that may occur during the clinical course of a patient who has the index disease under study.[41] The term refers to associations between descriptive classes of disorders in a given time frame (e.g. year or lifetime).[42] A disease can have more than one comorbid other disease at the same time. Co-occurrence exist when at least one disorder of each type can be established independent of the other and is not simply a cluster of symptoms resulting from (a single) disorder. This term tends to refer mainly to cross-sectional associations between symptoms or syndromes.[42] Patients may not, at a given point in time, meet the full criteria for DSM-IV disorders and the following subjects can also meet criteria for the presence of co-occurrence: (1) those who are "prediagnosed", i.e. showing signs or symptoms of an evolving other disorder); (2) those who are "postdiagnosed", i.e. one or both diagnoses have been (partly) resolved; and (3) those who have acute signs or symptoms of a co-occurring condition (but do not meet formal DSM(-IV)

criteria).[43] BD patients with current no, moderate or excessive use of alcohol can have a “prediagnosis” or “postdiagnosis” of a co-occurrent diagnosis of AUD (abuse or dependence). Both definitions have advantages and disadvantages. Comorbidity and co-occurrence are both influenced by the diagnostic system that is used, the time window (current or lifetime) that is used and the use of clinical diagnostic procedures versus standardized diagnostic instruments.[42] Moreover, the definition of comorbidity in studies on bipolar disorders and AUD introduces the problem that only “pure” cases of AUD are included, leading to underestimating of the percentage of BD patients who have no diagnosis of AUD while using or having used excessive amounts of alcohol. On the other hand, the definition of co-occurrence can lead to an overestimation of co-existing AUD due to the inclusion of the categories “prediagnosis” or “postdiagnosis” of AUD. However, given the considerable overlap between the two definitions both are, as in the literature, used in this thesis.

AIMS OF THIS THESIS

Among the many unanswered questions regarding the comorbidity of BD and AUD two important research questions will be addressed in this thesis.

The first unanswered question concerns the early detecting of this comorbidity. The simultaneous presence of BD in SUD patients often remains unrecognized, because the episodic alterations in mood and energy in SUD patients are not recognized as BD symptoms. Detection of BD enables the clinician to provide a more suitable treatment for BD. Moreover, it is of great importance that this comorbidity is detected as early as possible because the number of (undetected)

BD episodes have found to predict outcome in BD in general.[43] Therefore, the first objective of this thesis is the question if a screening instrument for BD in patients referred to addiction treatment settings can improve the detection of BD.

The second unanswered questions relates to the effect of alcohol use (disorders) on the course of BD. A lot of BD patients and their clinicians are faced with the question whether moderate alcohol use can hamper the course of the illness. To answer this question we describe in this thesis the results of two different prospective studies that examine the effect of (actual) alcohol consumption and the presence of AUDs in bipolar patients using a fine-grained monitoring system and standardized assessment procedures.

STUDIES USED IN THIS THESIS

In this thesis we describe the results of three studies. Here we provide a brief description of the goals, the research questions and the design of these studies.

First study

Screening for bipolar disorder with the Mood Disorder Questionnaire (MDQ) in patients with alcohol or substance use. The MDQ study.

The aim of this study was to examine the screening properties of the Mood Disorder Questionnaire (MDQ[44-46]) in order to detect BD in treatment seeking SUD patients. The study took place in two addiction treatment centers, one in Amsterdam and one in Alkmaar (the Netherlands) between August 2005 and June 2007. Participants were a consecutive series of newly referred patients. A total of 403 treatment seeking patients (58% outpatients and 42% inpatients) with

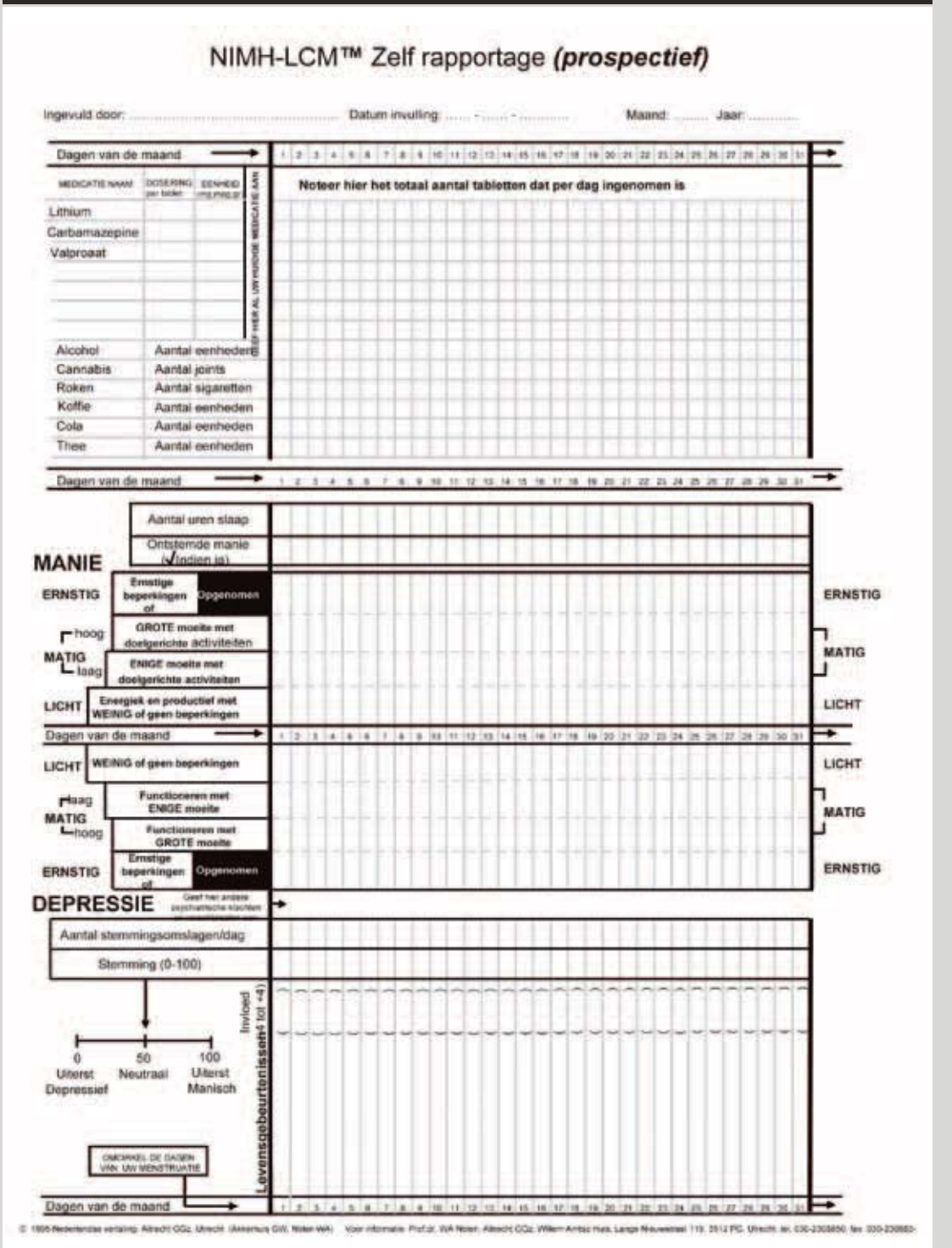
a SUD completed the MDQ and subsequently 111 MDQ positives and 59 MDQ negatives were assessed with a structured interview to establish the presence op BD. At intake (T1), the European Addiction Severity Index (EuropASI)[47] was administrated by trained professionals. This is a semi-structured interview measuring problem severity on a 10-point scale (0-9), including the following domains: medical condition, alcohol, drugs, family/social relations and mental problems. At baseline (T0), i.e. three days after intake, all patients were asked to complete the MDQ. At T1, i.e. after another 1-2 weeks, all abstinent patients with a positive score on the MDQ at T0 and a random 1:4 sample of abstinent patients with a negative score on the MDQ at T0 were, invited to complete the MDQ again. BD and SUD were assessed using the mood and SUD sections of the Structured Interview for DSM-IV Axis I Disorders/Patient version (SCID-I/P[48]); BD included BD-I, BD-II and BD-NOS. In addition, given the overlap with BD symptoms, Attention Deficit/Hyperactivity Disorder (ADHD) was diagnosed with the ADHD section of the Diagnostic Interview Schedule (DIS[10]), and borderline personality disorder (BPD) and antisocial personality disorder (APD) were diagnosed with the borderline and antisocial personality disorder sections of the Structured Interview for DSM-IV Personality Disorders (SIDP-IV).[49] These diagnostic assessments were performed by specially trained research psychologists who were blind for the MDQ score at T0. This assessment (T1) was performed later in order to avoid contamination by intoxication or withdrawal symptoms possibly still present at T0. All assessments were monitored by psychiatrists.

Second study

The effect of Alcohol, Drugs and Stimulants on the course and outcome of patients with bipolar disorders (ADS study)

The main objective of the second study was to get a better understanding of the effects of moderate alcohol use on the course and outcome of patients with BD. In this prospective follow-up study performed in the Netherlands between June 2003 and November 2005, 180 patients with BD (type I and type II) were asked to daily register for a period of 12 months their mood symptoms, their actual daily intake of alcohol, nicotine and caffeine, and their daily use of medication using the National Institute of Mental Health (NIMH) Self-Rating Prospective Life-Chart Method (LCM)[50-57] method (Fig. 1). It was a multicenter study with BD patients from 13 mental health institutes, two academic medical centers, one addiction treatment center and recruited through the Dutch Association for Manic-Depressives and Relatives. At study entry, the Structured Clinical Interview for DSM-IV (SCID-IV)[48] and the Personality Diagnostic Questionnaire 4+ (PDQ-4+)[58] were administrated by trained mental health care professionals. In order to compare the results of our study with other studies, data were also obtained by means of the Network Enrolment Questionnaire (NEQ) of the former Stanley Foundation Bipolar Network.[59,60] The Fagerström Test for Nicotine Dependence (FTND)[61] was administered and self-report data about substance use were obtained with a specially designed questionnaire about the present and past use of substances (quantity, frequency and age at onset), including information on caffeine, nicotine, alcohol, cannabis, ecstasy, amphetamines, lysergic acid diethylamide (LSD), cocaine, heroine and other drugs. At baseline

Figure 1. The National Institute of Mental Health Self-Rating Prospective Life-Chart.



and at every monthly visit during follow-up, LCM registrations were checked and approved by the research assistants who then also completed the Clinical Global Impression Scale-Bipolar version (CGI-BP)[62], the Global Assessment of Functioning Scale (GAF)[63], the Medical Outcome Scale 36-items, Short Form Health Survey (MOS-SF-36)[64] and a questionnaire concerning the direct and indirect medical care utilization of the prior month.

Third study

The European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) study

The main objective of the third study is to test if the results of EMBLEM study support our findings of the ADS study. Patients were part of the European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) study, a multicenter, prospective, observational study on the treatment and clinical, functional and economic outcomes of inpatients and outpatients with an acute manic or mixed bipolar episode performed between December 2001 and June 2004.[65,66] In brief, across 14 European countries a total of 3,681 inpatients and outpatients with an acute manic episode were enrolled at the discretion of the treating psychiatrist. Of these patients, 3,459 (94%) fulfilled all inclusion criteria: (a) 18 years and older, (b) baseline rating of CGI-BP mania ≥ 3, and (c) started or changed their oral medication for the treatment of mania (antipsychotics, anticonvulsants and/or lithium; not antidepressants or benzodiazepines) within the context of routine psychiatric care. The study had minimal exclusion criteria. Mania diagnosis was made by the psychiatrist's clinical evaluation based

on standard diagnostic criteria (generally DSM-IV[67], ICD-10[68]) or on clinical judgment. Treatment decisions were independent of the EMBLEM study and patients were not participating in any intervention study. During the acute treatment phase, assessments took place at baseline, 1, 2, 3, 6 and 12 weeks after baseline. During the maintenance phase patients were assessed at 6, 12, 18 and 24 months. At baseline, demographic and social characteristics such as age, sex, having a relationship and level of education were collected, as well as data on the psychiatric history such as age at onset of BD, rapid cycling in the previous year, history of suicide attempts, history of problems with alcohol, cannabis and other drugs (yes or no), current use of alcohol (see below), current use of cannabis and other drugs, compliance, and in – or outpatient status. Investigators were asked, based on their clinical experience and discretion and based on the patient's self-report, to assess whether patients had a lifetime alcohol problem. History of alcohol problems (lifetime) and current alcohol use (in the previous 3 months) were assessed at baseline, at 12 weeks and at 52 weeks follow-up based on patient self-report and investigator clinical experience and judgment. Based on this combination of information, patients were clinically divided in three alcohol use groups at baseline: (1) no alcohol use; (2) moderate alcohol use, i.e. alcohol use without alcohol-related problems; and (3) presence of an AUD, i.e. DSM-IV alcohol abuse, ICD-10 harmful use or DSM-IV/ICD-10 dependence. Severity of psychopathology was measured at each observation using the following assessment scales: the CGI-BP to assess the severity of the overall illness, mania, depression, and hallucinations/delusions (each item score 1-7).[62] During the acute phase (baseline -12 weeks), the Young Manic Rating

Scale (YMRS; 11 items, score 0-60)[69] and the shortened 5-item version of the Hamilton Depression Rating Scale (HAMD-5; score 0-18)[70] were also completed. Other outcome variables included: the number of suicide attempts; current alcohol, cannabis or other drug use over the period of 6-12 and 13-52 weeks.

OUTLINE OF THIS THESIS

- In chapter 2 the validity of the MDQ is tested to detect BD in a population treatment seeking SUD patients, including AUD patients.
- In chapter 3 the results of the ADS study are presented. The effects of no alcohol use versus moderate alcohol use versus excessive alcohol use on the course and outcome of BD patients are examined.
- In chapter 4 further results of the ADS study are presented, i.e. a fine grain analysis of the temporal relation between alcohol use and short-term mood switching probabilities. Multi-state models were used to assess the impact of the number of alcoholic drinks on the patients' transition through different mood state (depression, euthymia and mania).
- In chapter 5 the results of the EMBLEM study are shown. In this study the effect of no alcohol use, moderate alcohol use, i.e. alcohol use without alcohol-related problems, and the presence of an AUD is examined in a large European sample of patients with BD.
- Chapter 6 summarizes and discusses the main findings of the studies included in this thesis. Future perspectives for research will be discussed.

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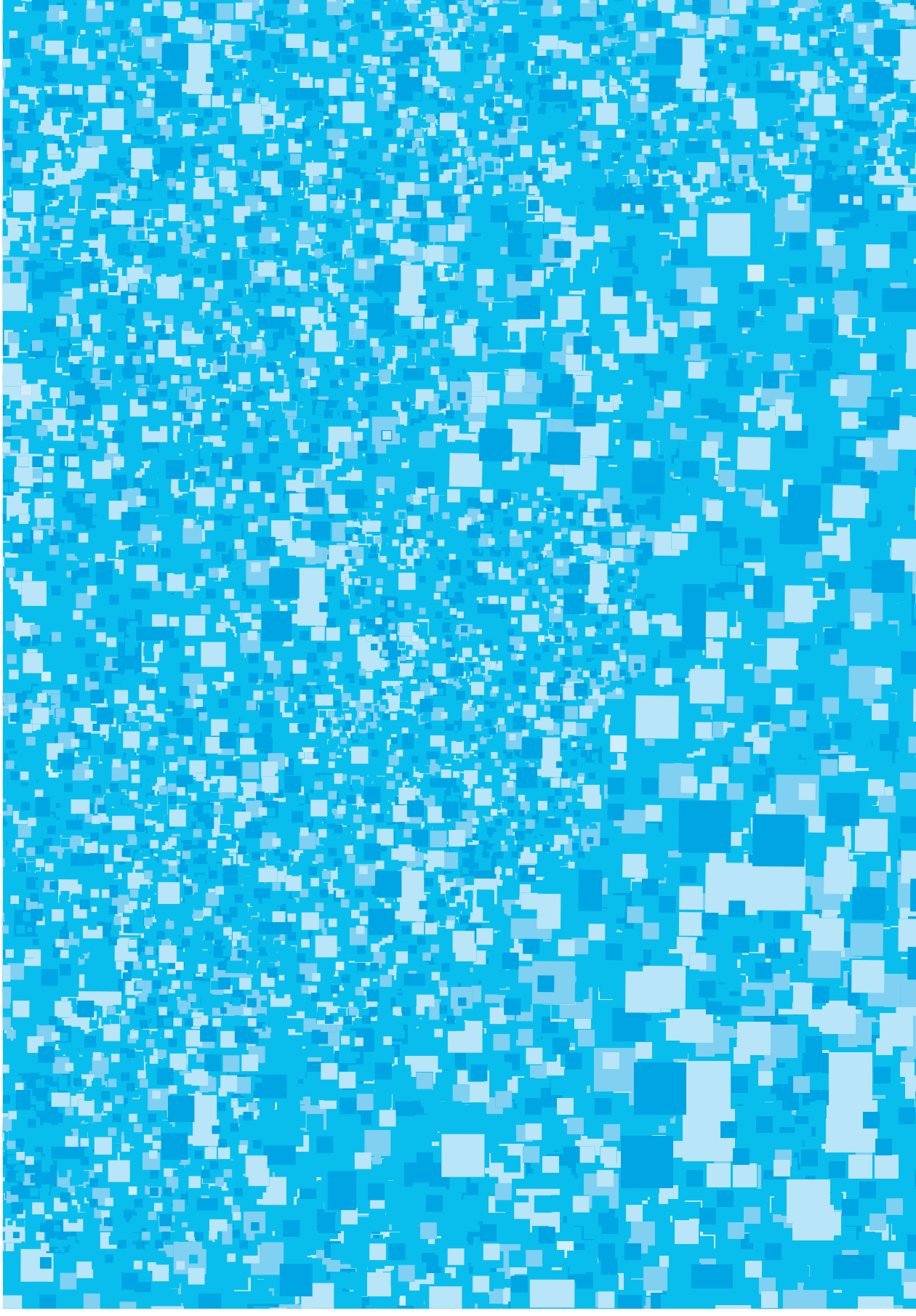

2

SCREENING FOR BIPOLAR DISORDERS IN PATIENTS WITH ALCOHOL OR SUBSTANCE USE DISORDERS

Performance of the Mood Disorder Questionnaire

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ABSTRACT

BACKGROUND Screening properties of the Mood Disorder Questionnaire (MDQ) to detect bipolar disorder (BD) in patients with substance use disorders are unknown.

METHODS 403 treatment seeking patients with a substance use disorder completed the MDQ and subsequently 111 MDQ positives and 59 MDQ negatives were assessed with the Structured Clinical Interview for DSM-IV to diagnose BD. In addition, given the overlap with BD symptoms, the presence of borderline personality disorder (BPD), antisocial personality disorder (APD) and attention deficit and hyperactivity disorder (ADHD), were assessed using the Diagnostic Interview Schedule and the Structured Interview for DSM-IV Personality.

RESULTS Of the 170 patients with a SCID interview, 35 patients (20.6%) met criteria for a lifetime diagnosis of BD. Twenty-three patients (62.8%) with BD had a positive MDQ score and 47 of the 135 patients (34.8%) without BD had a negative MDQ score resulting in a weighted sensitivity of .43, a weighted specificity of .57, a positive predictive value of .21, a negative predictive value (NPV) of .80 and an area under the curve of .50. The area under the curve of the MDQ to detect BPD, APD, ADHD and any externalizing disorder ranged from .55 (APD) to .63 (ADHD).

CONCLUSIONS The MDQ is not a suitable screening instrument for the detection of BD or other externalizing disorders but it could be used for ruling out the presence of BD in treatment seeking substance use disorder patients.

INTRODUCTION

Substance use disorders (SUD) frequently co-occur with other psychiatric disorders, including bipolar disorders (BD). Population based epidemiological studies have shown that subjects with an alcohol use disorder (AUD) or drug use disorder (DUD) are 5-6 times more likely to have a history of (hypo)manic and depressive episodes associated with BD than subjects without SUD.[1-3] Among the main causes of the world wide Top-20 of Years of Life Lived in Disability in 2000 of 15-44 years-olds (both sexes) AUD, BDs and DUD are ranking respectively 2nd, 5th and 16th. The frequent comorbidity of BD and SUD is, therefore, a substantial economical burden.[4-7] In many BD patients with comorbid SUD, BD remains unrecognized because the episodic alterations in mood and energy in patients with SUD are not recognized as symptoms of BD. Underdiagnosis of BD is more common in BD type II (BD-II) than in BD type I (BD-I), because episodes with manic symptoms but without dysfunction can be difficult to identify.[8,9]

Albanese et al.[10] showed that 29% of a sample of 295 Caucasian males admitted to a substance abuse program had a form of BD and half of them had not been previously diagnosed with BD and consequently were not treated for it. In addition, the US National Depressive and Manic-Depressive Association 2000 Survey of individuals with BD showed that 37% reported alcohol and substance abuse during the time that they were not or improperly treated for their BD, while alcohol and substance abuse dropped to 14% when treatment was initiated.[9]

In order to improve the detection of BD in a population of treatment seeking SUD patients we decided to introduce a screening instrument: the Mood Disorder

Questionnaire (MDQ). The MDQ is a brief and easy-to-use self-report screening inventory for the detection of bipolar spectrum disorders.[11-14] The original MDQ[11] was validated in psychiatric outpatients with mainly mood disorders and showed a sensitivity of 0.73 and a specificity of 0.90. From 2000 on, the MDQ has been subject to validation in different patient groups and settings with different prevalences of BD-I, BD-II, and BD not otherwise specified (BD-NOS).[14] The MDQ has also been validated in the general population[13] and in a forensic setting.[15] In these studies, the Structured Clinical Interview for DSM-III-R or DSM-IV Axis-I disorders (SCID-I/P)[16,17] was used as the gold standard. The findings of these studies were rather mixed. Some studies showed (very) good sensitivity and or specificity.[14-20] However, Zimmerman et al.[21] reported inadequate sensitivity (0.64) and reasonable specificity (0.85) in a psychiatric outpatient sample. Therefore, in a attempt to improve its sensitivity, it was proposed to omit the requirement of impairment based on section C of the MDQ. Indeed, this modified MDQ, showed better sensitivity (0.75) but lower specificity (0.79) while the positive predictive value (PPV) remained below 30%.[14,21] The authors recommended further studies e.g. among patients with SUD.[21,22] Recently, Villagonzalo et al.[23] found that 49% of a group of 74 methadone maintenance patients screened positive for BD using the MDQ, although only 3 clients had an active diagnosis of BD on their medical records. However, in this study no standardized assessment was performed to diagnose the presence of DSM-IV BD and, therefore, the screening qualities of the MDQ is still unknown in treatment seeking SUD patients.

As far as we know, this is the first study examining the screening properties of the MDQ using the SCID as a gold standard to detect BD in patients with

SUD, in whom a relatively high prevalence of BD is expected. We, therefore, hypothesized that the MDQ would be a valid screen for the detection of BD in this population. Since symptoms of substance abuse can mimic manic symptoms we decided to add two questions to the original MDQ in order to allow us to exclude substance induced BD. We hypothesized that adding these questions would reduce false positives and therefore increase specificity.[24]

Furthermore, we decided to also assess the presence of borderline personality disorder (BPD), antisocial personality disorder (APD) and attention deficit/ hyperactivity disorder (ADHD), because these disorders are very prevalent in patients with SUD and the symptoms of these disorders overlap with BD symptoms. We thus hypothesized that a considerable amount of patients with a positive screen would meet criteria for BPD, APD or ADHD but not for BD.

METHODS

Subjects and recruitment

The study took place between August 2005 and June 2007 in two addiction treatment centers in Amsterdam and Alkmaar (the Netherlands). The participants were a series of consecutive referred new patients. A total of 403 were recruited: 58% outpatients and 42% inpatients. Patients had to meet the following inclusion criteria: 1) in need of (see below) and seeking treatment for AUD or SUD, 2) being abstinent since seeking treatment (self report and clinical judgement), 3) able and willing to participate in the study, and 4) adequate command of the Dutch language. Patients with a score of less than 23 on the Mini Mental State Examination (MMSE)[25], indicating cognitive impairment, were excluded.

The study was approved by the Ethical Review Board of the participating centers and all patients provided written informed consent.

Need of treatment

At baseline, the European Addiction Severity Index[26] was administrated by trained professionals. This is a semi-structured interview measuring problem severity on a 10 point scale (0-9), including the following domains: medical condition, alcohol, drugs, family/social relations and mental problems. Patients with scores ≥ 4 are in need of (additional) treatment.

Screener: Mood Disorder Questionnaire (MDQ)

The original MDQ was translated into Dutch by two independent translators. The resulting consensus translation was then back translated into English by a native English mental health professional . In a consensus meeting where attention was paid to both semantic and conceptual equivalence, the three of them reviewed and approved the final version.[27]

The MDQ has three sections. The first section has 13 yes/no BD items derived from the DSM-IV criteria[28] and from clinical experience (section A). The MDQ screen is regarded to be positive if seven or more items from section A are present, if several of these items co-occur (section B) and if they caused moderate or serious problems (section C). Since substance use can mimic bipolar symptoms we added two questions to the original MDQ. First, participants were asked whether any of the endorsed section A symptoms ever happened during an episode with little or no substance use (section D). Second, participants

were asked whether they ever had an episode without section A symptoms in which they felt their normal self (section E). In summary: the MDQ classic is considered positive if sections A, B and C are fulfilled, whereas the adjusted MDQ is considered positive if the requirements for sections A, B, C, D and E are fulfilled.

Diagnostic instruments

BD and SUD were assessed using the mood and substance use disorders sections of the SCID-I/P, Dutch version.[29] BD included BD-I, BD-II and BD-NOS. ADHD was diagnosed with the ADHD section of the Diagnostic Interview Schedule (DIS)[30], and BPD and APD with the borderline and antisocial personality disorder sections of the Structured Interview for DSM-IV Personality.[31]

Design

At baseline, i.e. three days after intake (T0), all patients were asked to complete the MDQ. At T1, i.e. after another 1-2 weeks all still abstinent patients with a positive score on the MDQ at T0 and a random 1:4 sample of patients with a negative score on the MDQ at T0 were, after they had provided written informed consent, invited to complete the MDQ again and the diagnostic assessments (SCID-1/P, DIS, SIDP-IV, MMSE). These diagnostic assessments were performed by specially trained research psychologists who were blind for the MDQ score at T0. This assessment (T1) was performed later in order to avoid contamination by intoxication or withdrawal symptoms possibly still present at T0. All assessments were monitored by psychiatrists (JvZ or BvdB).

Statistical analysis

In order to check the random procedure to select MDQ negative patients at T0 for the full assessment at T1, sociodemographic and clinical characteristics between MDQ negatives with and without an assessment were compared using t-tests and Pearson's Chi-Square tests for nominal and ordinal data. P-values below 0.05 were considered statistically significant.

SCID diagnoses were used as external criterion for the calculation of the sensitivity, specificity, positive likelihood ratio (LR^+), negative likelihood ratio (LR^-), positive predictive value (PPV), and negative predicted value (NPV) of the MDQ. In order to take into account the different proportion of MDQ positives (111/161=0.689) and MDQ negatives (59/214=0.276) who were assessed with the SCID (Figure 1), estimates for sensitivity and specificity were weighted according to these sampling fractions.[32] In order to compare the MDQ performance using different external criteria and different MDQ versions (using only section A or sections A plus B) in a SUD population, receiver operating curve (ROC) analyses were conducted taking into account differences in sampling fractions between MDQ screen positives and MDQ screen negatives. As hypomanic episodes in DSM-IV are (by definition) not associated with marked impairment in social or occupational functioning as required for a positive MDQ score, there might be under-detection of BD II. Therefore, analyses were repeated without the impairment criterion (section C). Finally, since substance use can mimic manic symptoms, all analyses were repeated taking into account sections D and E.

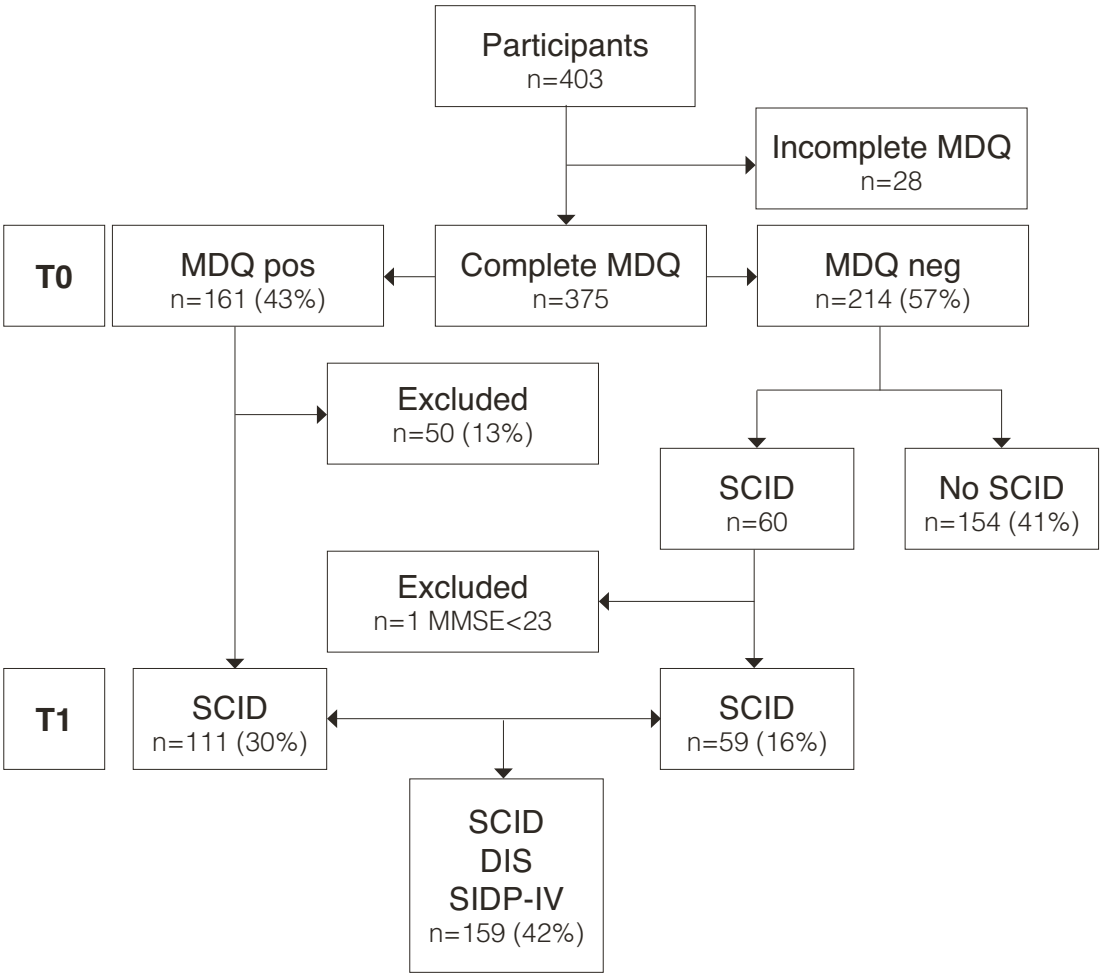
RESULTS

Recruitment and sample characteristics

After baseline (T0), 28 of the 403 included patients were excluded due to inadequate scoring of the MDQ (Figure1). Of the 375 remaining patients, 161 (43%) patients were MDQ positive and 214 (57%) were MDQ negative. All MDQ positives (N=161, 43%) and a random sample of the MDQ negatives (N=60, 28%) were approached for the second assessment (T1). A total of 50 MDQ positives (31%) were lost to follow-up due to relapse, drop-out or inability to be traced after discharge from the inpatient department. The data of one MDQ negative patient were excluded from further analyses due to a score of less than 23 on the MMSE at T1. As a result, the analyses of the operating characteristics of the MDQ included data of 111 of all 161 MDQ positives (68.9%) and 59 of all 214 MDQ negatives (27.6%). These fractions (0.689 and 0.276) were used as weighting factors in the calculations.

Because the MDQ is a screening instrument that is likely to be used early in the diagnostic process, in the primary analyses MDQ data at T0 were used in the comparison with the SCID at T1. In a secondary analysis we also compared MDQ data at T1 with SCID data at T1. It should be noted, however, that the test-retest correlation of the total sum scores of the MDQ section A scores (all cases N=170) between T0 and T1 was rather high (R= .604, p<.0001 [correlation is significant at the 0.01 level], R^2 =.36): test-retest correlation of the MDQ positive cases was .455 (R^2=.21) and for MDQ negative cases .608 (R^2=.37).

Figure 1. Fig.1. Flowchart of the study.



Mean age of all 375 eligible patients was 40.4 years (SD ±11.0) with MDQ negatives being somewhat older than MDQ positives (41.9 versus 38.4 years, p=.002). The majority (74%) of the patients were males with significantly more males among the MDQ positives (83%) compared to the MDQ negatives (70%) (p=.005). There were no significant differences regarding education level, employment status and EuropASI severity scores regarding medical condition, alcohol, family and social relations and mental problems. However, there was

Table 1. Sociodemographic Characterististics versus MDQ[a] results.

Characteristics	MDQ Positives N=161 (43%)	MDQ Negatives N=214 (57%)	Total Sample N=375	P[b]
Age, mean y (± sd)	38.45 (9.76)	41.93 (11.56)	40.43	**.002**
Gender n, (%)				**.005**
Male	133 (83%)	150 (70%)	300 (74%)	
Female	28 (17%)	64 (30%)	103 (26%)	
Education level n, (%)				.337
≤ High school	118 (73%)	142 (66%)	274 (68%)	
> High School	25 (16%)	44 (21%)	79 (20%)	
unknown	18 (11%)	28 (13%)	50 (12%)	
Employment status n, (%)				.192
employed	27 (17%)	39 (18%)	151 (38%)	
unemployed	81 (50%)	88 (41%)	179 (44%)	
unknown	53 (33%)	87 (41%)	73 (18%)	
EuropASI[c] mean (± sd)				
medical state	2.32 (1.83)	2.13 (2.02)	2.21 (1.94)	.415
alcohol	3.88 (2.48)	4.24 (2.40)	4.09 (2.44)	.183
drugs	3.70 (2.71)	2.37 (2.61)	2.94 (2.75)	**.000**
family/social relations	3.58 (2.08	3.10 (1.64)	3.30 (1.96)	.028
mental problems	4.62 (2.12)	4.09 (1.86)	4.32 (1.99)	.055

[a]Mood Disorder Questionnaire.

[b]Bolded P values denote significance.

[c]European version of the Addiction Severity Index, score 0-9.

a significant difference on the EuropASI severity rating drugs (p=.000) between the MDQ positive and negative patients (Table 1).

Patients with an assessment at T1 (N=170, 45%) did not differ significantly from patients without an assessment (N=205, 55%) in terms of age, gender,

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and employment status. However, MDQ positives at T0 with an assessment at T1 (N=111) were less educated than those without an assessment (N=50). Moreover, MDQ negatives at T0 with an assessment at T1 had a higher mean section A score (0-13) than MDQ negatives without an assessment (8.87; SD ±2.63 versus 5.42; SD ±3.25, p<.01). The severity of alcohol or drug use (ASI score) did not differ between these groups (data not shown).

Prevalence of mood and substance related disorders

Of the 170 patients with a SCID at T1, 35 patients (20.6%) met criteria for a lifetime diagnosis of BD (BD-I N=8 , BD-II N=25 and BD-NOS, N=2), 72 patients (42.4%) had a lifetime major depressive disorder, 10 patients (5.9%) a lifetime depressive disorder NOS, 10 patients (5.9%) met criteria for a substance-induced mood disorder with depressed features, 1 patient (0.6%) had a substance-induced mood disorder with manic features, and 1 patient (0.6%) a mood disorder due to a somatic condition. Forty-one patients (24.1%) did not meet criteria for any mood disorder.

Fifty-eight (34.1%) patients had one lifetime SUD diagnosis, 108 patients (63.5%) had two or more SUD diagnoses, and 4 patients (2.4%) had no lifetime SUD at all. Fifty-nine patients (34.7%) had a current diagnosis of AUD, 31 patients (18.2%) of cocaine or stimulant dependence, 26 patients (15.2%) of cannabis dependence, 8 patients (4.7%) of opiate dependence, and 5 patients (2.9%) of benzodiazepine dependence. Forty-one (24.1%) patients were problems users of alcohol and/or drugs but did not meet criteria of any current SUD.

Validity of the MDQ

Table 2 shows that 23 of the 35 patients (65.7%) with BD had a positive MDQ score and 47 of the 135 patients (34,8%) without BD had a negative MDQ score resulting in a weighted sensitivity of .43 and a weighted specificity of .57, a weighted LR^+ of 1.00, a weighted LR^- of 1.00, a PPV of .21, and a NPV of .80 (Table 3). As expected based on the LR^+ and the LR^-, the area under the curve (AUC) was .50 (95% CI .41-.61). Omission of the impairment criterion (section C), increases the number of patients with a positive MDQ score (N=111) and BD from 23 to 32 and decreases the number of patients with a negative MDQ score (N=59) and BD from 12 to 3, resulting in increased sensitivity of .85 at the expense of a decreased specificity of .24, a better LR^+ of 1.12 and a better LR^- of .63, a PPV of .23 and a NPV of .86.

Table 3 also shows that introduction of the D and E criteria results in an expected increase in specificity (.82) at the expense of a decrease in sensitivity (.21). Also restricting BD symptoms to substance free periods (criteria D and E) and removing functional impairment (criterion C: allowing BD I to be included as a

Table 2. Bipolar diagnosis (BD) according to SCID results at T1[a] versus MDQ score at T0[b].

	SCID		
	BD Positive	BD Negative	Total
MDQ			
Positive	23	88	111
Negative	12	47	59
Total	35	135	170

[a]Assessment at follow-up.

[b]Assessment at baseline.

Table 3. Weighted sensitivity, specificity, false positives, false negatives, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR-) of the MDQ at T0 (N=170).

	MDQ Classic (95%CI)	MDQ Classic +D+E (95%CI)	MDQ A+B (95%CI)	MDQ A+B+D+E (95%CI)
Sensitivity	.43 (.32 - .54)	.21 (.10 - .32)	.85 (.76 - .94)	.44 (.31 - .57)
Specificity	.57 (.50 - .64)	.82 (.77 - .87)	.24 (.18 - .30)	.69 (.63 - .75)
False positives	.43	.18	.76	.31
False negatives	.57	.79	.15	.56
PPV	.21 (.13 - .29)	.23 (.11 - .35)	.23 (.17 - .29)	.27 (.18 - .36)
NPV	.80 (.75 - .95)	.65 (.59 - .71)	.86 (.77 - .95)	.83 (.77 - .89)
LR+	1.00	1.17	1.12	1.42
LR-	1.00	.96	.63	.81

case) did not improve the sensitivity and specificity of the MDQ to detect BD (Table 3, last column). The positive and negative likelihood ratios (LR^+, LR^-) ranged from 1-1.42 and 1-.63, respectively.

Validity indicators based on the MDQ assessment at T1 were very similar and certainly not better than those based on the MDQ assessment at baseline (T0) (data not shown).

BD symptom related disorders

Of the 170 patients with a SCID at T1, 159 (94%) also completed all the other diagnostic instruments (DIS, SIDP-IV) at T1. Of the 31 patients (19.5%) with BD, 8 (25%) also had BPD, 2 (6.4%) APD and 10 (32.2%) ADHD. Of the 128 patients without BD, 15 (11.7%) had BPD, 29 (22.7%) APS, and 38 (29.7%) ADHD. The relative risks of the presence of BPD, APD and ADHD in patients with BD compared to patients without BD were 2.2 (95% CI 1.03 – 4.72) for BPD, 0.28 (95% CI 0.07 – 1.13) for APD, and 1.09 (95% CI 0.61 – 1.93) for

ADHD, meaning that BD relatively often co-occurred with BPD, the BD tended to co-occur less often with APD and that ADHD was equally present in patient with and without BD.

The standard MDQ operating characteristics with BD, BPD, APD, ADHD and any externalizing disorder (BD and/or BPD and/or APD and/or ADHD) as external criterion for this population are shown in Table 4. In order to compare the performance of the MDQ for these different external criteria, we calculated areas under the curve. The AUCs ranged from .51 (BD) to .63 (ADHD). The 95% CI of the AUCs of BD, BPD and APD all included 0.50, indicating that the standard MDQ performed not better than chance for these three disorders. The performance to detect ADHD and any externalizing disorder was slightly better with AUCs of .63 (95%CI .54-.72) and .60 (95%CI .51-.68) respectively, but 95% CI's largely overlapped with those of the AUC of the other external criteria (BD, BPD and APD).

DISCUSSION

The primary objective of this study was to evaluate the screening properties of the MDQ to detect BD in a treatment seeking population of patients with SUD. Our first hypothesis that the MDQ would be a valid screen due to an expected relatively high prevalence of BD in this population was not confirmed. With the SCID diagnosis of BD-I, DB-II or BD-NOS as "golden standard" (prevalence 21%), the performance of the MDQ in this population was very disappointing: sensitivity = .43, specificity = .57, PPV = .21, NPV = .80, and AUC = .50. These data show that the PPV and the NPV of the original MDQ (A+B+C) in this

Table 4: Prevalence and operating characteristics of the MDQ of 159 patients for borderline personality disorder (BPD), antisocial personality disorder (APD) and attention deficit/ hyperactivity disorder (ADHD) at T1.

	BD[a]	BPD	APD	ADHD	Any Externalizing Disorder
Prevalence, n (%)	31 (19.5)	23 (14.5)	31 (19.5)	48 (30.2)	98 (38)
Sensitivity, (95%CI)	.45 (.32 - .48)	.30 (.16 - .44)	1.00	.57 (.45 - .69)	.59 (.49 - .69)
Specificity, (95%CI)	.54 (.47 - .61)	.77 (.70 - .84)	.61 (.55 - .67)	.60 (.53 - .67)	.67 (.60-.74)
False positives	.46	.23	.39	.40	.33
False negatives	.55	.70	0	.43	.41
PPV[b], (95%CI)	.20 (.13 - .27)	.11 (.05 - .17)	.30 (.21 - .39)	.35 (.26 - .44)	.52 (.43 - .61)
NPV[c], (95%CI)	.79 (.72 - .86)	.79 (.72 - .86)	1.00	.79 (.72 - .86)	.73 (.66 - .80)
AUC[d], (95%CI)	.51 (.41 - .61)	.61 (.50 - .73)	.55 (.44 - .66)	.63 (.54 - .72)	.60 (.51 - .68)
LR+[e]	.98	1.30	2.56	1.43	1.79
LR-[f]	1.02	.91	0	.72	.61

[a]Different operating characteristics of BD compared to Table 3 due to a different number of patients (159 vs 170).

[b]Positive predictive value.

[c]Negative predictive value.

[d]Area under the curve.

[e]Positive likelihood ratio.

[f]Negative likelihood ratio.

population are (almost) the same as the prevalence and 1-prevalence, indicating that knowledge from the MDQ did not improve the prediction of the presence or absence of a BD at all (which is also indicated by the AUC of 0.50, the LR^+ of 1.00 and the LR^- of 1.00, i.e. validity indicators that are not better than estimates based on prevalence information only). It should be noted that a relatively high prevalence of a condition in a sample results in increased values of positive and negative predictive power.[33] In our sample the prevalence of BD according to the SCID diagnosis was 21% (35/170, Table 2) and this resulted in overly optimistic negative and positive predictive values.

Due to the small number of patients in some of the diagnostics groups it

was not possible to investigate whether these characteristics were better for patients with a BD-I diagnosis compared to patients with a BD-II diagnosis. However, omission of the impairment criterion (section C) did not result in a substantial improvement of the screening capacity of the MDQ.

Furthermore, our second hypothesis that addition of two extra questions (section D and E) to the MDQ would improve the specificity without (seriously) lowering the sensitivity was only partly confirmed. In fact, specificity increased from .57 to .82, while sensitivity decreased from .43 to .21. The latter (sensitivity of .21) is of course unacceptable for an instrument that aims to detect potential cases of BD in patients seeking treatment for a substance use disorder.

Our third hypothesis that the high prevalence of BPD (14.5%), APD (19.5%) and ADHD (30.2%) in our treatment seeking AUD and SUD patients would result in a high rate of false positives (FPs) and thus in low specificity was confirmed (Table 4). The FP rate of the classic MDQ was indeed rather high (46%) resulting in low specificity (.54). This is consistent with the findings of Zimmerman et al.[34] who showed in their study of 534 psychiatric outpatients that BPD was 4 times more frequently diagnosed in the MDQ positive group than in the MDQ negative group, indicating that the MDQ can also detect externalizing disorders other than BD. We therefore hypothesized that the MDQ would be able to perform best in the detection of any externalizing disorder rather than BD alone. However, broadening the external criterion to any externalizing disorders did not really improve the performance of the MDQ in this population (AUC= .60, 95%CI .51 - .68).

What can we conclude? First, based on our findings, we can not recommend the original nor any of the adapted versions of the MDQ as a useful screening

instrument to detect the presence (or absence) of BD in a population of treatment seeking patients with SUD. We even can not recommend the MDQ in this population as a screener for the presence or absence of any externalizing disorder. Still, it is very important that BD is detected early in patients with SUD. According to Benazzi et al[35], the most important clinical symptoms of patients with BD-II, the type of BD that is hard to detect, are energized activity and irritable mood associated with racing thoughts, but these symptoms are also very common among almost all cocaine and amphetamine users, even among those without BD. When we obtained our disappointing/unexpected findings, we thought it all over again. Based on our clinical experience/impression, we then thought the key questions that every patient who seeks help in an addiction center should be asked, would be if (s) he had ever had an episode without using alcohol or drugs that was characterized by (1) lack of need to sleep, (2) energized activity and/or (3) irritable mood associated with racing thoughts. However, a post-hoc analysis of our data based on these three questions (+ section B and C) did not substantially improve the performance of the MDQ. Thus, the problem of how to detect BD in an addiction population remains unsolved. On the other hand, with a NPV of .80 one could argue that the MDQ is a reasonable good tool to rule out BD in addiction settings where a psychiatric interview is not standard at intake: only those who screen positive need to have a proper diagnostic assessment, essentially decreasing the burden of psychiatric interview for BD at intake.

The current study has both strengths and limitations. The strengths of our study are the relatively large sample size in a difficult, but very relevant, population when compared to previous studies (see also: Chung et al.[14], page

465), and the diagnoses of BPD, APD and ADHD diagnoses that were based on structured assessments by specially trained interviewers. Nevertheless, the sample size is also small as indicated by the relatively broad 95% confidence intervals. However, the general picture is still very clear and the limited sample size is not a serious problem for the interpretation of our findings. The first limitation is the relatively short detoxification period. However, this limitation can also be seen as a strength of the study, because clinicians like to do the screening as soon as possible after intake. The second limitation is more important. This limitation relates to the fact that the MDQ negatives with a SCID were not fully representative for all MDQ negatives in terms of their MDQ score. MDQ negatives with a SCID had a significantly and substantially higher mean MDQ section A score at T0 than MDQ negatives without a SCID ($d=1.17$; $p < .01$). This may have caused an underestimation of the validity of the MDQ due to a biased increase in the number of false positives. In order to estimate the possible effect of this unexpected design weakness, we performed a post-hoc sensitivity analysis in which we moved 6-8 of the 12 false negative patients (Table 2) to the true positive category. However, this procedure failed to substantially improve the overall performance of the MDQ to detect BD in a treatment seeking population of SUD patients. Another limitation is that the reliability of the diagnostic evaluation was not formally tested. This could also have led to a poor performance of the screener. Stewart and El-Mallakh[36] and Goldberg et al.[37] reported overdiagnosis of BD in patients with active SUD when diagnosed by psychiatrists. However, it seems unlikely that we overdiagnosed BD in our study population given the PPV of only .20 and a false positive rate

of .46 (Table 4). Finally, one could argue that many of the patients in the "non-bipolar" group may in fact have a softer version of BD that was not identified by the SCID. However, we explicitly looked for sub-threshold cases and included bipolar NOS in the group of patients with a bipolar disorder.

CONCLUSION

The MDQ is not a suitable screening instrument for the detection of BD or other externalizing disorders, but it could be used to rule out the presence of BD in treatment seeking substance use disorder patients.

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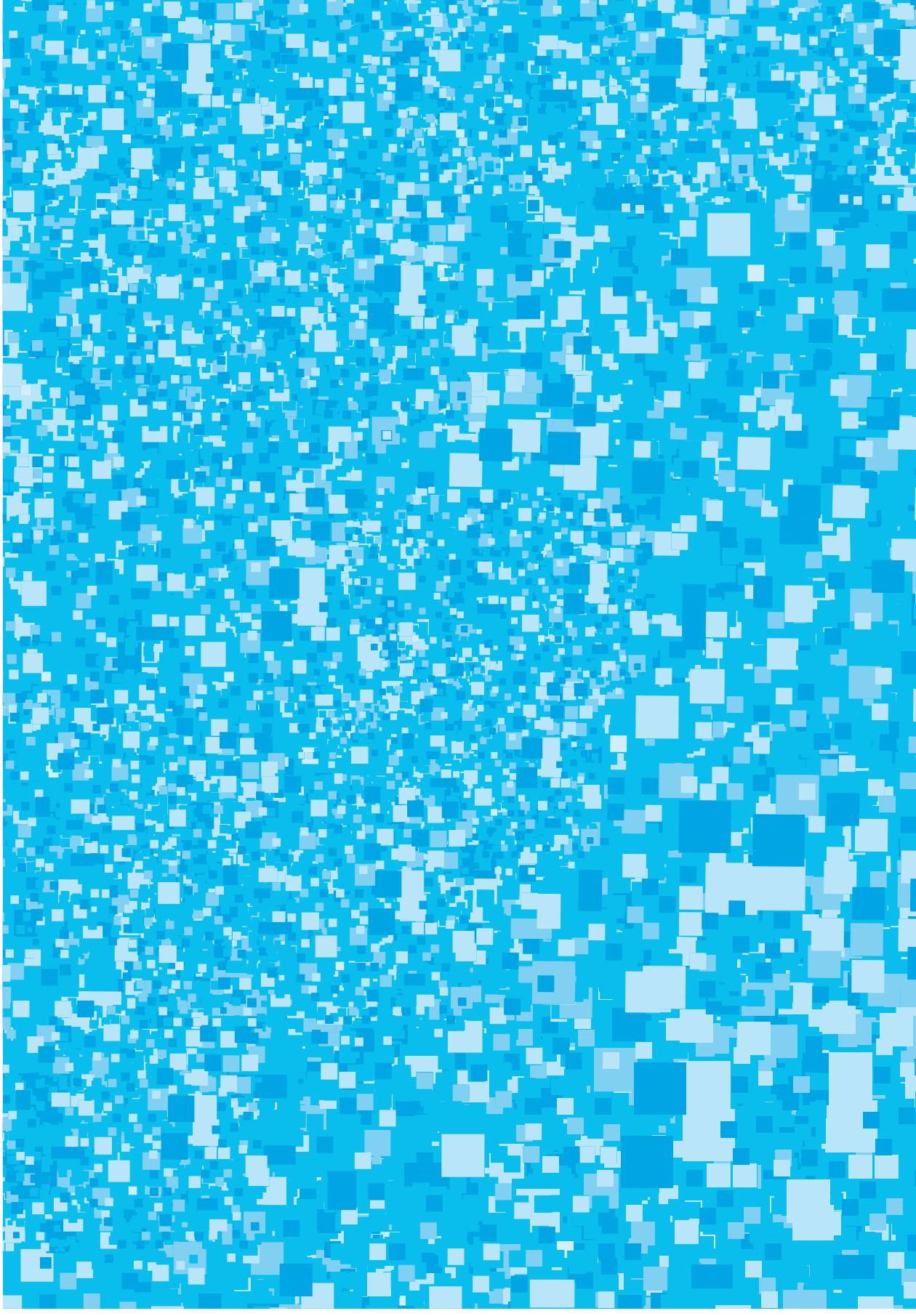

3

THE EFFECT OF MODERATE AND EXCESSIVE ALCOHOL USE ON THE COURSE AND OUTCOME OF PATIENTS WITH BIPOLAR DISORDERS

A prospective study

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ABSTRACT

OBJECTIVE Comorbid alcohol use disorders (AUDs) are frequently associated with negative effects on course and outcome of bipolar disorder. This prospective cohort study assessed the effect of actual alcohol use (no, moderate and excessive) on the course and outcome of patients with bipolar disorders.

METHOD Between June 2003 and November 2005 137 outpatients (aged 23-68 years) with DSM-IV-diagnosed bipolar I (66%) or II (34%) disorder rated their mood and the number of alcohol units consumed daily for a period up to 52 weeks with the National Institute of Mental Health Self-Rating Prospective Life-Chart Method (LCM). At baseline, the Structured Clinical Interview for DSM-IV was administrated, and demographic, social and clinical characteristics were obtained. At monthly visits, the Clinical Global Impressions Scale-Bipolar Version (CGI_BP), the Global Assessment of Functioning (GAF) scale and the Medical Outcomes Study 36-item Sort-Form Health Survey (MOS-SF-36) were rated. Based on the alcohol use in the first 4 weeks of follow-up, patients were assigned to one of three groups: no/incidental, moderate, or excessive alcohol use.

RESULTS None of the sociodemographic and clinical characteristics at baseline were significantly different between the three drinking groups, with the exception of – and as a consequence of the group assignment – the prevalence of lifetime and current diagnosis of AUD. Also, no differences between the three drinking groups were found on any of the clinical outcome variables, ie number of days ill (depressed, hypomanic/manic, and total); severity of depression, mania, and overall bipolar illness (LCM); GAF score; CGI-BP (depression, mania, and overall) and all the subscales

of the MOS-SF-36. Also, the number of episodes according to DSM-IV and the Leapfrog method showed no significant differences between the drinking groups.

CONCLUSION In this sample of patients and with the sensitive measurement of mood and drinking status over a full year, we could not confirm the findings of other studies indicating a negative effect of excessive alcohol use on the course of bipolar illness. This study found that neither moderate nor excessive use of alcohol has a negative effect on the course and outcome of bipolar illness. Possible explanations for these findings are discussed.

INTRODUCTION

Many patients with bipolar disorders (BDs) use alcohol on a regular basis. About 50% of patients with bipolar disorders meet lifetime criteria for comorbid substance use disorders (SUDs).[1-6] The negative effects of comorbid SUDs (including alcohol use disorders [AUD]) on course and outcome of bipolar disorder are well documented.[5,7] Previous studies found that bipolar disorder with comorbid SUD is associated with an earlier age of onset[8-11] but, in other studies, also with a later age at onset[12-14], a higher number of episodes[15], longer episodes[16], more symptoms during inter-episode intervals[17,18], a higher probability to experience syndromal recurrence[13,19], more mixed episodes[20], a higher number of total mood-related symptoms and manic symptoms at presentation[21], more hospitalizations[3,22], more suicidality[23], decreased treatment adherence[17,18], and poorer response to treatment[16,24] compared to bipolar disorder without comorbid SUD.

In contrast, the effects of actual alcohol consumption, including moderate use, in bipolar disorder are less well known. Therefore, we did a search of Embase Psychiatry (1997 - 2nd quarter 2008), Medline (1950 - present), and PsycInfo (1958 - May 2008) with the following search words: *mania, manic depressive illness, bipolar disorder, and moderate alcohol use, alcohol consumption, alcoholism, alcohol abuse, alcohol dependence, drinking behaviour, and social drinking*. In addition, cross-references from the obtained articles were also used to find other articles on this subject. This search resulted in 10 published studies that addressed the effects of (moderate) alcohol use on the course and outcome of bipolar disorder: 5 retrospective studies and 5 prospective follow-up studies. The 5 prospective studies[19,23,25-27] and 1 of the retrospective studies[28] mainly looked at

previous and/or current AUD without further specification of the actual amount of alcohol intake. The main findings of these 5 prospective studies were that AUD in BD patients was associated with syndrome recurrence in adolescents[19], poor residential status and occupational outcome[25], and shorter time in remission.[25,26] In addition first episode patients for whom AUD predated BD were older and were more likely to recover than patients with BD only and patients for whom BD predated AUD, while patients for whom AUD developed after the onset of BD spent more time in affective episode and had more AUD symptoms.[24,27]

The other 4 studies[21,22,29,30] (also) looked at the actual amount of alcohol intake. The frequency and volume of alcohol consumption in these studies, all with a retrospective design, was assessed in different ways. Reich et al.[22] measured alcohol consumption (excessive-moderate and chronic-episodic) by using prior records of patients. Salloum et al.[21] assessed alcohol use with a 4-point scale (absent-mild-moderate-severe misuse, rated by a clinical investigator) based on the report of patients about their alcohol use during the period of two weeks before their participation in the study. McKowen et al.[29] used the timeline follow back method.[31] With this method, patients retrospectively charted the amount of alcohol and number of drinking days in a calendar-like fashion over a 30-day episode before entering the study. Goldstein et al.[30] preformed the only study that addressed the association of moderate alcohol use and illness severity in bipolar disorders using the Khavari Alcohol Test to assess the frequency and volume of overall alcohol consumption, as well as consumption of beer, wine, and spirits.[32] The most important findings of these 4 studies were that moderate or excessive alcohol use was found to be associated with (1) being hospitalized

versus never been hospitalized[22]; (2) more frequently having a rapid cycling course and a recent diagnosis[29]; (3) more mood lability, more manic symptoms, more other drug use, and more impairment in overall functioning[21]; and (4) more lifetime manic episodes and emergency department visits in men and with more lifetime depressive and hypomanic episodes in women.[30]

All 10 studies have considerable limitations. In the 5 retrospective studies, recall bias may have influenced the reliability and validity of the data, whereas in the 5 prospective studies, only a very spaced follow-up was performed with periods between the various assessments ranging between 4 and 192 weeks. In addition, only use/abuse of alcohol in general was assessed and almost never the actual amount of alcohol intake. As a consequence, almost no data are available about the effect of moderate alcohol consumption on the course and outcome of bipolar disorder. In addition, it is difficult to compare the results of the studies due to variations in patient populations (e.g. hospitalized versus non-hospitalized), in diagnostic assessments and criteria, and in definitions of episodes and thresholds. Finally, most of the studies did not specify whether patients also used illegal drugs, which is relevant as there is a strong correlation of AUD with drug abuse and dependence.[33]

In conclusion, to our knowledge, there is no well-designed prospective follow-up study that compared the effect of actual amounts of alcohol use on the course and outcome of patients with bipolar disorders. Therefore, we conducted a prospective cohort study in which patients with a bipolar disorder were asked to register their mood symptoms and their actual alcohol use every day for a period of 12 months. We hypothesized a priori that the course and outcome of

bipolar patients with moderate use of alcohol would not differ from patients who did not or only occasionally use alcohol. We also hypothesized that patients with excessive use of alcohol would have a significantly worse course and outcome compared to patients with no or occasional as well as patients with moderate use of alcohol.

METHOD

Subjects and recruitment

Patients had to meet the following inclusion criteria: (1) aged 18-75 years; (2) meeting Diagnostic and Statistical manual of Mental Disorders, Fourth Edition (DSM-IV) criteria[34] for bipolar I disorder or bipolar II disorder; (3) not having a serious physical illness, that might influence the diagnosis or course of bipolar disorder, according to the clinical judgment of the treating physician; (4) able and willing to participate in the study for 1 year; (5) with adequate command of the Dutch language. The study was approved by the Medical Ethical Review Committee of the University Medical Center Utrecht (The Netherlands). All patients gave written informed consent after full explanation of the study.

Between June 2003 and November 2005, a total of 180 outpatients were approached: 128 patients from 13 mental hospitals, including 2 academic medical centers; 4 patients from one addiction treatment center; and 48 patients through the Dutch Association for Manic-Depressive Patients and Relatives. Of these, 158 patients (87%) entered baseline assessment. The other 22 patients

were excluded because they did not give informed consent (n = 18), had no adequate command of the Dutch language (n = 1), had too severe alcoholism (n = 1), suffered from a substance-induced mood disorder (n = 1), or had a schizoaffective disorder (n = 1).

From the158 patients who completed the baseline assessment, 137 subjects (76%) participated in the study for at least 2 months, 125 patients (69%) participated for at least 6 months, and 104 patients (58%) completed the whole year. Analyses were based on the 137 patients with follow-up data during at least two months. Reasons for the 33 non-completers beyond two months were to against the daily registrations (n = 16), developing a depressive (n = 2) or manic episode (n = 2), worsening of their alcohol dependence (n = 2), non-compliance (n = 2), death by a natural cause (n = 1) or liver coma due to alcoholism (n = 1) and other reasons (n = 7).

Assessment

At entry the Structured Clinical Interview for DSM-IV (SCID-I)[35] was administrated by trained mental health care professionals. In order to compare the results of our study with other studies, data were also obtained by means of the Network Enrolment Questionnaire of the former Stanley Foundation Bipolar Network.[36,37] These data included demographic and social characteristics, such as marital status, educational background, past and current level of occupational functioning and household income, and clinical characteristics such as family history of psychiatric illness, estimated prior course of illness variables (number of prior episodes, number of hospitalizations, history of rapid cycling, history

of alcohol induced depression, hypomania, mania and cycle acceleration), treatment adherence, and number of past suicide attempts. Self-report data about substance use were obtained with a questionnaire about the present and past use of substances (quantity, frequency, and age at onset), including information on caffeine, nicotine, alcohol, cannabis, ecstasy, amphetamines, lysergic acid diethylamide (LSD), cocaine, heroine, andother drugs.

During the full year of the study, patients rated their mood with the National Institute of Mental Health (NIMH) Self-Rating Prospective Life Chart Method (LCM) every day. The LCM is a reliable method for the measurement of severity of mood symptoms (mania or depression) and related level of dysfunction on a five-point scale (0 = no, 2.5 = mild, 5 = low moderate, 7.5 = high moderate, and 10 = severe dysfunction), which also allows to assess hypomanic, manic, and depressive episodes in patients with bipolar disorders.[38-45] Using the LCM, patients were also asked to report daily on their use of medication and their intake of alcohol (number of alcohol units), for which patients got written and verbal instructions about the standard units of alcohol in beer, wine, and spirits. One unit was defined as 12 ml pure alcohol (equals about 10 gram of alcohol) equaling 100 ml of wine (12% alcohol), 250 ml of beer (5% alcohol), or 35 ml of liquor (35% alcohol).[46]

At baseline and at every monthly visit during follow-up, the LCM registrations were checked and approved by the research assistants who then also completed the Clinical Global Impression Scale-Bipolar Version (CGI-BP)[47], the Global Assessment of Functioning (GAF) scale[48], the Medical Outcomes Study 36-Items, Short-Form Health Survey (MOS-SF-36)[49], and a questionnaire concerning the direct and indirect medical care utilization of the prior month.

Outcome measures

Based on the LCM registrations (up to 1 year), the following clinical outcome measures were calculated per first 4 weeks and per year: (1) the number of manic days (LCM score at least low moderate mania), the number of hypomanic days (LCM score mild mania), the number of depressed days (LCM score at least low moderate depression) and the total number of days ill; (2) the mean severity of mania, depression, and overall bipolar illness over the observation period (mean LCM score for each pole [manic or depressed] separately or the maximum of both poles [overall]; days on which patients switched mood states at least once were assigned to the most severe depression score and the most severe mania score); and (3) the number of episodes based on DSM-IV criteria and on the so-called NIMH Leapfrog method as previously described by Denicoff et al.[41] In addition, monthly assessment questionnaire outcomes were obtained: (4) GAF- scores, (5) CGI-BP scores and (6) MOS-SF-36 scores.

Based on DSM-IV, manic episodes were counted if they included a minimum score on the LCM of 7 days of at least low moderate mania (or hospitalization), hypomanic episodes were counted if they included a minimum of 4 days of an LCM score of mild mania, and depressive episodes were counted if they included a minimum of at least 14 days with an LCM score of low moderate depression (or hospitalization).

According to the Leapfrog method, a manic episode required a minimum of 1 day of moderate or severe mania, a hypomanic episode required a minimum of 2 days of mild mania, and a depressive episode required 2 days of moderate depression or 1 day of severe depression. In addition, an episode was

considered ended with a switch in mood polarity (from mania to depression or vice versa), after at least 2 weeks of complete euthymia, or when the euthymic interval between 2 successive hypomanic, manic or depressive episodes was at least 1 day greater than the longest duration of the adjacent episode of the same polarity.[41,50]

Outcome predictors

In order to distinguish different types of drinking patterns at baseline, subjects were assigned to three different groups (no or incidental use, moderate use, or excessive use), based on the average number of units of alcohol per week that patients used in the first 4 weeks of the study. We chose the Dutch standard of about 10 gram of pure alcohol per standard drink (unit) and the following a priori defined drinking levels: level I (no or incidental use) as 0-2 units of alcohol/week (n = 44); level II (moderate use) for males as 3-21 units/week and for females as 3-14 units/week (n = 49); and level III (excessive use) for males as 22 or more units/week and for females as 15 or more units/week (n = 44).[46] Males were considered to have a heavy drinking day if they consumed 5 or more units per day, and females were considered if they consumed 4 or more units per day.[51]

Weekly alcohol intake (no, moderate, and excessive) and the number of heavy drinking days during the first 28 days and of the follow-up period were used as the main predictors of outcome. In addition, lifetime or current AUDs and SUDs (alcohol excluded) were used as predictors of outcome.

To gain insight into the validity and stability of the operationalization of alcohol level, the number of switches between alcohol levels during the observation

period was studied. A switch from one level to another between 2 consecutive weeks was indicated according to the definition of alcohol level, accompanied by the demand that a difference of at least 5 drinks between two weeks should be present. Application of this definition to the alcohol levels found at baseline (first 4 weeks) showed that most switches occurred between the moderate and excessive drinking levels (mean ± SD number of switches per year: level I, 1.7 ± 3.5; level II, 6.9 ± 6.0; level III, 5.2 ± 6.3; $F = 10.8$ $p < .01$).

In the total sample of N = 137, 44 subjects (32%) did not change their alcohol level at any time during the observation period. The majority (n = 28) of these 44 non switchers remained in the first, no-drinking level I. From the other 93 subjects who switched levels at least 1 time, 38 subjects (28%) switched alcohol level more than 5 times during follow-up. The majority of changes occurred between level II and III. Spearman rank correlation test between alcohol level in the first 4 weeks and during follow-up was .81 ($p < .01$), indicating good correspondence between initial and follow-up levels, and, as such, the two measurement periods were usable for further analysis.

Confounders

A positive family history of SUDs, more than 10 prior manic or depressive episodes, a history of prior rapid cycling, and poor occupational functioning at study entry, which have been found to predict outcome of bipolar disorder in general, were considered as potential confounders for the relation between alcohol-use levels and 12-month clinical course and outcome.[50]

Table 1. Sociodemographic characteristics at baseline of participants with no or incidental alcohol use (Level I), moderate alcohol use (Level II) or excessive alcohol use (Level III)[a].

Characteristics	Level I n=44 (32%)	Level II n=49 (36%)	Level III n=44 (32%)	Total n=137	Statistics	P value
Age, mean (SD), y	46.7 (9.4)	44.4 (10.9)	46.8 (10.2)	45.9 (10.2)	$F_2 = 0.85$	.43
Gender, male	22 (50)	26 (53)	24 (55)	72 (53)	$X^2_2 = 0.19$	.91
Marital Status					$X^2_2 = 1.95$	.38
With partner	18 (41)	24 (49)	25 (57)	67 (49)		
Without partner	25 (57)	25 (51)	19 (43)	69 (50)		
Unknown, n	1 (2)			1 (1)		
Annual income, €					$X^2_2 = 1.16$	.56
< 20,000	30 (68)	28 (57)	24 (55)	82 (60)		
≥ 20,000	14 (32)	18 (37)	18 (41)	50 (36)		
Unknown, n		3 (6)	2 (5)	5 (4)		
Educational Level					$X^2_2 = 1.51$	.47
≤ High School	22 (50)	20 (41)	23 (52)	65 (47)		
> High school	21 (48)	29 (59)	21 (48)	71 (52)		
Unknown, n	1 (2)			1 (1)		
Job matches qualification					$X^2_2 = 1.18$	.55
Yes	3 (7)	6 (12)	6 (14)	15 (11)		
No	41 (93)	43 (88)	38 (86)	122 (89)		
Unable to work					$X^2_2 = 1.06$	.59
Yes	24 (55)	22 (45)	20 (45)	66 (48)		
No	20 (45)	27 (55)	24 (55)	71 (52)		

[a]Baseline characteristics are presented as n (%) unless noted otherwise.

Table 2. Clinical characteristics at baseline of participants with no or incidental alcohol use (Level I), moderate alcohol use (Level II) or excessive alcohol use (Level III).

Characteristics	Level I n=44 (32%)	Level II n=49 (36%)	Level III n=44 (32%)	Statistics	P value
Diagnosis, n (%)					
Bipolar I Disorder	29 (66)	31 (63)	30 (68)		
Bipolar II Disorder	15 (34)	18 (37)	14 (32)		
				$X^2_2 = 0.25$	.88
Lifetime Diagnosis, n (%)					
Alcohol use disorder (abuse and dependence)	18 (41)	13 (27)	29 (66)	$X^2_2 = 14.8$	**.001**
Drug abuse and dependence	11 (25)	7 (14)	11 (25)	$X^2_2 = 2.16$	.34
Anxiety disorder	18 (41)	16 (33)	13 (30)	$X^2_2 = 1.35$	.51
Current diagnosis, n (%)					
Alcohol use disorder (abuse and dependence)	1 (2)	4 (8)	22 (50)	$X^2_2 = 43.8$	**<.001**
Drug abuse and dependence	2 (5)	4 (8)	2 (5)	$X^2_2 = 0.75$	.69
Anxiety disorder	6 (14)	7 (14)	6 (14)	$X^2_2 = 0.01$	.99
Parental history, n (%)					
Depression	29 (66)	29 (59)	23 (52)	$X^2_2 = 1.69$	.43
Bipolar disorder	11 (25)	24 (49)	20 (45)	$X^2_2 = 6.3$	.04
Alcoholism	9 (20)	15 (31)	13 (30)	$X^2_2 = 1.42$	.49
Drug abuse and dependence	2 (5)	1 (2)	4 (9)	$X^2_2 = 2.42$	.30
Age at onset of bipolar disorder, mean (SD), y	23.8 (9.6)	24.3 (9.7)	24.3 (10.6)	$F^2 = 0.05$	.96
Duration bipolar disorder, mean (SD), y	23 (10.1)	19.8 (11.9)	22.6 (12.4)	$F^2 = 1$	.36
No. of episodes, mean (SD)					
Depression	17.1 (30.8)	13.7 (20.3)	14.8 (17.8)	$F^2 = 0.23$	.80
Mania or hypomania	12.7 (19.9)	14.7 (24.6)	14.0 (19.7)	$F^2 = 0.1$	.91
No. of hospitalizations, mean (SD)					
Depression	.85 (1.5)	0.7 (1.2)	1.1 (3.2)	$F^2 = 0.47$	.62
Mania or hypomania	1.2 (1.6)	1.2 (2.1)	1.7 (3.0)	$F^2 = 0.66$	.52
Age at onset acohol use disorder (abuse and dependence), mean (SD),y	22.7 (7.8)	25.3 (12.3)	26.2 (9.5)	$F^2 = 0.65$	.53
Rapid cycling, n (%)	16 (36)	15 (31)	12 (27)	$X^2_2 = 0.87$	.65
History, n (%)					
Alcohol-induced depression	4 (9)	4 (8)	3 (7)	$X^2_2 = 0.31$	.86
Alcohol-induced mania or hypomania	3 (7)	3 (6)	4 (9)	$X^2_2 = 0.17$	.91
Cycle Acceleration	2 (5)	1 (2)	4 (9)	$X^2_2 = 2.0$	.36
No. of serious suicide attempts (1 or more)	9 (20)	12 (24)	9 (20)	$X^2_2 = 0.20$	.91

[a]Bolded P values denote significance.

Statistical analysis

All analyses were performed with the data of the 137 patients who completed at least 2 months of registration after baseline. No significant differences ($p < .10$) were found in the sociodemographic and baseline variables on mood symptoms, alcohol use, and other drug use between the 104 patients who completed the full study and the 33 patients with at least 2-month, but less than 12-month, follow-up data.

We used the 3 initial levels of alcohol use (no or incidental, moderate, and excessive use during the first 4 weeks of registration) as the main predictors for outcome variables.

Explorative analysis of the homogeneity of variance showed that some of the dependent variables scored significantly on the Levene statistic, indicating differences in variance (possibly due to outliers) in these variables for the three distinct alcohol levels. After log transformation of these variables, these differences in variance disappeared. Thus, the transformed scores for these variables were entered into the analyses.

Variables based on life-chart data with less than 365 days of observations were corrected with the use of the length of the actual observation period (values were multiplied by 365 and divided by number of observations).

Means and standard deviations on outcome variables were generated, and χ^2 tests or F tests of means were used to assess differences between the 3 alcohol levels on outcome variables using a significance level of $a = .01$.

Table 3. Outcome in patients with no or incidental alcohol use (Level I),

Variable	Level I, n=44 (32%)		Level II, n=49 (36%)	
	First 4 Weeks Mean (SD)	Follow-up Year[a] Mean (SD)	First 4 Weeks Mean (SD)	Follow-up Year[a] Mean (SD)
No. of heavy drinking days[c]	0.02 (0.15)	0.35 (1.4)	2.1 (2.6)	2.1 (2.6)
No. of drinks/days	0.06 (0.09)	0.18 (0.4)	1.3 (0.7)	1.3 (0.9)
No. of days ill per 4 weeks				
No. of depressed days[d]	5.2 (8.4)	5.0 (6.8)	4.2 (7.7)	4.2 (6.5)
No. of hypomanic days[d]	3.8 (6.8)	3.3 (4.6)	2.8 (4.8)	3.1 (4.5)
No. of manic days[d]	1.5 (5.8)	0.96 (2.6)	0.69 (2.7)	0.73 (1.65)
Total no. of days ill	10.5 (12)	9.2 (8.3)	7.7 (10.7)	8.0 (8.3)
Mean severity (LCM)				
Depression[e]	1.4 (1.7)	1.4 (1.5)	0.91 (1.4)	1.1 (1.3)
Mania[f]	0.63 (1.3)	0.49 (0.76)	0.39 (0.77)	0.44 (0.62)
Overall	2.2 (2.0)	2.2 (1.6)	1.4 (1.6)	1.6 (1.3)
GAF (1-100)	68 (13)	68 (9.7)	73 (9.0)	72 (9.9)
CGI-BP (1-7)				
Depression	2.2 (1.2)	2.3 (0.99)	1.8 (1.0)	2.1 (0.86)
Mania	1.5 (.90)	1.5 (0.62)	1.4 (0.80)	1.4 (0.43)
Overall	2.5 (1.3)	2.4 (1.1)	1.9 (1.2)	2.2 (0.90)
MOS-36-SF score[g]				
Physical functioning	85 (20)	85 (18)	84 (21)	87 (14)
Social functioning	67 (24)	65 (17)	65 (22)	66 (17)
Physical problems	65 (44)	64 (29)	56 (43)	68 (28)
Emotional problems	58 (45)	56 (32)	57 (40)	57 (28)
Mental Health	65 (19)	64 (15)	63 (18)	65 (13)
Vitality	55 (19)	53 (14)	53 (20)	57 (14)
Pain	83 (20)	73 (19)	73 (23)	73 (14)
General Health	61 (19)	60 (19)	60 (24)	61 (17)
No. of episodes (DSM-IV) per year				
Depressive episodes		1.1 (1.9)		0.62 (1.3)
Hypomanic episodes		3.3 (5.0)		2.9 (3.4)
Manic episodes		0.33 (1.1)		0.40 (1.1)
N episodes (Leapfrog Method) per year[h]				
Depressive episodes		2.7 (4.5)		2.3 (2.9)
Hypomanic episodes		5.1 (7.9)		4.6 (5.8)
Manic episodes		2.1 (5.3)		1.5 (3.3)

[a]Follow-up year per 4 weeks of LCM registration.

[b]Bolded P values denote significance.

[c]Heavy drinking defined as ≥ 5 units/day (males) and ≥ 4 units/day (females).

[d] See text for explanation.

[e]Range from 0 till –10. See text for explanation.

[f] Range from 0 till +10. See text for explanation.

[g]Score MOS-36-SF range from 1-100. Higher score correlates with better functioning, better health and fewer problems.

[h]See text for explanation.

Abbreviations: CGI-BP = Clinical Global Impression Scale-Bipolar version, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, GAF = Global Assessment of Functioning scale, LCM = National Institute of Mental Health (NIMH) Self-Rating Prospective Life-Chart Method, MOS-SF-36 = Medical Outcome Study 36-Item Short-Form Health Survey.

moderate alcohol use (Level II), or excessive alcohol use (Level III)

Level III, n=44 (32%)		Statistics First 4 weeks			Statistics Year		
First 4 Weeks Mean (SD)	Follow-up Year[a] Mean (SD)	F	df	P[b]	F	df	P[b]
17.2 (6.9)	13.5 (7.4)	223	2	**<.001**	110	2	**<.001**
5.3 (2.1)	4.5 (2.4)	197	2	**<.001**	103	2	**<.001**
5.4 (8.6)	5.0 (7.0)	0.29	2	.75	0.23	2	.80
3.9 (6.3)	2.3 (3.1)	0.56	2	.57	o.79	2	.45
0.27 (1.1)	0.34 (0.7)	1.6	2	.21	1.4	2	.24
9.5 (9.8)	7.6 (7.9)	0.76	2	.47	0.4	2	.65
1.5 (1.7)	1.4 (1.5)	2.0	2	.14	0.94	2	.40
0.40 (0.63)	0.27 (0.37)	1.0	2	.37	1.7	2	.18
2.0 (1.8)	1.8 (1.6)	2.3	2	.10	0.71	2	.49
70 (11)	68 (10.5)	2.1	2	.13	2.2	2	.11
2 (1.1)	2.3 (1.0)	1.7	2	.19	0.77	2	.46
1.6 (0.90)	1.5 (0.58)	0.51	2	.60	0.04	2	.96
2.5 (1.1)	2.3 (0.93)	3.1	2	.05	0.91	2	.41
84 (18)	85 (15)	0.06	2	.94	0.23	2	.80
63 (28)	62 (19)	0.21	2	.81	0.91	2	.41
67 (39)	64 (27)	0.86	2	.43	0.25	2	.77
54 (42)	56 (30)	0.10	2	.90	0.00	2	.99
61 (18)	61 (13)	0.54	2	.58	0.81	2	.45
53 (21)	54 (14)	0.18	2	.83	0.84	2	.44
80 (23)	69 (18)	0.26	2	.08	0.55	2	.58
54 (22)	56 (15)	0.17	2	.20	0.95	2	.40
	0.91 (1.5)				1.1	2	.33
	2.1 (2.6)				1.2	2	.29
	0.12 (.39)				1.2	2	.30
	2.4 (2.6)				0.14	2	.87
	3.2 (4.3)				1.1	2	.33
	0.98 (2.0)				1.0	2	.37

RESULTS

Sample characteristics at baseline

The 137 patients returned 44,808 days with LCM data (mean ± SD = 327 ± 76 per patient; range, 62 - 365 days per patient). The mean ± SD of recorded LCM days for alcohol use per group level I, II, and III were respectively 339 ± 66, and 327 ± 80, 317 ± 80 and did not differ significantly (F_{136} = .99, p >.10). Thirty-seven patients (84%) of level I completed 90% or more of the 365 days of life-chart registration, versus 38 patients (78%) in level II and 33 patients (75%) in level III. There was no significant difference in number of recorded life charts days between the three group levels (p > .5).

Sociodemographic data at baseline are shown in table 1. Patients in the three drinking groups were comparable with respect to all sociodemographic variables: mean age, 46 years; males, about 50%; with partner, about 50%; high school education, about 50%; and not able to work, about 50%.

The clinical characteristics at baseline, as presented in table 2, show that 90 of the patients (66%) had a bipolar I disorder (46 male, 44 female) and 47 (34%) had a bipolar II disorder (25 male, 22 female). The gender distribution within the bipolar I and II groups did not differ significantly, X^2_1= .01, p = .53 (results not presented). Of the 137 patients 52% had a BD only; in 21% of the patients BD predated AUD by 1 year or more; and in 27% of the patients, AUD predated BD with a year or more.

None of the clinical characteristics were significantly different between the three drinking groups, with the exception of – and as a consequence of the assignment – the prevalence of lifetime and current diagnosis of AUD: 66% of

the level III patients had a lifetime AUD, and 50% had a current AUD; 26% and 8% of the level II patients had a life time or current AUD; and 41% and 2% of the level I patients had a life time or current AUD. The only patient of the level I group with current AUD at baseline stopped his alcohol intake at the start of the LCM registration. Current abstainers can either be life time abstainers or abstinent former alcoholics. Therefore, baseline comparisons were also performed without those level I patients with a lifetime diagnosis of AUD. Again, there were no significant differences except the differences in AUD diagnosis. Since neither of the baseline characteristics and the a priori confounders (positive family history of SUDs, more than 10 prior manic or depressive episodes, a history of prior rapid cycling, and poor occupational functioning at study entry) were significantly different for the three drinking groups, prediction of outcome by drinking level was not corrected for baseline variables.

Outcome and outcome prediction

Table 3 shows that there were large and significant differences between the three groups in the number of heavy drinking days and drinks per drinking day during the first 4 weeks and during further follow-up. Surprisingly, no differences between the three drinking groups were found in any of the clinical outcome variables, i.e. not in terms of the number of days ill (depressed, hypomanic/manic, and total), severity of depression, mania and overall bipolar illness, GAF score, CGI-BP score (depression, mania, and overall), and all the subscales of the MOS-SF-36. Also, the number of episodes according to the DSM-IV and the Leapfrog method showed no significant difference between the drinking groups.

Because the number of drinks per week of level III has no upper limit, the same outcome analyses were made with the top 10% of heavy drinking day patients and the 22 patients (50%) of level III patients with a current AUD at baseline. Again, no significant differences were found in outcomes between the groups. To exclude a possible negative effect on outcome of the level I patients with a lifetime diagnosis of AUD, additional follow-up comparisons were performed without those level I patients. Once more, there were no significant differences in outcome between the groups. In order to check for potential confounding of the relationship between drinking levels and outcome by the presence of a lifetime AUD diagnosis at baseline, we repeated the analyses for those subjects with no lifetime AUD (n = 77). Again, no significant differences were found between the three alcohol group levels with respect to mood severity scores, number of episodes, and number of ill days.

DISCUSSION

The main result of our study is that we found no differences in clinical baseline characteristics nor in the one-year course and outcome between bipolar patients with no or incidental alcohol use, moderate alcohol use, and excessive alcohol use as assessed during the first 4 weeks of the study.

These findings confirm the first part of our hypothesis – that the prospective course and outcome of bipolar patients with moderate use of alcohol would not differ from patients who did not or only occasionally use alcohol. This is in contrast with the findings of Goldstein and colleagues[30], who found that even

small amounts of alcohol had a negative effect on several clinical characteristics. It is difficult to compare the results of our study with those of Goldstein and colleagues, because in the latter study, only bipolar patients without any lifetime or current SUD (inclusive alcohol) and who exceeded the weekly maximum intake for their gender were included. In our sample 27% of the patients with moderate alcohol use had, at baseline, a lifetime diagnosis of AUD, 8% had a current AUD, 14% had a lifetime drug use disorder, and 8% had a current drug use disorder. However, these differences between the studies do not explain why no effect of moderate alcohol compared to no or incidental use on outcome was found in the current study.

To our surprise, the second part of our hypothesis – that patients with excessive use of alcohol would have a significantly worse 12-month course and outcome compared to both bipolar patients with no or occasional drinking and those with moderate drinking – was not confirmed. Thus, our data are not in line with the findings from the literature showing that excessive use of alcohol or the presence of an AUD predicts a negative course and outcome of patients with a bipolar disorder in terms of the severity of the illness and social functioning. Moreover, we did not find any association between excessive alcohol use and gender, suicidality, or family history of AUD, as other studies did.

What are the possible explanations for these unexpected findings regarding the patients with excessive alcohol use?

First, our patients with excessive alcohol use may have been less ill than the patients in previous studies. Despite the fact that they used alcohol in excessive

amounts and had many heavy drinking days at baseline (17.2 per first 4 weeks) and during the follow-up (13.5 per 4 weeks), “only” 50% of them met DSM-IV criteria for a current AUD diagnosis and 66% for a lifetime AUD, while in all previous studies (except the Goldstein et al study[30]), comparisons were made between bipolar patients with or without AUD, alcohol misuse, or alcoholism. However, a post hoc analysis of the current study among the participants with a higher drinking threshold for excessive use and current AUD at baseline also did not reveal that this subgroup was associated with a worse outcome. Second, our patients with excessive alcohol use may have had lower rates of abuse and dependence of other drugs. In the current study, “only” 25% had a lifetime drug use disorder and only 5% had a current drug use disorder. The percentage of patients in the previous studies who, next to alcohol, also used other drugs/ substances, were, if mentioned, higher (35%).[21] In these studies, however, no correction for comorbid drug use was reported in the analyses. This means that part of the observed effect of heavy alcohol use on the course of bipolar disorders in other studies may have been the result of comorbid drug abuse or dependence. Third, the negative effect of excessive alcohol use on the outcome of BD may have an effect only in the early years of the disorder, whereas its effect levels out with longer illness duration and a higher number of previous episodes. This is supported by a previous study[52] in the Danish case register with 22 years of registration that found that concurrent alcoholism increased the risk of recurrence of episodes during the initial course of unipolar and bipolar disorder but that it had no effect on recurrences later in the course of the illness. In our sample, the mean illness duration was about 22 years and the mean

number of episodes was more than 20. Indeed, the age of the patients in the four referred studies[22,23,29,30] was 4-12 years younger than in our study. In line with this explanation are the findings of a 7 year follow-up study[53] showing that younger patients (aged 17-26 years) may have a greater likelihood that alcohol use and bipolar symptoms increase and decrease in unison. Fourth, the differences between the findings in our study and those in the literature may reflect a difference between Europe and the US, where 9 of the 10 previous studies were conducted. Indeed, there are indications that bipolar disorder in Europe starts at a later age and has a more benign course than in the US.[54] In the (former Stanley Foundation) Collaborative Bipolar Network, US patients reported a higher frequency of comorbid substance misuse than European patients (47 % versus 27%).[54] In our sample, 29 of the 137 patients (21%) had a lifetime diagnosis of drug abuse or dependence, which is comparable to the above European data and, indeed, lower than the 35% as found in the US study by Salloum et al.[21] Similar differences may exist in the effects of excessive alcohol use on the course of the disorder, although no simple explanation for such a difference is currently available. Fifth, all participants (including the patients with excessive use) in our study reported to be very adherent to their prescribed medication, both at baseline and during follow-up, ie, to have taken their medication on more than 90% of the recorded days, according to their LCM registration. It should be noted that self-reported adherence has a specificity of 90%, and that patients may over-estimate their actual adherence with 17%.[55,56] Generally, non-adherence is very common (20%-70%) among BD patients and has a negative effect on the course and outcome of bipolar disorder.[57,58] Moreover, current SUD, but not past

SUD, is associated with treatment non-adherence.[59] Adherence (medical and behavioral) with treatment grows with time, which could be an explanation that patients in their early course (0-10 year) of bipolar illness suffer more from the effects of excessive use of alcohol. The high rate of adherence in our sample could be an important protective factor for the effect of excessive alcohol use on clinical outcome. Sixth, the close monitoring with monthly assessments of the patients may have had a positive effect on outcome, and a possible reason why the negative effects on outcome of excessive drinking were nullified. Seventh, it can not be excluded that excessively drinking patients were significantly different from occasionally and moderately drinking patients in aspects that were not measured in the current study and that these aspects had a positive effect on outcome, thus compensating for the negative effect of excessive alcohol use. A final possibility is that patients sensitive to the negative effects of alcohol were not present in the current study due to the rather serious requirements for participation, including the daily registration of mood and alcohol and substance use. They may for instance be over represented among the 18 of the 180 patients (10%) who were approached and who refused to participate. However, it seems unlikely that this relatively small group would have changed the results completely.

Our study has both strengths and limitations. The major strengths include the prospective design with 12 months of daily follow-up assessments, the broad spectrum of confounders that were considered, and the broad range of outcome parameters that were included. A major limitation is selection and its effect on the external validity of our findings. Thirty eight of the 137 patients (28%)

were members of the Dutch Association for Manic Depressives and Relatives, and they should be considered as very motivated patients and adherent to the therapy. Finally, 1 year of detailed follow-up may not be long enough to catch the negative effects of excessive use of alcohol on the course of BD.

CONCLUSION

Despite the methodological strengths of our study, we could not confirm the findings of previous studies that excessive use of alcohol has a negative effect on the course and outcome of bipolar illness. We also did not find that moderate use of alcohol has a negative effect. Previous studies showing such negative effects had different designs and partly included other types of patients, such as patients in an earlier phase of their illness and/or with more comorbid drug abuse and poorer medication compliance. Our findings suggest that recommendations to patients with BD to refrain from alcohol completely[30] are not applicable to all patients with BD. Based on the results of the other studies, recommendations as such should be given, especially to BD patients in the early course of their illness.

Nevertheless we support recommendations from others[28,56,58,60] that both BD patients with and without alcohol use or a comorbid AUD should be stimulated and controlled for their regular use of medication and that patients with a comorbid AUD should receive integrated treatment for their BD and AUD.[61]

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4

THE EFFECT OF ALCOHOL USE ON THE COURSE OF BIPOLAR DISORDERS

One year follow-up study using the daily Prospective Life Chart Method

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ABSTRACT

OBJECTIVES Relatively little is known about the temporal relationship between alcohol use and subsequent mood changes in patients with bipolar disorder and available findings are inconsistent. The present study is a fine grain analysis of the temporal relation between alcohol use and short-term mood switching probabilities.

METHODS Included were 137 patients with bipolar disorder who daily rated their mood symptoms and the number of alcohol units consumed for a period up to 52 weeks with the NIMH self-rated Prospective Life Chart Method. At baseline the SCID-IV was administered and demographic, social and clinical characteristics were obtained. Multi-state models were used to assess the impact of the number of alcoholic drinks on the patients' transition through different states of mood (depression, euthymia and mania).

RESULTS The effect of alcohol use on the change in mood states was limited. For women in a depressive state, higher alcohol use was associated with a shorter time before entering the euthymic state (HR = 1.18, 95% [1.03 – 1.36], p<.05), whereas for men in an euthymic state higher alcohol use was associated with a longer time before entering a manic state (HR = 0.81, 95% CI: [0.71 – 0.92], p < .05). The correlation between the consumed number of drinks per week and the average mood severity score of the following week was -0.01 (p<.001), indicating that only 0.01% of the variance in mood severity in this population is explained by alcohol use. Possible explanations for these findings are discussed.

CONCLUSIONS The current study with a fine grain analysis suggests that alcohol use does not have a direct effect on the course of bipolar disorder in patients using mood stabilizers.

INTRODUCTION

About 50% of all patients with bipolar disorder (BD) have a comorbid alcohol use disorder (AUD), which may affect the outcome of BD.[1-5] However, findings regarding the effects of comorbid AUD on the course and outcome of BD are inconsistent. On the one hand, a series of negative effects of comorbid AUD has been reported such as more frequent and longer symptomatic episodes, more residual symptoms during inter-episode intervals, a higher probability of syndromal recurrence, more mixed episodes, and decreased treatment adherence.[6,7] On the other hand, these negative effects of comorbid AUD on the course of bipolar illness were not confirmed in a sample of patients with BD adequately treated for their bipolar illness.[6] Moreover, very little is known about the temporal relationship between alcohol use and mood changes in patients with BD. Do depressive or manic symptoms precede alcohol use, do they coincide, or does alcohol use precede depressive or manic symptoms?

We are aware of only four studies looking at the relationship between alcohol use and mood states in patients with bipolar disorder. Fleck et al.[8] followed 71 BD type I (BD-I) patients with no prior hospitalization and minimal treatment of whom 35% had a lifetime AUD for up to 7 years (mean 3.09 years, SD=1.67) with weekly measures of the degree to which the patients' severity of alcohol use was related to the severity of mood symptoms. They did not find a consistent temporal relation of BD and AUD symptoms. Baethge et al.[9] followed 166 first-episode BD-I patients of whom 45% met criteria for a substance use disorder (SUD) for up to 8 years (mean 4.54 years, SD=2.46) with weekly assessments until discharge and then a follow-up with 6-12 month intervals.

They found that dysthymia, subthreshold depression and depression, pooled as depressive morbidity, were associated with alcohol use in the preceding or the same quarter of the year but not in the following quarter. However, there was no such relationship between subthreshold mania, hypomania and mania, pooled as manic morbidity, and alcohol use. Jaffee et al.[10] followed 115 patients with a current BD (80% BD-I) and SUD monthly for up to 8 months. They found that days of (heavy) alcohol use (≥3 drinks/day) and an increase in days of (heavy) alcohol use each significantly predicted the presence of a depressive episode in the subsequent month when controlling for current depression and current drug use. Finally, Prisciandaro et al.[11] followed 30 patients with co-occurring bipolar disorder (50% BD-I) and alcohol dependence to examine the impact of depressive symptoms and alcohol craving on proximal (i.e., 1 week later) alcohol use. They showed that depressive symptoms and alcohol craving significantly predicted the transition in the following week from light to a heavy drinking (≥5 for men, ≥4 for women) or continuation of heavy drinking.

Although all four studies had a prospective design, they used retrospective assessment procedures (Longitudinal Interval Follow-up Evaluation [LIFE][12] and Timeline Followback method [TLFB])[13] to assess the severity of mood symptoms and the number of drinks, respectively. Therefore, recall bias may have influenced the validity of the results of these studies. In addition, the actual amount of alcohol use was not measured in these studies, because they used a global measure such as severity of alcoholism (none, moderate or severe [8,9]); the presence of heavy drinking days (≥3 drinks for men and women[10]; or ≥5 drinks for men and ≥4 drinks for women[11]); or the degree of alcoholism according

to the Addiction Severity Index (score 0-9).[10,14]

To our knowledge, there is no well-designed follow-up study that prospectively examined the temporal relationship of the *actual amounts of daily alcohol use and daily mood symptoms* in patients with BD with and without a comorbid AUD. Therefore, we conducted a prospective cohort study in which BD patients with and without comorbid AUD were asked to register their mood symptoms and their actual alcohol use every day over a period of one year. Based on previous studies[6,8-11] and our clinical impression we hypothesized: (1) that alcohol use has a direct effect on the course of illness, i.e. that alcohol use predicts the occurrence or worsening of depressive but not of manic symptoms in the subsequent week, and (2) that these effects would be stronger in males than in females.

METHOD

Subjects and recruitment

The details of the study design have been published elsewhere.[6] In short, patients had to meet the following inclusion criteria: 1) age between18-75 years; 2) meeting DSM-IV criteria[15] for BD-I or bipolar II disorder (BD-II) with or without comorbid AUD; 3) no serious physical illness, that might influence the diagnosis or course of bipolar disorder, this according to the clinical judgment of the treating physician; 4) able and willing to participate in the study for one year; 5) and adequate command of the Dutch language. The study was approved by the Medical Ethical Review Committee of the University Medical Center Utrecht (the Netherlands). All patients gave written informed consent after full explanation of

the study.

A total of 180 outpatients were approached. Of these, 158 patients entered baseline assessment. From the 158 eligible patients who completed the baseline assessment, 137 subjects (87%) participated in the study for at least 2 months, 125 patients (79%) for at least 6 months, and 104 patients (66%) completed the full 12 months. Analyses were based on the 137 patients with follow-up data during at least two months. Reasons for the 33 non-completers beyond two months were aversion against the daily registrations (N=16), developing a depressive (N=2) or manic episode (N=2), worsening of their alcohol dependence (N=2), non-compliance (N=2), death by a natural cause (N=1) or liver coma due to alcoholism (N=1) and other reasons (N=7). All patients were treated according to the Guideline for the treatment of bipolar disorders from the Dutch Psychiatric Association.[16]

Assessments

At study entry the Structured Clinical Interview for DSM-IV (SCID-IV)[17] was administered by trained mental health care professionals. In order to compare the results of our study with previous studies, data were also obtained by means of the Network Enrolment Questionnaire (NEQ) of the former Stanley Foundation Bipolar Network.[18,19] These data included demographic and social characteristics such as marital status, educational background, past and current level of occupational functioning and household income and clinical characteristics such as estimated prior course of illness variables (number of prior episodes, history of rapid cycling, history of alcohol induced depression, (hypo)mania and cycle

acceleration), and number of past suicide attempts.

During the full year of the study, patients rated their mood with the NIMH self-rated Prospective Life Chart Method (LCM™) every day at the end of the day. The LCM is a reliable method for the measurement of severity of mood symptoms (mania or depression) and the related level of dysfunction on a five-point scale (0=no, 2.5=mild, 5=low moderate, 7.5=high moderate, and 10=severe dysfunction)[20-27] in patients with bipolar disorder. Using the LCM, patients were also asked to report daily on their use of medication, as well as their intake of alcohol (number of standard drinks), for which patients got written and verbal instructions about the standard units of alcohol in beer, wine and spirits. One unit was defined as 12 ml pure alcohol (equals about 10 gram of alcohol) equaling 100 ml of wine (12% alcohol), 250 ml of beer (5% alcohol) or 35 ml of liquor (35% alcohol).[28]

Every month during the follow-up session, LCM registrations were checked and approved by a research assistant.

Statistical analysis

All analyses were performed with the data of the 137 patients who completed at least 2 months of registration after baseline. No significant differences ($p<.10$) were found in the sociodemographic and clinical data at baseline, including illness severity symptoms, alcohol use and other drug use between the 104 patients who completed the full study and the 33 patients with at least two months but less than 12 months follow-up data.

Multi-state models[29,30] were used to assess the impact of the number of alcoholic

Figure 1. Illustration of the multi-state model indicating the direct transitions (arrows) between states (boxes) that are allowed.

drinks on the patients' transition through different states of mood (depression, euthymia and mania). Mood and level of dysfunction rated with the LCM were combined into a single mood severity score by adopting the original LCM score if mood was manic and multiplying the LCM score by -1 if the mood was depressive. For the primary analysis, the data were aggregated to week level by computing the weekly average for number of drinks consumed per day (total number of drinks consumed in a week divided by 7) and the weekly average for the mood severity scores. Three different mood states were distinguished. Based on the patient's average of mood severity scores in a week, the patient's mood state in that week was classified as depressive (average ≤ -5, i.e. depressive with at least low moderate level of dysfunction), manic (average ≥ 2.5, i.e. (hypo)mania with at least mild level of dysfunction) or euthymic (average between -5 and 2.5, i.e. normal functioning, including depression with mild level of dysfunction). In order to perform the analyses, a theoretical model was adopted where patients could switch from depression to euthymia (and vice versa) and from euthymia to mania (and vice versa). The model with the four transitions is shown in Figure 1. Analyses were performed using multi-state Markov models, which allow the investigation of the impact of covariates on the transition rates between the states. Models were fitted using the 'msm-package' version 0.9.5 in R.[31] Mood state

was used as the dependent variable and the variable “number of drinks” was included as a time-varying covariate in the models. Our main interest was in determining the impact of the reported number of alcohol units consumed on the occurrence of switches between mood states. We preferred to use clinically relevant cut-off values for mood states and, therefore, multi-state Markov models were used rather than hidden Markov models. Hidden Markov models are useful when the data itself is used to define outcome states that are only observed indirectly through some operationalization, such as the unobserved drinking states considered by Prisciandaro et al.[11]

The role of gender as a possible confounder and effect modifier was investigated by inclusion of gender as a covariate in the model and inclusion of its interaction with number of drinks in the model, respectively. Nested models were compared by means of likelihood ratio tests. Likelihood ratio tests compare the fit of more complex models with an additional covariate to (nested) simpler models without this covariate. The more complex model is accepted only if the likelihood ratio test is significant.

Hazard ratios (HRs) for the four different transitions between states depicted in the model (Figure 1) will be considered as effect-sizes. The hazard ratio can be interpreted as an instantaneous relative risk of switching from one mood state to another associated with an increase in weekly consumption of alcohol of one standard unit per day. In this context, a switch is defined as the first occurring transition from the current mood state into a different mood state (without passing other mood states), therefore hazard ratios are only defined for the four transitions depicted in Figure 1. Transition probabilities for switches

between states over one-week intervals together with their 95% confidence intervals were estimated for different combinations of gender and number of drinks.

Correlation between weekly average of alcohol consumption and mood severity on the group level was determined for the whole sample and separately for the subsamples of males and females using the method proposed by Bland and Altman[32] which accounts for repeated observations made on the same patient. On the individual level, the Pearson's correlation between weekly average of alcohol consumption and mood severity was computed for each patient separately.

RESULTS

Sample Characteristics at baseline

Sociodemographic and clinical data at baseline are shown in Table 1. Mean age was 46 years, about 50% was male, had a partner, had high school education, and was not able to work.

Ninety (66%) patients had a bipolar I disorder (46 male, 44 female) and 47 (34%) patients had a bipolar II disorder (25 male, 22 female). Gender distribution within BD I and BD II groups did not differ significantly, X^2= .01, df= 1, p= .53.

Of the 137 patients, 77 (56%) had no lifetime AUD, 60 (44%) had a lifetime AUD, and of these 27 (20% of the total sample) had a current AUD. In 12 (21%) of the 60 BD patients with a lifetime AUD, BD predated AUD one year or more, in 16 (27%) patients AUD predated BD with a year or more, and in 31 (52%) patients the ages of onset of BD and AUD were within one year. Forty seven

Table 1. Sociodemographic and clinical characteristics at baseline of participants

	Total N=137
Age, years Mean (SD[a])	45.9 (10.2)
Male (%)	72 (53)
Marital status (%)	
with partner	67 (49)
Annual income (%)	
< 20.000 €	82 (62)
≥ 20.000 €	50 (38)
unknown	5
Educational level (%)	
≤ High school	65 (48)
Job matches qualification	
No	122 (89)
Unable to work	
Yes	66 (48)
Diagnosis n (%)	
Bipolar I disorder	90 (66)
Bipolar II disorder	47 (34)
Lifetime diagnosis n (%)	
Alcohol use disorders (abuse and dependence)	60 (44)
Drug abuse and dependence	29 (21)
Anxiety disorder	47 (34)
Current diagnosis n (%)	
Alcohol use disorder (abuse and dependence)	27 (20)
Drugs abuse and dependence	8 (6)
Anxiety disorder	19 (14)
Age onset bipolar disorder, mean (SD)	24.1 (9.9)
Duration bipolar disorder, years (SD)	21.7 (11.5)
N of episodes, mean (SD)	
Depression	15.1 (23.4)
(hypo)Mania	13.8 (21.5)
Age onset Alcohol use disorders (abuse and dependence)	24.7 (9.6)
mean (SD)	25
Mean number of daily drinks n (SD), [mean range]	1.96 (2.36) [0-14]
Males[b]	2.45 (2.84) [0-14]
Females[c]	1.43 (1.51) [0-6]
Rapid cycling n (%)	43 (31)
History n (%)	
Alcohol induced depression	11 (8)
Alcohol induced (hypo)mania	10 (7)
Cycle acceleration	7 (5)
Number of serious suicide attempts n (%)	
1 or more	30 (22)

[a]Standard Deviation.

[b]Maximum number of daily drinks is 33.

[c]Maximum number of daily drinks is 26.

(34%) patients had life time anxiety disorder and 19 (14%) a current anxiety disorder. Based on NEQ information, only a small number of patients reported a history of alcohol induced depression (n=11 [8%]), mania (n=10 [7%]) or cycle acceleration (n=7 [5%]). Of the 137 patients, 44 (32%) patients used no alcohol at all or used alcohol only incidentally (0-2 unit/week), 49 (36%) patients used moderate amounts of alcohol (females: 3-14 unit/week, males 3-21 units/week), and 44 (32%) patients used excessive amounts of alcohol (females ≥ 15 units/

Table 2: Likelihood ratio tests for pairwise comparison of the fit of multi-state models of increasing complexity. A p-value below 0.05 indicates that the fit of the model with the additional covariate or interaction is significantly better than the fit of the nested model.

Model	Nested model	-2 log LR	df	p-value
Gender	Constant only	31.238	4	<0.001
Number of drinks	Constant only	15.229	4	0.004
Gender + Number of drinks	Gender	11.402	4	0.022
Gender + Number of drinks + Interaction	Gender + Number of drinks	14.020	4	0.007

Table 3. Hazard ratios for the time to transition from one mood state to another, associated with an increase in weekly consumption of alcohol use of one standard unit alcohol per day.

From	To	Hazard Ratio (95% CI)[a]	Hazard Ratio (95% CI)
		Male	Female
Depression	Euthymia	0.95 (0.90 - 1.01)	**1.18** (1.03 - 1.36)
Euthymia	Mania	**0.81** (0.71 - 0.92)	1.01 (0.85 - 1.18)
Mania	Euthymia	0.94 (0.84 - 1.05)	1.12 (0.94 - 1.34)
Euthymia	Depression	1.03 (0.97 - 1.11)	0.97 (0.82 - 1.14)

[a]CI = Confidence Interval.

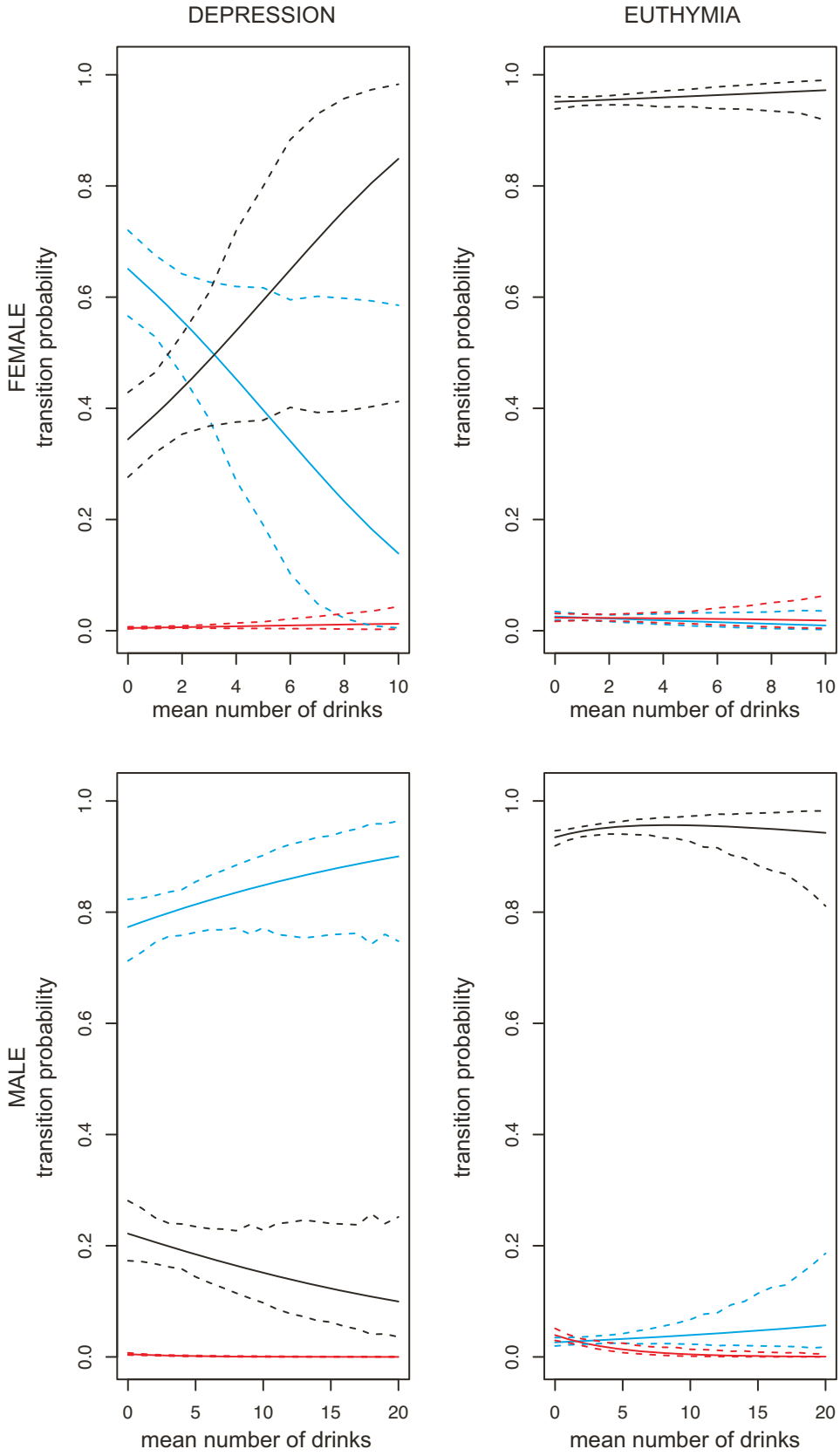
Bolded Hazard ratios are significantly different from 1 at a two-sided significance level of 0.05.

week, males ≥ 22 units/week).

The group of 137 patients returned 44.808 days with LCM data (mean 327 ± 76 per patient; range 62 - 365 days per patient). The overall retention rate was 78%. Thirty-seven patients (84%) of the incidental alcohol using group completed 90% or more of the 365 days of LCM registration, versus 38 patients (78%) in moderate alcohol using group and 33 patients (75%) who used excessive amounts of alcohol. There was no difference in number of recorded days with LCM data between the no/incidental alcohol use group, the moderate alcohol use group and the excessive alcohol use group ($P > .5$). Of the total sample of 6401 weeks, 8.6% of the weeks were scored as depressed, 2.9% as manic and 88.5% as euthymic.

Temporal relation between alcohol use and subsequent mood state

Table 2 shows that likelihood ratio tests for all four pairs of nested models are significant. Therefore, the most complex model with gender, number of drinks and their interaction was selected as the model with best fit and hazard ratios and transition probabilities will be reported separately for men and women. Table 3 shows the estimated hazard ratios (HRs and 95% confidence intervals) for the transitions in the model (Figure 1). The hazard ratios show a different picture for males and females. For women in a depressive state, higher alcohol use was associated with shorter times to enter a euthymic state (HR = 1.18, 95% [1.03 – 1.36], p<.05), whereas for men in an euthymic state higher alcohol use was associated with longer times to enter a manic state (HR = 0.81, 95% CI: [0.71 – 0.92], p < .05). Figure 2 displays estimated transition probabilities between the mood states for a one-week interval, based on the multi-state model, as a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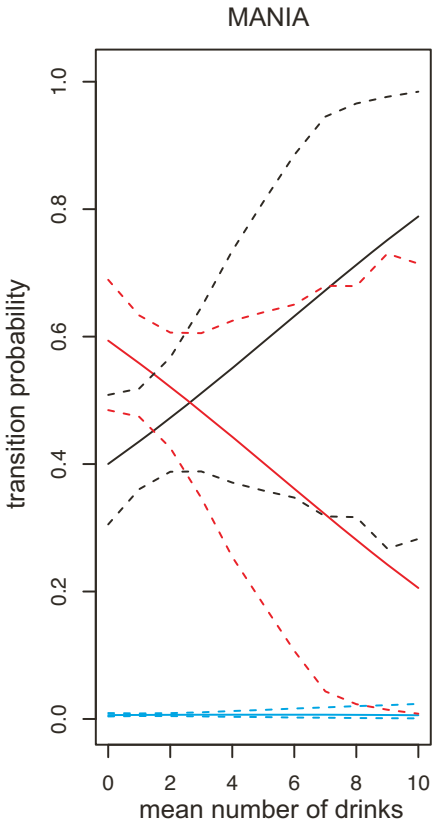


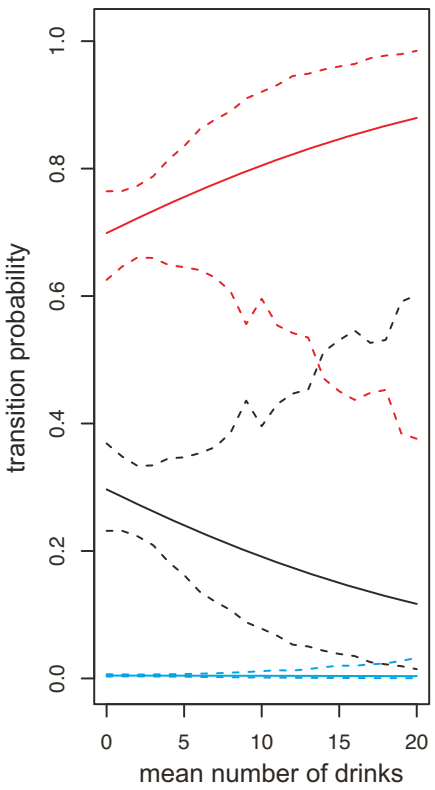


Figure 2. Estimated probabilities (0-1.0) of switching from depression, euthymia and mania[a] to depression*, euthymia or mania in the next week as a function of the weekly average of number of drinks per day. Females 0-10 drinks/day, males 0-20 drinks/day.

[a]Mania includes also hypomania.

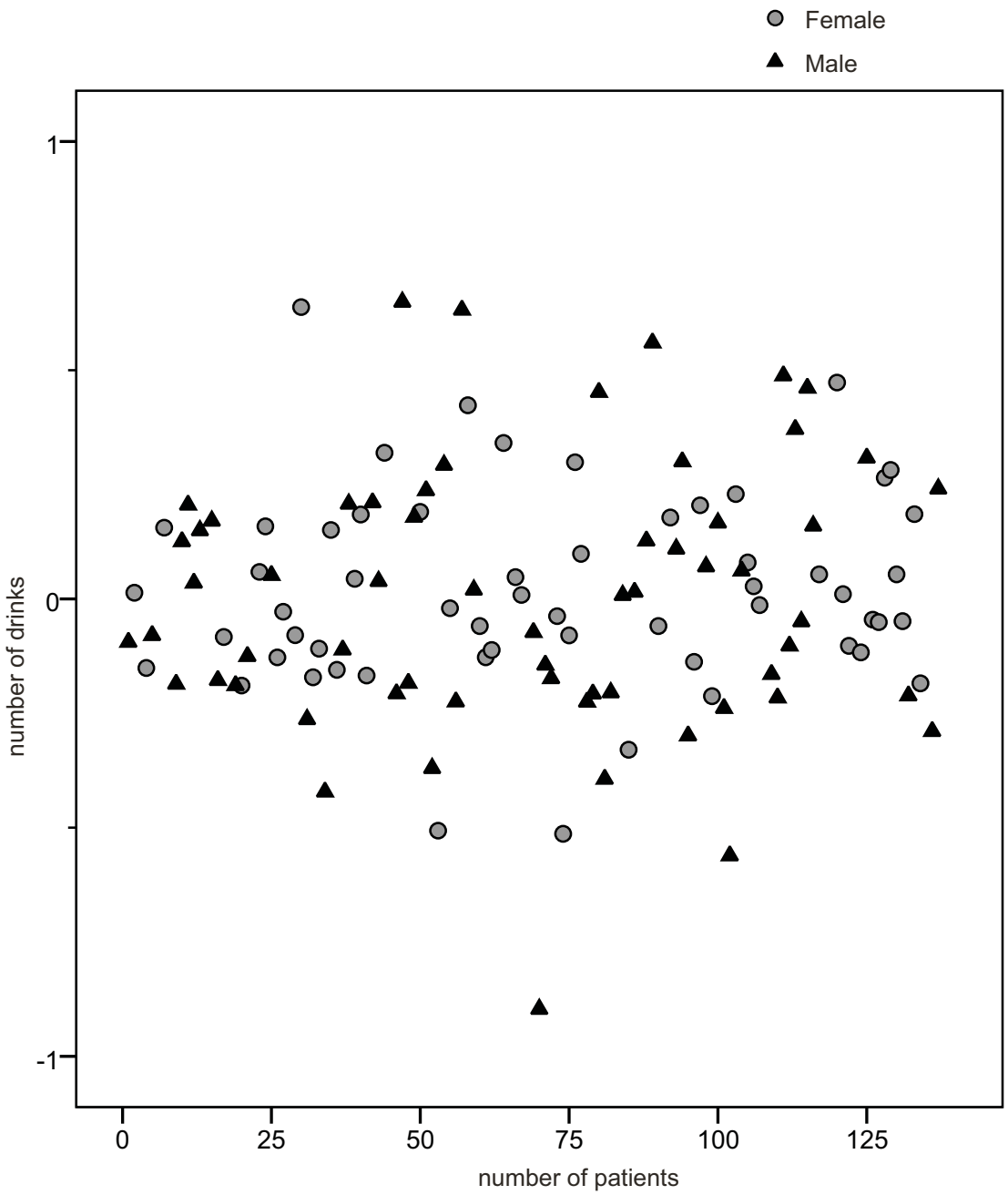
*

___ probability of switch to depression.
___ probability of switch to euthymia.
___ probability of switch to mania.
- - - boundaries of 95% confidence intervals (CI) of switch to depression.
- - - boundaries of 95% CI intervals of switch to euthymia.
- - - boundaries of 95% CI intervals of switch to mania.

function of the weekly average of number of drinks per day (females 0-10 units and males 0-20 units). Note that this plot also includes transition probabilities for transitions from manic to depressive state and vice versa which are not displayed in Figure 1. However, according to the model in Figure 1 such transitions are possible in a one-week interval but only via the euthymic state. In addition, the probabilities for 'transitions' between the same states are plotted, i.e. the probability of being in the same state at the start and end of the one-week interval (either caused by not switching at all during the interval or returning to the same state by a combinations of transitions).

The correlation between the consumed number of drinks per week and the average mood severity score of the following week on the group level was significant, but very small (correlation: -0.01, $p<.001$). In line with results from the multi-state models, the correlation in the subsample of males was -0.001 ($p<.01$), indicating increased negative scores (more depressed mood or less manic mood) following higher alcohol consumption, whereas the correlation for in the subsample of females was 0.02 ($p<.001$), indicating increased positive scores (less depressed or more manic) after higher alcohol consumption. Figure 3 shows individual Pearson's correlations between the average number of drinks and average mood severity score one week later with different symbols for males and females. The majority of correlations is grouped around $r = 0$. However, individual correlations range from very strongly negative -0.90 to strongly positive +0.65 (SD 0.26).

Figure 3. Correlations of individuals between average number of drinks and severity one week later.



DISCUSSION

Our main findings are that the use of alcohol was significantly, but rather weakly, associated with subsequent transitions in mood state in patients with BP. In depressed women higher alcohol use was significantly associated with a shorter time before returning to a euthymic state, whereas in euthymic men higher alcohol use was significantly associated with a longer time before becoming manic (Table 3). Thus, although the findings in men and in women show some positive effect of alcohol consumption on mood states, these effects are different. In particular, estimated hazard ratios (Table 3) and transition probabilities (Figure 2) seem to suggest that an increase of alcohol consumption in depressed and manic women decreases the time to become euthymic, whereas in depressed and manic men it slightly increases the time to become euthymic. For women this may suggest some kind of self-medication, whereas for men the mechanism is unclear. Moreover, it should be noted that this is an observational study and therefore any causal inference should be made very cautiously. Furthermore, only two hazard ratios reached statistical significance and confidence intervals around transition probabilities were broad for transitions from depressive and (especially) manic states.

Despite the fact that a number of findings reached statistical significance, one can seriously doubt the clinical relevance of these findings. With a correlation for the total sample of -0.01, only 0.01% of the variance in mood severity in this population is explained by alcohol use. On the individual level correlations varied widely, which suggests that other factors may play a role in the relationship between alcohol use and mood severity. Therefore, we tend to conclude that the

current findings suggest that the short-term effect of alcohol use on the course of BD is very limited. Thus, from a clinical perspective we have to reject our first hypothesis: in the current sample, higher levels of alcohol use do not predict the occurrence or worsening of depressive symptoms in the subsequent week. The second hypothesis – that the hypothesized negative effect of alcohol on subsequent depressive states would be stronger in males than females- is also not confirmed.

Our conclusion that alcohol use does not have a short-term effect on the course of BD is consistent with our previous findings from the same study[6] where we did not make optimal use of the available fine grain LCM data such as we did now using the multi-state Markov model: in the current sample neither moderate nor excessive use of alcohol is associated with an unfavourable long-term outcome. However, our findings challenge the results of some other studies: the study of Jaffee et al.[10] showing that alcohol use in BD patients increased the risk of a depressive episode in the next month; the study of Fleck et al.[8], suggesting that there is no direct relation between levels of alcohol use and BD symptoms; and the study by Baethge et al.[9] who found an association between depressive mood and alcohol use in the preceding or same quarter, which is opposite to the findings for women in our study.

What can be the reason for these apparent differences? A possible explanation for the difference in results between our study and the Jaffee et al. study[10] could be that 68% of their patients was drug dependent (mainly marijuana and cocaine) compared to only 6% of the patients in our study. That alcohol use of their BD patients increased the risk of a depressive episode in the next month

in their sample could be explained as a possible (potentiating) add-on effect of alcohol on the negative effects on outcome (depression) of drug use.[33,34] The differences between our study and the Fleck et al.[8] and Baethge et al.[9] studies may be explained by the fact that they included a much younger population (about 21 and 28 years compared to 46 years in our study). The effect of (excessive) alcohol use on the outcome of BD may have an effect only in the early years of the disorder, whereas its effect levels out with longer illness duration and a higher number of previous episodes. This is supported by a previous study[35] using the Danish case register that found that concurrent alcoholism increased the risk of recurrence of episodes during the initial course of unipolar and bipolar disorder but that it had had no effect on recurrences later in the course of the illness (i.e. less switching when the duration of BD is longer).

Another possible explanation for the lack of clinically relevant HRs and correlations for the total sample is that (almost) all participants (including those with excessive alcohol use) in our study reported to be very adherent to their medication. According to their LCM registration, they took their mood stabilizers on more than 90% of the recorded days.[6] The high rate of adherence in our sample could be an important protective factor for the transition to another state (as represented by the low transition rates from euthymic state as shown in Figure 2). The high adherence is also likely to have limited the number of manic and depressive episodes reported. This in turn may have caused the transition probabilities to have broad confidence intervals and may have prevented some of the hazard ratios to reach statistical significance.

One could suggest that we did not include patients with severe alcohol use.

However, 32% (n=44) of the patients was using alcohol excessively with on average 175 (SD=96, range 10-365) heavy drinking days per year (females ≥ 4 units/day, males ≥ 5 units/day) and an average 4.54 (SD=2.4, range 1-14) drinks per day. Fourteen (10%) of the heaviest drinking patients consumed a mean of 7.18 drinks (SD=2.4, range 5-14) per day with an average of 287 heavy drinking days (SD=43, range 234-365). In addition, the sample included 44 patients with moderate use of alcohol. Therefore, we like to conclude that our total sample is representative for outpatients with BD, at least for those adherent to medication.

Our study has both strengths and limitations. The major strengths are the full prospective design with 12-months of daily follow-up assessments of mood symptoms and actual amounts of alcohol use, the one year high overall retention rate, the gender outcomes, and the fine grain analysis of the data[6] using multi-state Markov models. A limitation could be that the euthymic state was defined rather broad, leading to loss of transitions between euthymia and mild (-2.5) and low moderate (-5) depression and euthymia and mild (+2.5) mania. A further limitation is selection and its effect on the external validity of our findings. Twenty-eight percent of our patients were member of the Dutch Association of Manic Depressives and Relatives and they should be considered as very motivated patients and extremely adherent to the therapy.

Further research could shed more light on the complex interplay between BD and AUD when prospective different illness duration groups of BD patients are followed while they report on their daily alcohol intake (units), instead of using current or lifetime DMS diagnoses of AUDs.

CONCLUSION

Together with the previously reported results from this study[6], the current report suggests that (excessive) alcohol use has no clinically relevant direct effect on the course of BD in patients adherent to the use of mood stabilizers. Thus, becoming adherent to mood stabilizers appears to be of the utmost importance in order to prevent possible negative effects of (excessive) alcohol use on the course of BD.

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5

THE EFFECT OF ALCOHOL USE ON 12 MONTH CLINICAL OUTCOME OF PATIENTS WITH ACUTE MANIA OR MIXED BIPOLAR EPISODE

Results of the Emblem study

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Submitted

ABSTRACT

OBJECTIVES: To determine the effect of alcohol use and the presence of an alcohol use disorder on course and outcome in bipolar patients prospectively followed for 12 months in the European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) study.

METHODS: Patients (N=3,302) were divided in three groups based on their alcohol use at baseline: no alcohol use (57%), moderate (i.e. non-problematic) alcohol use (32%), and alcohol use disorder (11%). Outcome measures included the four domains of the Clinical Global Impressions-Bipolar Disorder scale, the 5-item Hamilton Depression Rating Scale, and the Young Mania Rating Scale.

RESULTS: After control for differences in sociodemographics, no significant differences were found between the groups with regard to the symptomatic outcomes at 12 and 52 weeks. In a post-hoc analysis, three subgroups with a stable alcohol use pattern during follow up were compared. Stable AUD patients scored significantly higher on the CGI-BP (overall and mania) compared to stable moderate users and stable non-users, whereas stable moderate users and non-users did not significantly differ in CGI-BP outcomes.

CONCLUSIONS: The current study shows that alcohol use and the presence of an AUD at baseline are not associated with negative outcomes of the treatment of mania, but that continued excessive or problematic alcohol use is associated with unfavorable outcomes. The latter effect is possibly mediated or modified by a lack of treatment compliance in patients with a stable AUD.

INTRODUCTION

Bipolar disorders (BDs) are highly co-morbid with alcohol use disorders (AUDs; i.e. alcohol abuse or dependence).[1-10] In the general population about 50% of persons with BD type I have a lifetime history of AUD compared to only 13.5% in those without a psychiatric disorder.[9] At the same time, mania co-occurs much more frequently in persons with AUD than in individuals without AUD (OR=3.5).[11]

The negative effects of comorbid AUD in BD patients are well documented. For instance, comorbid AUD has shown to be associated with more severe mood symptoms and more manic symptoms at presentation[12], with more hospitalizations[13], with poor occupational outcome[14], with shorter remissions[14,15], and a more frequent rapid cycling course.[16] In men with BD and comorbid AUD, more lifetime manic episodes and emergency department visits have been reported than in BD men without comorbid AUD, whereas more lifetime depressive and hypomanic episodes have been reported in BD women with comorbid AUD.[17] Results regarding the association between AUD and the age at onset of BD are conflicting as both an earlier and later age at onset have been reported.[18-20] While manic or depressed BD patients with substance use disorder (SUD) had more lifetime suicide attempts than manic or depressed BD patients without SUD in some studies[10,21], AUD was not associated with more suicide attempts in other studies among BD patients.[22-25]

However, it is difficult to compare the results of the various studies due to variation in patient populations, diagnostic assessments and the way alcohol use was measured. Most studies have serious methodological limitations. For instance, in studies about the effect of alcohol on the course of BD with

a retrospective design[12,13,17], recall bias may have influenced the reliability and validity of the data. In addition, most of the studies did not specify whether patients in addition to their AUD also used illegal drugs, even though a strong correlation of AUD with other SUDs has been demonstrated.[25] Finally, only alcohol abuse and dependence were studied, whereas the effect of moderate alcohol use (i.e. alcohol use without related problems) on the course of illness has rarely been investigated.

In a recent one-year prospective cohort study, we assessed the effect of both moderate and excessive alcohol use (for definition see below) on the course and outcome of 137 outpatients with BD (age 23-68 years; 66% BD I and 34% BD II; mean duration of BD 22 years).[26] In this prospective study, patients rated their mood and the number of alcohol units consumed daily for a period of up to 52 weeks with the Self-Rating Prospective Life-Chart Method (LCM). Based on the alcohol use in the first 4 weeks of follow-up, patients were assigned to one of three groups: (1) no or incidental alcohol use (i.e. 0-2 units/week for both males and females [1 unit contains 10 gram pure alcohol]), (2) moderate alcohol use (i.e. 3-21 units/week for males, 3-14 units/week for females), or (3) excessive alcohol use (22 or more units/week for males, 15 or more units/week for females). The findings of this study did not confirm the unfavorable effects of moderate[17] or excessive alcohol use[12-15,18-25] on course and outcome of BD: no significant differences between the three drinking groups on clinical outcome variables were found, i.e. number of episodes, number of days ill (depressed, hypomanic/manic and total), severity of depression, severity of mania, and social function. Possible post-hoc explanations for this unexpected

finding included: (a) only 50% of the excessive drinking patients met DSM-IV[27] criteria for AUD, (b) relatively low rate of other SUDs, (c) relatively small effect of alcohol abuse in later phases of BD, (d) high compliance with BD medication in the study population, (e) protective effect of the close monitoring of patients, and (f) selection due to the requirement that patients had to agree with daily registration of mood, alcohol use and drug use.

The current study aims to replicate our previous findings in a large, international cohort of patents with a manic or mixed episode of BD who were in active treatment at the start of the study and who were prospectively followed for 12 months. We hypothesized, based on our previous study[26], that BD patients with no alcohol use, BD patients with moderate (non-problematic) alcohol use and BD patients with AUD at baseline would not significantly differ on clinical outcomes after 12 and 52 weeks follow-up.

METHODS

Study design and subjects

Patients were part of the European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) study, a prospective, observational study on the treatment and clinical, functional and economic outcomes of inpatients and outpatients experiencing an acute manic or mixed bipolar episode.[28,29] In brief, across 14 European countries a total of 3,681 in- and outpatients with an acute manic episode were enrolled at the discretion of the treating psychiatrist. Of these patients, 3,459 fulfilled all inclusion criteria: (a) 18 years and older, (b) baseline rating of CGI-BP mania ≥ 3, and (c) started or changed their oral medication

for the treatment of mania (antipsychotics, anticonvulsants and/or lithium; not antidepressants or benzodiazepines) within the context of routine psychiatric care.). The study had minimal exclusion criteria. Mania diagnosis was made by the psychiatrist's clinical evaluation based on standard diagnostic criteria (generally DSM-IV, ICD 10) or on clinical judgment. Treatment decisions were independent of the EMBLEM study and patients were not participating in any intervention study.

Ethical approval and patient informed consent were obtained according to local legal requirements. During the acute treatment phase, assessments took place at baseline, 1, 2, 3, 6 and 12 weeks after baseline. During the maintenance phase patients were assessed at 6, 12, 18 and 24 months. The current report analyzed data collected in the first year of the study (12 and 52 weeks follow-up).

ASSESSMENTS

Sample characteristics

At baseline, demographic and social characteristics such as age, sex, having a relationship and level of education were collected, as well as data on the psychiatric history such as age at onset of BD, rapid cycling in the previous year, history of suicide attempts, history of problems with alcohol, cannabis and other drugs (yes or no), current use of alcohol (see below), current use of cannabis and other drugs, compliance, and in- or outpatient status. Investigators were asked, based on their clinical experience and discretion and based on the patient's self-report, to assess whether patients had a life time alcohol problem.

Alcohol use

History of alcohol problems (present in lifetime or not) was assessed at baseline and current alcohol use (categorized as none, use, abuse or dependence in the previous 3 months) was assessed at baseline, at 12 weeks and at 52 weeks follow-up based on patient self-report and investigator clinical experience and judgment. Based on this combination of information, patients were divided into three alcohol use groups at baseline: (1) no alcohol use (i.e. no lifetime alcohol problems and no current alcohol use); (2) moderate alcohol use, i.e. current alcohol use without alcohol-related problems; and (3) presence of an AUD, i.e. current alcohol abuse or dependence.

Outcome

Severity of psychopathology was measured at each observation using the following assessment scales: the Clinical Global Impressions Scale for Bipolar Illness (CGI-BP) to assess the severity of the overall illness, mania, depression, and hallucinations/delusions (each item score 1-7).[30] During the acute phase (baseline -12 weeks), the Young Manic Rating Scale (YMRS; 11 items, score 0-60)[31] and the shortened 5-item version of the Hamilton Depression Rating Scale (HAMD-5; score 0-18)[32] were also completed. Other outcome variables included: the number of suicide attempts; current alcohol, cannabis or other drug use over the period of 6-12 and 13-52 weeks.

STATISTICAL ANALYSES

The distribution of baseline characteristics of the sample, including socio-demographic and clinical measures, was analyzed using descriptive statistics. Differences between the three alcohol groups were tested using Chi-squares or Fisher's exact tests in case of categorical variables and Kruskal-Wallis tests in case of numerical variables. Given the large sample size, a 2-sided alpha of 0.01 was used as a justifiable significance level for comparisons between groups. In addition, clinical significance was a priori defined as an absolute difference in percentages of at least 5% in the case of categorical variables or a standardized effect size (SES) of at least 0.3 in the case of continuous measures (CGI-BP, YMRS and HAMD-5).

The effect of the stable alcohol use groups on 12 and 52 weeks outcome was estimated in a series of multiple linear regression analyses with the CGI-BP (overall, mania, depression, hallucinations/delusions), HAMD-5 and YMRS as dependent variables. In order to control for potential confounders, the following variables were included in the analysis: age, sex, relationship, education, country, current patient status, history of suicide attempts, history of rapid cycling, current duration of mania and compliance. Given the presence of six outcome variables, we applied a restrictive significance level of $p<0.01$.

RESULTS

Baseline findings

A total of 3,459 subjects entered EMBLEM. Alcohol use assessments at baseline were missing for 157 patients (4.6%) and they were excluded from the analyses. Of the remaining 3,302 patients, 1,886 patients (57.1%) did not use alcohol, 1,055 patients reported moderate use of alcohol (32.0%) and 361 fulfilled study criteria for an AUD (10.9%).

Table 1 shows the sociodemographic and clinical characteristics of these three groups. Groups were statistically different ($p<.001$) and clinically different (absolute difference ≥5% or d ≥0.3) in terms of age, gender, partnership, level of education, treatment setting, age at onset of BD, history of suicide attempts, rapid cycling in previous year, history of problems with alcohol, cannabis and other drugs, and current cannabis and substance use and compliance. Patients with AUD were younger, had an earlier age at onset of BD and were more frequently inpatients at baseline, living alone, rapid cyclers during the previous 12 months, had more suicide attempts in the past and were more often male than patients with no use of alcohol. The same applied to a lesser extend (except age) to the patients with moderate use of alcohol compared to the group that did not use alcohol. Almost all patients with AUD also had a previous history of alcohol problems, whereas about one third had a history of cannabis problems and were current cannabis users. About a quarter had a history of problems with other substance(s) and one fifth was a current user of other substance(s). Approximately 50% of the patients of the no alcohol use and the moderate alcohol use group were almost always compliant to the prescribed medication

Table 1. Sociodemographic and illness characteristics at baseline of 3302 acutely manic patients with no use, moderate use and abuse/dependence of alcohol.

	No use of alcohol	Moderate use of alcohol	Alcohol use disorder	Total	
	N = 1886 (57.1%)	N = 1055 (32.0%)	N=361 (10.9%)	N = 3302 (100%)	p-values[a]
Age, mean ± SD, y	46.0 ± 13.8	42.8 ± 13.2	42.7 ± 11.7		**<.0001**
Sex, Male, n (%)	652 (35.6)	570 (56.3)	221 (63.1)	1443 (43.7)	**<.0001**
Relationship					
Not living together, n (%)	1038 (55.1)	609 (57.8)	255 (70.8)	1902 (57.6)	**<.0001**
Highest education n (%)					**<.0001**
None	29 (1.6)	18 (1.8)	5 (1.4)		
Primary school	411 (22.1)	138 (13.5)	56 (15.7)		
Secondary school	441 (23.8)	231 (22.5)	93 (26.1)		
Secondary school (upper)	431 (23.2)	259 (25.2)	89 (25.0)		
Post-secondary vocational training	227 (12.2)	205 (20.0)	61 (17.1)		
University	317 (17.1)	175 (17.1)	52 (14.6)		
Total				3238 (98.1)	
Current patient status					
Outpatient, n (%)	1183 (62.9)	619 (58.9)	178 (49.3)	1980 (60.0)	**<.0001**
Age at onset bipolar disorder					
mean ± SD, y	30.6 ± 11.3	28.9 ± 10.4	28.2 ± 10.1		**<.0001**
Suicide attempts, n (%)					
≥ 1	473 (27.2)	286 (29.2)	123 (37.4)	882	**<.0009**
Rapid cycler previous year					
Yes, n (%)	302 (17.9)	129 (13.5)	79 (25.5)		**<.0001**
Alcohol use problem in history					
Yes, n (%)	144 (7.8)	379 (36.6)	333 (93.8)	856 (25.9)	**<.0001**
Cannabis use problem in history					
Yes, n (%)	123 (6.7)	202 (19.6)	123 (34.8)	448 (13.6)	**<.0001**
Other drugs use problem in history					
Yes, n (%)	79 (4.2)	110 (10.5)	85 (23.6)	274 (8.3)	**<.0001**
Current Cannabis use, n (%)					
None	1783 (96.4)	815 (80.2)	223 (67.6)	2821 (88.3)	**<.0001**
Use	43 (2.3)	138 (13.6)	48 (14.5)	229 (7.2)	
Abuse/dependence	23 (1.2)	63 (6.2)	59 (17.9)	145 (4.5)	
Total				3195	

Table 1, CONTINUED. Sociodemographic and illness characteristics at baseline of 3302 acutely manic patients with no use, moderate use and abuse/dependence of alcohol.

	No use of alcohol	Moderate use of alcohol	Alcohol use disorder	Total	
	N = 1886 (57.1%)	N = 1055 (32.0%)	N=361 (10.9%)	N = 3302 (100%)	p-values[a]
Current Substance use, n (%)					
None	1837 (98.0)	941 (89.6)	282 (79.2)	3060 (93.3)	**<.0001**
Use	18 (1.0)	82 (7.8)	25 (7.0)	125 (3.8)	
Abuse/dependence	20 (1.1)	27 (2.6)	49 (13.8)	96 (2.9)	
Total				3281	
Current duration of mania, n (%)					
< 1 week	385 (20.7)	173 (16.5)	56 (15.7)		.0052
1-2 weeks	630 (33.8)	359 (34.3)	101 (28.3)		
3-4 weeks	463 (24.9)	285 (27.2)	103 (28.9)		
5-8 weeks	231 (12.4)	139 (13.3)	52 (14.6)		
> 8 weeks	153 (8.2)	90 (8.6)	45 (12.6)		
Total				3265 (98.9)	
Compliance					**<.0001**
Medication not prescribed	385 (19.1)	248 (23.6)	91 (25.3)		
Almost always complies	1004 (53.7)	495 (47.1)	128 (35.7)		
Complies half the time	374 (20.0)	214 (20.4)	90 (25.1)		
Almost never complies	135 (7.2)	94 (8.9)	50 (13.9)		
Total				3281 (99.4)	
CGI-BP					
Overall[b], n	1860	1036	357	3253 (98.5)	
mean ± SD	4.61 ± 1.05	4.67 ± 1.04	4.90 ± 1.02		**<.0001**
Mania[c], n	1882	1049	360	3291 (99.7)	
mean ± SD	4.72 ± 0.98	4.82 ± 0.93	4.93 ± 0.97		**<.0001**
Depression[c], n	1849	1042	351	3242 (98.2)	
mean ± SD	1.90 ± 1.20	1.78 ± 1.16	1.92 ± 1.32		.0214
Hallucinations/delusions[c], n	1879	1051	360	3290 (99.6)	
mean ± SD	2.90 ± 1.77	3.01 ± 1.80	3.08 ± 1.77		.0925
Total YMRS[d], n	1869	1043	358	3270 (99.0)	
mean ± SD	25.78 ± 10.12	26.91 ± 9.37	28.74 ± 10.54		**<.0001**
Total HAM-D[e], n	1815	1016	342	3173 (96.1)	
mean ± SD	3.04 ± 2.83	2.65 ± 2.85	3.16 ± 3.40		**<.0001**

Only patients without missing values on relevant variables were included in the individual analyses

[a]Bolded p-value denote significance.

[b]Clinical Global Impression Scale, Bipolar version Overall in the 12 month prior to enrolment (1-7).

[c]Clinical Global Impression scale, Bipolar version Mania, Depression, Hallucinations/delusions assessment current status at baseline (1-7).

[d]Young Manic Rating Scale (0 - 60).

[e]Hamilton Depression Rating 5- item scale (0-18).

Table 2. Clinical characteristics and severity of illness (raw data) at 12 and 52 weeks

	Outcome at 12 weeks				
	No use of alcohol at baseline	Use of alcohol at baseline	AUD at baseline	Total N=2593	p-value[a]
Current alcohol use, n (%)					**<.0001**
None	1366 (91.7)	390 (46.8)	114 (42.4)	1870	
Use	118 (7.9)	419 (50.2)	108 (40.1)	645	
Abuse/dependence	6 (0.4)	25 (3.0)	47 (17.5)	78	
Total	1490	834	269	2593	
Current cannabis use, n (%)					**<.0001**
None	1457 (97.7)	762 (91.7)	229 (85.1)	2448	
Use	26 (1.7)	57 (6.9)	28 (10.4)	111	
Abuse/dependence	9 (0.6)	12 (1.4)	12 (4.5)	33	
Total	1492	831	269	2592	
Current substance abuse, n (%)					**<.0001**
None	1466 (98.3)	769 (95.7)	248 (92.2)	2510	
Use	17 (1.1)	29 (3.5)	16 (5.9)	62	
Abuse/dependence	9 (0.6)	7 (0.8)	5 (1.9)	21	
Total	1492	832	269	2593	
Suicide attempts, n (%)					**.0006**
0	1477 (99.1)	822 (98.8)	259 (96.3)	2558	
≤ 1	13 (0.9)	10 (1.2)	10 (3.7)	33	
Total	1490	832	269	2591	
CGI-BP[b,c]					
Overall, n	1483	832	268	2583	
mean ± SD	2.64 ± 1.32	2.66 ± 1.28	2.69 ± 1.32		.7312
Mania, n	1493	833	268	2594	
mean ± SD	2.21 ± 1.27	2.16 ± 1.18	2.22 ± 1.23		.8517
Depression, n	1478	828	268	2574	
mean ± SD	1.75 ± 1.09	1.80 ± 1.17	1.80 ± 1.12		.7807
Hallucinations/delusions, n	1493	833	266	2592	
mean ± SD	1.52 ± 0.97	1.58 ± 1.03	1.57 ± 1.01		.5704
Total YMRS[d], n	1464	815	261	2540	
mean ± SD	6.38 ± 7.68	6.31 ± 7.35	7.23 ± 7.59		.0422
Total HAM-D[e], n	1445	809	261	2515	
mean ± SD	2.09 ± 2.61	2.17 ± 2.62	2.20 ± 2.57		.6065

[a]Bolded p-value denote significance.
[b]Clinical Global Impression scale, Bipolar version (1-7).
[c]Score over episode from 6-12 and 13-52 weeks.
[d]Young Manic rating scale (0-60).
[e]Hamilton Depression Rating 5-item scale (0-18).
[f]Not assessed.

of patients with no use, moderate use or abuse/dependence of alcohol at baseline.

	Outcome at 52 weeks				
	No use of alcohol at baseline	Use of alcohol at baseline	AUD at baseline	Total N=1627	p-value[a]
Current alcohol use, n (%)					**<.0001**
None	882 (90.6)	228 (46.6)	65 (39.9)	1175	
Use	89 (9.1)	245 (50.1)	71 (43.3)	405	
Abuse/dependence	3 (0.3)	16 (3.3)	28 (17.1)	47	
Total	974	489	164	1627	
Current cannabis use, n (%)					**<.0001**
None	995 (98.0)	455 (93.0)	150 (91.5)	1560	
Use	13 (1.3)	25 (5.1)	10 (6.1)	48	
Abuse/dependence	6 (0.6)	9 (1.8)	4 (2.4)	19	
Total	974	489	164	1627	
Current substance abuse, n (%)					**<.0001**
None	962 (98.8)	479 (98.0)	154 (93.9)	1595	
Use	6 (0.6)	8 (1.6)	9 (5.5)	23	
Abuse/dependence	6 (0.6)	2 (0.4)	1 (0.6)	9	
Total	974	489	164	1627	
Suicide attempts, n (%)					.1364
0	963 (99.2)	482 (99.2)	159 (97.5)	1604	
≤ 1	8 (0.8)	4 (0.8)	4 (2.5)	16	
Total	971	486	163	1620	
CGI-BP[b,c]					
Overall, n	968	484	163	1615	
mean ± SD	2.40 ± 1.45	2.24 ± 1.29	2.34 ± 1.34		.3383
Mania, n	971	488	164	1623	
mean ± SD	1.98 ± 1.34	1.80 ± 1.11	1.91 ± 1.15		.1720
Depression, n	963	483	161	1607	
mean ± SD	1.67 ± 1.02	1.62 ± 0.98	1.72 ± 0.98		.3504
Hallucinations/delusions, n	972	488	164	1624	
mean ± SD	1.40 ± 0.92	1.38 ± 0.84	1.36 ± 0.82		.9201
Total YMRS[d], n	n.a.[f]	n.a.[f]	n.a.[f]		
mean ± SD					
Total HAM-D[e], n	n.a.[f]	n.a.[f]	n.a.[f]		
mean ± SD					

versus only 35% of the AUD group ($p < .0001$). The illness characteristics of the three groups at baseline were significantly different for the CGI-BP overall, CGI-BP mania, total YMRS and HAMD-5 scores, but effect sizes were small ($d<0.3$, data not shown) and therefore these symptom differences between the alcohol use groups are considered not to be clinically significant.

Follow-up

Of the 3,302 patients with baseline data, 2,593 (78.5%) had 12 week follow-up data and 1,627 (49.3%) also had 52 week follow-up data (Table 2). The loss to follow-up at 52 weeks was mainly caused by the fact that Denmark, Germany, Spain and Switzerland (with about 25% of the patients) did not participate in the maintenance phase (13-52 weeks) of the study. There were no significant differences between the three alcohol use groups in the fraction of patients lost to follow-up at 12 weeks ($p > .5$) and 52 weeks ($p > .7$).

During the first 12 weeks, 46.8% of the patients with moderate use of alcohol at baseline had stopped drinking alcohol. Of those with an AUD at baseline, 42.4 % did not use alcohol anymore and 40.1% were using alcohol without problems, indicating that only 17.5% of the patient with AUD at baseline reported persistent AUD over the first 12 weeks follow-up (Table 2). For patients who used or abused cannabis and/or other substances at baseline, the use and abuse of these substances had also diminished significantly at 12 weeks (data not shown). Table 2 shows that similar changes in alcohol use were reported at 52 weeks follow-up.

Table 3 Clinical outcome at 52 weeks follow-up for subgroups with stable alcohol use pattern.[a]

CGI-BP[b]	Parameter estimate	Standard error	t value	Pr > (t)[c]	95% CI[d]
Overall					
stable AUD[e] vs stable moderate use	0.8848	0.3081	2.87	**0.0042**	0.280 - 1.490
stable AUD vs stable no use	0.8185	0.2994	2.73	**0.0064**	0.231 - 1.406
stable moderate use vs stable no use	-0.0663	0.1241	-0.53	0.5930	-0.310 - 0.177
Mania					
stable AUD vs stable moderate use	0.9353	0.2681	3.49	**0.0005**	0.409 - 1.462
stable AUD vs stable no use	0.7983	0.2611	3.06	**0.0023**	0.286 - 1.311
stable moderate use vs stable no use	-0.1370	0.1062	-1.29	0.1973	-0.345 - 0.071
Depression					
stable AUD vs stable moderate use	0.5436	0.2385	2.28	0.0229	0.075 - 1.012
stable AUD vs stable no use	0.4627	0.2326	1.99	0.0470	0.006 - 0.919
stable moderate use vs stable no use	-0.0809	0.0937	-0.86	0.3882	-0.265 - 0.103
Hallucinations/delusions					
stable AUD vs stable moderate use	0.3178	0.1969	1.61	0.1069	-0.069 - 0.704
stable AUD vs stable no use	0.2804	0.1918	1.46	0.1442	-0.096 - 0.657
stable moderate use vs stable no use	-0.0374	0.0783	-0.48	0.6330	-0.191 - 0.116

[a]Multiple linear regression analyses with dependent variables CGI overall, mania, depression and hallucinations/delusions, independent variables stable alcohol levels and covariates age, sex, relationship, education, country, current patient status, history of suicide attempts, history of rapid cycling, current duration of mania and compliance.

[b]Clinical Global Impression Scale, Bipolar Version (1-7).

[c]Bolded P values denote significance.

[d]Confidence Interval.

[e]Alcohol Use Disorder.

Table 2 also shows that there were no statistically significant or clinically relevant differences in clinical outcome measures at 12 or 52 follow-up between the three baseline alcohol use groups.

However, because of the high remission rates of (problematic) alcohol use during the follow-up period, further post-hoc analyses were performed comparing subgroups with stable levels of alcohol use during 12 weeks follow-up (no alcohol use N=1,366, moderate alcohol use N=419, and AUD N=47, see Table 2) and 52 weeks follow-up (no alcohol use N=882, moderate alcohol

use N=245, and AUD N=28, see Table 2) using the same outcome variables and the same covariates. At 12 weeks there were no significant differences in outcomes between the groups (data not shown). At 52 weeks there were significant differences ($p<0.01$) between the stable AUD group and the stable no alcohol use and stable moderate alcohol use groups on the CGI-BP overall and mania (sub)scales but not on the CGI-BP depression and hallucinations/ delusions (sub)scale (see Table 3). There were no significant differences on the CGI (sub)scales between the stable no alcohol use and the stable moderate alcohol use group.

Since current abstainers and moderate alcohol users at baseline can be former alcoholics (life time AUD at baseline), all comparisons at baseline, 12 and 52 weeks were also performed after exclusion of patients with a history of alcohol problems (N=144+379+333=856, see Table 1). In this second series of post-hoc analyses there were no significant differences in clinical outcomes between the alcohol use groups (data not shown).

DISCUSSION

The current study shows that at baseline, the three patient groups (no use of alcohol, moderate, non-problematic use of alcohol and AUD) were statistically different from each other on demographic characteristics, treatment setting, age at onset of BD, history of suicide attempts, rapid cycling in the previous year, substance use characteristics, compliance, CGI-BP overall and mania, YMRS and HAMD-5 (Table 1). However, with the exception of rapid cycling in the previous year, history of suicide attempts and compliance, these differences

in baseline characteristics were not considered clinically significant due to the small effect sizes (<5% or d<0.3). This conclusion is consistent with the findings of our previous study[26] where we also found no significant baseline differences between the alcohol use groups and illness severity indicators. The outcomes (CGI-BP, YMRS, and HAM-D) of the three baseline alcohol use groups did not significantly differ after 12 and 52 weeks follow-up (Table 2) and this is also consistent with our previous one-year prospective cohort study.[26] These findings confirm our hypothesis – that the outcome (CGI-BP, HAM-D and YMRS) of bipolar patients after 12 and 52 weeks follow-up is not dependent on their alcohol use at baseline.

It should be noted, that 57% of the patients were alcohol abstainers at baseline, while only 31% of the European general population are last-year alcohol abstainers[33], suggesting that many of the patients of this study followed the non-drinking advices of their psychiatrists.

The alcohol use patterns changed considerably during follow-up with 40-50% of the patients with moderate and AUD becoming fully abstinent at the time of follow-up. Therefore, in a post-hoc analysis, patient groups with stable alcohol use patterns between baseline and follow-up (stable no alcohol use, stable moderate alcohol use, and stable AUD) were compared on clinical outcomes at 12 and 52 weeks. Again there were no significant differences in outcome between the stable moderate alcohol use group and stable no alcohol use group. However, there was a large and clinically significant difference in outcome on the CGI-BP overall and mania (sub)scales between the small stable AUD group (N=28) versus the stable moderate alcohol use group (N=245) and

the stable no alcohol use group (N=882) showing an unfavorable course of the stable AUD group (Table 3).

What could be the explanation for the absence of a negative association between baseline (problematic) alcohol use and clinical characteristics at baseline and at 12 and 52 weeks? First of all this may be explained by the fact that all patients entered the study in a manic of mixed episode for which treatment was initiated or changed. However, this does not explain the lack of significant group differences at baseline. It is also unlikely to explain the large reductions in (problematic) alcohol use at 12 and 52 weeks (with 42% and 40%, respectively) follow-up in patients with an AUD at baseline since there is no clear evidence that antimanic medication is effective in the treatment of BD patients with co-morbid alcohol use disorders[34] and 19-25% of the patients was not prescribed additional medication at all (see table 1). Second, there was an average of 14-16 years of BD illness duration, and the negative effect of alcohol may be restricted to the early years of the disorder, whereas this negative effect levels out with longer illness duration. It is known for instance from a Danish case register study[35] with 22 years of monitoring that concurrent alcoholism increased the risk of recurrence of episodes during the initial course of unipolar depression and BD, while it had no effect on recurrences later in the course of the illness. In line with this explanation are the findings of a 7-year follow-up study[36] showing that younger patients (aged 17-26 years) may have a greater likelihood that alcohol use and bipolar symptoms increase and decrease in unison. Third, the differences between the European EMBLEM study and our previous study compared to those in the literature may reflect a difference between

Europe and the US, where most of the previous studies[12-25] were conducted. Indeed there are indications that BD in Europe not only starts at a later age but also has a more benign course than in the US. In the (Stanley Foundation) Bipolar Collaborative Network, US patients reported an earlier age at onset and a higher frequency of comorbid substance abuse than European patients (47% versus 27%).[37] In the current sample only 14% reported life-time cannabis use problems and only 8% other life-time drugs use problems, which is even lower than in our previous study and indeed much lower than the 35% found in the US study by Salloum et al.[38] Fourth, we may have missed an effect due to the non-standardized and therefore possibly inaccurate assessment of alcohol use and alcohol use disorders in the current study. This could have led to an overestimation of the severity at baseline, with a misinterpretation of excessive alcohol use during an acute manic episode as indicative of an AUD leading to great instability of the AUD diagnosis.[39] A final explanation may be the instability of alcohol use patterns and alcohol use disorders.

The presence of significant effects of stable alcohol use patterns on various clinical outcome measures (GCI-BP overall, mania and depression) at 52 weeks follow-up (see table 3) are consistent with most of the currently available (mainly US) based studies.[12-24] The difference with our previous study could be explained by the difference in compliance of the EMBLEM sample of 35-50% (see table 1) compared to a compliance of over 90% in our pervious sample.[26] There were no reports on compliance in most of the other articles.[12-25] Compliance (medical and behavioral) with treatment grows with time, which could be an explanation that patients in their early course (0-10 year) of BD

suffer more from the effects of excessive use of alcohol than the patients of the current study in which the mean duration of illness was about 15 years. The rather low rate of compliance in this sample could be an important explanation because a high compliance seems to be a protective factor against the negative effect of excessive alcohol use on clinical outcomes.[26]

The current study has both strengths and limitations. The most important strengths are the international nature, the large sample size, the relatively high 12 weeks follow-up rates, the distinctions between different levels of alcohol use, and the correction of the findings for a broad range of potential confounders. The study also has limitations. First, the large number of countries and investigators participated in the EMBLEM study forced us to use simple non-standardized scales to measure alcohol use, abuse and dependence, which could easily be completed during daily practice. However, the non-validated nature of this scale may have hampered the distinction between moderate non-problematic use versus abuse and dependence. Also, there may have been underreporting of the category “alcohol use with problems” (AUD), which can have obscured the difference between moderate alcohol users and AUD. Second, a structured diagnostic interview was not administrated. Diagnoses (of both BD and AUD) were based on clinical judgment of the psychiatrist, in line with daily clinical practice. On the other hand, given the large number of doctors participating in EMBLEM and its simple methodology, the patients enrolled reflect those patients who are treated throughout Europe but at the same time are not representative of all bipolar patients.

CONCLUSION

In conclusion, the results of the EMBLEM study that no negative effects of baseline (excessive) alcohol use could be demonstrated on the outcome of treatment of mania after 12 and 52 weeks follow-up, are in line with the findings of our previous study.[26] We believe that this is most likely related to the relatively lack of comorbid substance use disorders other than AUD, and – most importantly – the adequate acute and long-term treatment of mania, including possible good compliance with medication in those patients who remained in the current study.

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6

SUMMARY AND GENERAL DISCUSSION

INTRODUCTION

In this chapter the main findings of this thesis will be summarized and discussed. Important questions will be: are our findings clinically relevant and should they have consequences for daily practice? Finally, future perspectives for research will be discussed.

Is the Mood Disorder Questionnaire a suitable instrument to detect bipolar disorders (BD) in treatment seeking substance use disorder (SUD) patients in an addiction treatment center?

An important problem of clinicians is to detect BD as early as possible in patients seeking treatment in mental health and addiction centers. Till now psychiatrists were not very successful in early detection of this illness in mental health centers: there is still underdiagnosis of BD resulting in a delay of 6-10 years before patients get their accurate diagnosis.[1] The aim of our first study (chapter 2) was therefore to detect BD in patients seeking treatment for a SUD in addiction centers. The Mood Disorder Questionnaire (MDQ)[2] was the screening instrument of choice and was compared to the Structured Clinical Interview for DSM-IV (SCID) diagnosis, in this study used as the gold standard.

Our first hypothesis, that the MDQ is a valid screen for the detection of BD in a treatment seeking addiction population was not confirmed. With a BD prevalence of 20.6% according the SCID, a sensitivity of .43, a specificity of .57, an AUC of 0.50 and a positive and negative predictive value of the MDQ of .21 and .80, respectively, the MDQ has no added value in the detection of BD treatment

seeking SUD patients. Adapting the MDQ by leaving out the requirement of impaired functioning did not improve performance of the MDQ.

The second hypothesis that the addition of two extra questions to the original MDQ, about the relationship of BD symptoms with concurrent substance use, would improve the specificity without (seriously) lowering the sensitivity was only partly confirmed. Another hypothesis that the high prevalence of borderline personality disorder (BPD), antisocial personality disorder (APD) and attention deficit/ hyperactivity disorder (ADHD) in our treatment seeking substance use disorder (SUD) sample would result in a high rate of false positives (FPs) and thus in low specificity, was confirmed. Obviously, the MDQ is able to detect externalizing disorders other than BD. However, broadening the external criterion to any externalizing disorders, did not substantially improve the performance of the MDQ in this population (AUC=0.60 compared to AUC=0.50).

Our main conclusion from this study is that we can not recommend the original nor any of the adapted versions of the MDQ as a useful screener to detect the presence of BD or any externalizing disorder in a population of treatment seeking patients with SUD.

Discussion

Till now, there is only one other study[3] that examined the performance of the MDQ (together with the Hypomania Checklist-32 [HCL-32][4]) in detecting BD among 152 outpatients with SUD of whom 33 were SCID BD positive. With about the same prevalence of 22% compared to our study (21%), Nallet et al.[3] found a better performance of the MDQ than in our study (sensitivity=.67 specificity=.77,

AUC not reported; PPV=.45, NPV=.89). They concluded, in contrast to our study, that the MDQ performed adequately in SUD patients. In the latter study patients with SUD were recruited among those who were newly referred to treatment or already in contact with specialized facilities for alcohol and opiate treatment of a community mental health and psychiatric outpatient clinic that was part of a university clinic. A possible explanation of the difference in performance is that in the Nallet et al.[3] study one third of the total sample had been abstinent during the last month, whereas in our study they were only 3 days abstinent at baseline. Moreover, in the Nallet et al.[3] study two thirds of the alcohol-dependent patients were treated with antidepressants and almost all of the opiate-dependent patients were treated with methadone, showing that patients were already in active treatment. Our patients were seeking treatment, i.e. they did not have any treatment at baseline, suggesting that their severity of illness was probably greater than the patients of the Nallet et al.[3] study, i.e. having a higher number of SUD related symptoms that may overlap with hypomania symptoms.

The comparison of the results of our study and the study by Nallet et al.[3] shows the possible impact of the composition of a sample, and the timing of screening on the performance of the MDQ.

Clinical relevance

For clinical practice the performance of the MDQ in BD detection in a treatment seeking population of addiction centers is rather disappointing. The problem of underdiagnosis or overdiagnosis of BD in treatment seeking populations of addiction centers is not solved. With a NPV of .80 in our study and .89 in the

study by Nallet et al.[3], one may argue that the MDQ is a reasonable good tool to rule out the presence of BD in addiction settings where a psychiatric interview is not standard at intake. Only those who screen positive need to have a proper diagnostic psychiatric assessment, essentially decreasing the burden of psychiatric interviews for BD at intake. However, with a PPV of .20 it means that five patients with a positive MDQ have to have a psychiatric assessment in order to detect one patient with a comorbid BD. Other studies on the performance of the MDQ, also show low PPV's (.20-.30) and high NPV's (.80 - .96), supporting our negative conclusion.[5-7]

Taking into account that the nature of a sample and the timing of the assessment may have an impact on the performance of the MDQ one can wonder if the MDQ has possibly a better performance when the assessment takes place later on in the diagnostic process, i.e. when the patient is stabilized (e.g. longer abstinence leading to less recall bias). However, the problem of the high false positive rates of BPD, ASP and ADHD will probably not be solved.

Future perspectives

What steps could be taken in order to improve the detection of BD in a treatment seeking addiction population?

- One may wonder if screening of BD in a treatment seeking addiction population would improve when two or three screening instruments are used together. For instance, one could combine the MDQ with the HCL-32[8] or with the Bipolar Spectrum Diagnostic Scale (BSDS).[9,10] The HCL-32 showed a sensitivity of .39 and a sensitivity of .91 (PPV =.39, NPV=.94)

in an outpatient SUD population[3] and does not add additional screening power. Lee et al.[10] combined the BSDS with the MDQ in an outpatient population with a current major depressive disorder. They found a combined sensitivity of .90 and a combined specificity of .74 (requiring at least one of the instruments to meet the criteria for a positive result) and conclude that the combined use of the MDQ and the BSDS is more effective than the use of either of these instruments. However Zimmerman et al.[11] administered the BDRS in an outpatients population and concluded that, with a sensitivity of .83, a specificity of .68, a PPV of .21 and a NPV of .98, the BDRS was only excellent at ruling out a diagnosis of BD. Therefore, one can not expect that the combination of the MDQ with one of the other instruments to improve the screening of BD in a SUD treatment seeking population.

- The detection of BD in a treatment seeking population will not improve if one exclusively relies on screening instruments based on DSM/ICD criteria. Moreover, solving the problem of overdiagnosis (i.e. a low PPV) of BD by tightening the diagnostic criteria is nearly impossible.[12] Therefore, changing the diagnostic criteria does not seem the solution for the current problem.
- Nevertheless, a future direction of research could be the development of a better screening instrument, adjusted to the use in an addiction population. The approach of developing such an instrument should be based on categorical diagnostic criteria and a “probabilistic” (or likelihood) approach. First of all core questions, based on the DSM-5/ICD11 symptoms of (hypo) mania, with the highest patients-clinician concordance should be used, those with the lowest should be left out. Goldberg et al.[12] showed that

the MDQ-questions about excessive spending, increased goal-directed activity and hypersexuality had the highest patient-clinician concordance, while questions as irritability, racing thoughts and distractability had the lowest patient-clinician concordance. Only the questions with the highest concordance should be included in a new screening instrument.

- Another possibility to improve the screening instrument is increasing the PPV. In a population of treatment seeking addiction patients, with a high prevalence of about 21% (our study and the Nallet et al.[3] study), one could increase the prior probability by assessing factors that are statistically associated with BD, such as a positive BD family history, early age at onset of BD and the presence of recurrent depressive episodes[13,14], prescription or use of mood stabilizers in the past[15] which do occur more often in patients with BD than with unipolar depression. For instance, a parental history of BD increases the risk in the offspring to about 20%.[16] Therefore, questions about family history, early age at onset, recurrent depression and the use of mood stabilizers should also be included into the new instrument.
- A third way of improving the performance of self-rating screening instruments is, in order to diminish recall bias, to use collateral information (spouse, partner, child, parent, friend) for the completion of the MDQ at intake.
- Finally, one may use the self-rating instrument as a semi-structured interview. For example, Goldberg et al.[12] showed that when a psychiatrist reviewed the responses of the MDQ from inpatients with mood symptoms and substance misuse, patients more often scored a positive MDQ (56%) than the clinician (30%) ($p<.001$), resulting in a substantial decrease in the number of false

positives. However, this latter possibility will be an important economical burden for the diagnostic process.

We therefore have to conclude that still a lot of work needs to be done to develop a suitable (self-report) screening instrument that will have high sensitivity, specificity, PPV and NPV in order to detect BD in a treatment seeking addiction population.

Alcohol and the course of bipolar disorders

In order to answer two important questions of BD patients and their doctors we conducted two studies. The first question was whether moderate use of alcohol has negative effects on the course and outcome of BD patients (chapter 3). The second – more detailed – question concerned the temporal relationship between alcohol use and subsequent mood changes in patients with BD (chapter 4).

The effect of moderate and excessive alcohol on the course and outcome of patients with bipolar disorders; a prospective study.

This is the first detailed prospective study in which BD patients were included who rated their mood symptoms and the number of alcohol units consumed on a daily basis for a period of up to 52 weeks (chapter 3). Based on their alcohol use in the first 4 weeks of follow-up, patients were assigned to one of three groups: patients with no or incidental use of alcohol, patients with moderate alcohol use, and patients with excessive alcohol use. We hypothesized that while excessive use would have a negative effect on the course and outcome of BD, moderate use of alcohol would not have a negative effect.

Surprisingly, we found that neither moderate nor excessive use of alcohol had a negative effect on course and outcome of BD. Thus, we could not confirm previous studies indicating a negative effect of excessive alcohol use on the course of BD. Even patients with a mean of 17 heavy drinking days in the first 4 weeks and 13 heavy drinking days per 4 weeks during follow-up had no worse outcome (mania, depression, overall) than patients who did use no or only moderate amounts of alcohol. The most plausible explanations for these findings are:

- The high medication adherence (>90% of the recorded days) of our patients using moderate or excessive alcohol compared with other study populations (chapter 3). Non-adherence is significantly associated with rapid cycling, suicide attempts, earlier age at onset (AAO), current anxiety and AUD.[17]
- The fact that studies that reported negative effects of alcohol use on BD were mainly done in the US while our study was done in the Netherlands. In a study form the previous Stanley Foundation Bipolar Network, performed in four US sites and three European sites (two in Germany and one in the Netherlands), Post et al.[18,19] showed that the US sample, compared to the European sample had a significantly higher incidence of positive family history of BD, major depressive disorder, rapid cycling and comorbid SUD. Belliver et al.[20] tested the AAO of an American BD I sample (N=2275) and an European BD I sample (N=3616) of which about 80% were patients of the European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) study (chapter 5). They found three different distribution groups of AAO.

Sixty-three percent of the US sample (mean AAO: 14.5 ± 4.9 years) were part of the early-onset group, compared to only 25% of the European group (mean AAO: 19 ± 2.7 years). Early age onset of BD and the associated treatment delay is associated with a more adverse outcome in adulthood.[16,19] The delay in treatment is independently associated to more days of depression, greater mean of severity of depression and less days of euthymia[19] and prospectively with a greater risk for recurrence, chronicity of mood symptoms and functional impairment.[21, 22]

- Attenuation of the negative response (number of episodes) to alcohol with increasing illness duration. Concurrent alcoholism may have increased the risk of recurrence of episodes during the initial course of unipolar and bipolar disorder yet may have no effect on recurrences later in the course of the illness.[23] Our patient group had a long mean duration of illness (21 years). The negative effects of alcohol could be much stronger in patients with a shorter duration of illness (0-5 year, 6-10 year).

Our findings were striking and showed that the effects of alcohol on BD are more complicated than one liners such as *"booze is bad"* suggest, an overall conclusion that can be distilled from most US studies. Our data collection approach of daily reporting the alcohol use distinguished our study from other studies that used DSM-III or DSM-IV diagnoses of AUD and SUD as predictors. Only 50% of our excessive alcohol using group did meet the criteria of a current DSM diagnosis of AUD. There is a gray area between excessive alcohol use (males > 21 units /week, females >14 units/ week) and fulfilling the DSM-IV

criteria of AUD.[24] Another explanation may be the instability of alcohol use patterns and alcohol use disorders.[25] The DSM may lack ecological validity because the criteria of AUD may not cover the reality in daily practice. In our study (chapter 3), even patients with a current AUD did not show any negative effect on course and outcome of BD. In focusing on the actual daily use of alcohol, the results of our study are much more imbedded in daily life. Advice to patients in terms of number of units alcohol instead of having a disorder, may fit in more closely with daily experiences of patients. “How many units of alcohol per day can I use without having a negative effect on my mood?” Having or not having the diagnosis of an AUD is not very informative for patients. Our “units- per-day” approach is not only more informative, but also more straight forward and more suitable for daily practice (and for research!). In daily practice, the actual amount counts.

Effect of alcohol use on the course of bipolar disorder: one year follow-up study using the daily Prospective Life Chart Method.

In order to get more insight into the direct effect of alcohol on the daily course of BD we studied the temporal relationship between the actual amounts of daily alcohol use and subsequent daily mood changes (chapter 4). Do depressive or manic symptoms precede alcohol use, do they coincide, or does alcohol use precede depressive or manic symptoms? We used data from the same study that was used to answer the question regarding the prediction of the effect of baseline alcohol use on the course and outcome of BD (chapter 3).

Based on previous studies and our clinical impression we hypothesized: (1) that alcohol use would have a direct and more or less immediate effect on

the course of illness, i.e. that alcohol use would predict the fast occurrence or worsening of depressive but not of manic symptoms in the subsequent week, and (2) that these effects would be stronger in males than in females.

To disentangle the complex interplay between alcohol and bipolar disorder we used Multi-State Markov models assessing the impact of the number of alcoholic drinks on the patients' transition through different mood states. The transition model had three mood states (depression, euthymia and mania) with four possible switches of mood: from depression to euthymia and visa versa, and from mania to euthymia and vice versa). Mood states were used as the dependent variable and "number of drinks" was included as a time-dependent covariate. Our main interest was to determine the impact of the reported number of alcohol units on the occurrence of switches between mood states.

The study showed that higher alcohol use in women was significantly associated with a faster switch from depression to euthymia, whereas for men higher alcohol use was significantly associated with a slower switch from euthymia to mania. These findings are striking and counter intuitive. Moreover, the correlations between the consumed number of drinks per week and the average mood severity score of the following week in the subsamples males and females were significant and in line with the results of the Multi-state Models analyses. Although the correlations were significant, they were very small, so one can doubt the clinical relevance of these findings. From a clinical perspective we had to reject our first hypothesis: in the current sample, higher levels of alcohol use did not predict the occurrence or worsening of depressive symptoms in the subsequent week. Our second hypothesis – that the hypothesized negative effect of alcohol

on subsequent depressive states would be stronger in males than females - was also not confirmed.

In combination with the already reported findings from the same study (chapter 3) our conclusion is that moderate as well as excessive use of alcohol has no clinically relevant short-term effect on mood switches in patients with BD and no long-term effect on the course and outcome of BD. It should be noted, however, that this is true for the group as a whole and that there were large individual differences ranging from patients with a strong negative effect of alcohol use on mood state through patients with no effect of alcohol on mood to patients with a clear positive effect of alcohol use on mood state. This latter finding means that no general advice can be given and it supports the need for staging and profiling[26-28] ultimately resulting in a personalised diagnosis and tailor made treatment and advice.

The results reported in chapter 3 and 4 show that the design of our study with daily reporting of the actual amount of alcohol use and the actual mood state provides new possibilities for statistical analysis (e.g. fine grain analysis with multi-state model) that sheds more light on the complex interplay between alcohol and BD. Based on these findings, it became evident that the current opinion that alcohol always has negative effects on the course and outcome of BD is not valid. Being adherent to the prescribed medication may protect BD patients for the negative psychiatric effects of alcohol. It should be noted, however, that excessive alcohol use is related to negative somatic problems and that there were large individual differences with regard to the negative effects of alcohol on the psychiatric status of our BD patients.

Effect of alcohol use on 12 month clinical outcome of patients with acute mania or mixed bipolar episode. Results of the EMBLEM study.

In this study (chapter 5) we tried to replicate our findings of chapter 3 in a different patient cohort. In this large European study (N=3,302) of BD patients included during a manic or mixed episode we were able to study the effect of alcohol on the course and outcome during a follow-up period of 3 months and one year. Similar to chapter 3, patients were divided at baseline into three groups: no alcohol use (n=1886, 57%), moderate (i.e. non-problematic) alcohol use (n=1055, 32%), and alcohol use disorder (AUD: n=361, 11%). These three patient groups were statistically different from each other on demographic characteristics, treatment setting, age at onset of BD, history of suicide attempts, rapid cycling in the previous year, substance use characteristics, compliance, CGI-BP overall and mania, YMRS and HAMD-5. However, with the exception of rapid cycling in the previous year, history of suicide attempts and compliance, these differences in baseline characteristics were small and not considered clinically relevant. At 12 and 52 weeks follow-up there were no statistically significant or clinically relevant differences in clinical outcome measures between the three baseline alcohol use groups. Because about 50% of the patients stopped using alcohol during follow-up, we did a post-hoc analysis with those patients of the three groups who maintained their baseline alcohol use level during follow-up. Stable AUD patients (patients who kept the diagnosis of AUD during follow-up) scored significantly higher at 52 weeks on the CGI-BP, indicating higher clinical severity of their psychiatric condition (subscales overall and mania) compared to stable moderate users and stable non-users, whereas stable moderate users

and non-users did not significantly differ in CGI-BP outcomes from each other. The observed effect of AUD may have been mediated or modified by a lack of treatment compliance in patients with a stable AUD since only 36% of the AUD patients was fully treatment adherent.

Our main findings that alcohol use and the presence of an AUD at baseline were not associated with negative outcomes at 12 and 52 weeks follow-up were in line with our findings reported in chapters 3 and 4. However, the outcome in stable AUD patients in the EMBLEM study, who were less treatment adherent, show that continued excessive use of alcohol may have a negative effect in the course and outcome of (at least some) BD patients. It also shows that treatment adherence is crucial to prevent negative effects of alcohol on the course of BD.

Clinical relevance

The results of our three studies on the relationship between alcohol use and BD symptoms over time (chapter 3, 4 and 5) strongly suggest that our European bipolar patients (as a group) probable do not have to worry too much about the effects of moderate alcohol use (14 units for females and 21 units for males per week) on the course of their BD, on the condition that they are and stay adherent to their BD medication. Due to the more severe course of illness of US BD patients[16,18,19], compared to European BD patients, we can not reassure US BD patients about the effects of moderate use of alcohol on their bipolar illness. The negative effect of excessive alcohol use on the physical health of BD patients and the general population[29] prevents reassurance of both US and European BD patients with excessive alcohol use, although our studies showed that excessive

use of alcohol had no negative effects on the course and outcome of (treatment adherent) European BD patients.

In daily practice we advice the use of the prospective, self rated version of the Life Chart method (LCM) in order to detect whether the daily alcohol intake (units) of BD patients (especially during the early years of illness [0-10 years]) has a negative effect on mood symptoms. Another advantage by daily reporting with the LCM is the developing awareness of the patient of his alcohol use. The number of heavy drinking days per 4 weeks at baseline (17.2 days) in our excessive alcohol using group decreased with about 22% during follow-up (13.5 days) possibly as a consequence of the daily monitoring of their alcohol use.
There is much to gain with lowering daily alcohol use. In the general population reduction from 10 units to 5 units of alcohol per day decreases the risk of death (absolute risk of dying from an alcohol-attributable disease and injury) substantially from 16% to 2 % for males and from 8% to 1% for females compared to a very small decrease in death risk (<1%) when alcohol use is diminished from 3 to 0 units per day.[29]

Although our studies did not find that alcohol use had an effect on recurrence of episodes (in our very adherent study population), recurrence of episodes remains a major aspect of BD and excessive alcohol use in patients with a poor adherence to their mood stabilizing medication. Post and Kalivas[30] postulated that intermittent stressors, mood episodes and bouts of cocaine all show not only sensitization to themselves, but also to each other (cross-sensitization). The model of kindling or sensitization to environmental stressors as model for illness progression (recurrence) suggests that in the long course of BD less and

less stress factors are needed to develop a subsequent mood episode, leading to recurrence and cycle acceleration.[31-33] Post and Kalivas[30] concluded that due to these interacting cross-sensitization processes, each type of sensitization (stress, symptom episode and substance use sensitization) contributes to faster illness progression and greater illness burden. It is important to prevent episodes (BD and SUD) in order to prevent increasingly severe manifestations of BD and SUD.

In the complex interplay of BD and alcohol, no matter what has the earliest AAO, it requires an active role of the psychiatrist to detect and prevent this dual recurrence.

However, it is unclear whether the excessive use of alcohol also plays a role in the interacting (cross-) sensitization processes.

Future research

As shown in this thesis, the assessment of the effect of alcohol and SUD on the course and outcome of BD beyond the DSM criteria is clinically relevant.[34] Future studies on the comorbidity of BD and SUD that use only DSM criteria (i.e. leaving out those patients with excessive use of alcohol who do not meet criteria for SUD) will not contribute in getting a more comprehensive picture of this comorbidity. In order to disentangle the complex interplay of alcohol and illicit drugs, and to evaluate whether differences between populations moderate study outcomes, one suggestion would be to perform a large prospective multisite-study with different populations in different parts in the world (not only US and Europe), In this study it is important to measure the actual amount of

daily (or weekly) alcohol and drugs, daily (or weekly) mood state and medication adherence. A good instrument for these measures is the Life Chart Method (LCM). Data on sociodemographic and clinical characteristics, family history, and treatment adherence should be collected. The effect of the actual amount of alcohol and substance use, the duration of illness (0-5, 6-10 and >10 years) with different clinical characteristics per illness duration are key variables that should be studied. Treatment adherence is expected to be less in the early years of illness and comorbid drug use (cannabis and other drugs) and is thought to be more prevalent with younger age and shorter duration of illness. A series of meta-analyses of 49 mainly US studies[35] found that lower current age and lower age at onset, male gender, being unmarried, having BD I, having a comorbid anxiety disorder and a history of suicide attempts predicted comorbid SUD (including AUD) with BD and should be considered as confounding factors.

A positive family history of SUD, more than 10 prior manic or depressive episodes, a history of prior rapid cycling and poor occupational functioning at study entry, which have been found to predict outcome of bipolar disorder in general, have also to be considered as potential confounders for the relation between alcohol use levels and 12 month clinical course and outcome.[36]

The Canadian Network for Mood and Anxiety Treatments (CANMAT) and the International Society for Bipolar Disorders (ISBD) collaboratively updated the CANMAT guidelines for the management of patients with BD (2013 update)[37] and the updated British Association for Psychopharmacology (BAP) guidelines[38] showed that untill now there is no conclusive evidence on how to treat BD-AUD and BD-SUD comorbidity, although there seems to be some benefit (improvement

in drinking outcomes, not in improving mood) of the combination of valproate and lithium in this population.[39,40] Therefore, future studies should also investigate the effect of different pharmacological approaches for treatment of the BD patients with comorbid substance use (harmful use, abuse and dependence).[38]

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NEDERLANDSE SAMENVATTING

(Summary in Dutch)

In de inleiding van dit proefschrift (**hoofdstuk 1**) wordt besproken dat ongeveer 50% van de patiënten met een bipolaire (manisch-depressieve) stoornis (BD) in zijn of haar leven ook een alcohol- en/of drugsverslaving heeft gehad. Het tegelijkertijd voorkomen van een alcohol- en/of drugsverslaving heeft volgens, vooral Amerikaanse (USA) onderzoeken, een negatieve invloed op het beloop van de BD. Zo is er, vergeleken met patiënten zonder alcohol- en/of drugsverslaving, sprake van een vroegere start van de stoornis, frequentere en langere episoden, meer en ernstiger symptomen per episode, een snellere terugval naar de ziekte, meer gemengde episoden (zowel manische als depressieve symptomen), meer ziekenhuis opnames, verminderde therapietrouw, een verminderde reactie op medicatie en meer suïcides. Er is echter nog weinig onderzoek gedaan naar het effect van gematigd (sociaal) alcoholgebruik op het beloop van BD. Patiënten met BD vragen zich vaak af of gematigd gebruik van alcohol een negatief effect heeft op hun ziekte en tot nu toe was daar geen duidelijk antwoord op te geven.
Een andere vraag is of er mogelijk onderdiagnostiek van BD bij verslaafden optreedt. Door de hoge comorbiditeit van BD met alcohol- en/of drugsverslaving (50%), kan verwacht worden dat veel verslaafden vermoedelijk ook een bipolaire stoornis hebben. Omdat de symptomen van een bipolaire stoornis en van een verslaving gedeeltelijk overlappen zou dit tot onderdiagnostiek van de bipolaire stoornis kunnen leiden bij patiënten die zich in verband met hun verslaving aanmelden bij instellingen voor verslavingszorg.

In dit proefschrift staan daarom twee vragen centraal.
De eerste vraag is of het screeningsinstrument voor bipolaire stoornissen, de Mood Disorder Questionnaire (MDQ), een valide instrument is om op een betere manier bipolaire stoornissen te detecteren bij patiënten die zich aanmelden bij de verslavingszorg. De tweede vraag is of gematigd (sociaal) gebruik van alcohol een negatief effect heeft op het beloop van patiënten met een BD.

In **hoofdstuk 2** van dit proefschrift wordt verslag gedaan van het onderzoek naar het opsporen van bipolaire stoornissen bij patiënten die zich aanmelden bij de

verslavingszorg. Hiertoe werden patiënten, bij aanmelding in de verslavingszorg, gevraagd om bij de intake de MDQ in te vullen. Dit screeningsinstrument heeft een redelijk goede sensitiviteit en goede specificiteit bij het opsporen van bipolaire stoornissen bij patiënten van poliklinieken voor stemmingsstoornissen. Na de intake werden alle patiënten die positief op de MDQ scoorden en een op de vier patiënten met een negatieve score op de MDQ nader onderzocht met een aantal meetinstrumenten om zo doende de diagnose van BD te kunnen bevestigen. Aangezien er een overlap in symptomen is tussen de BD, de borderline persoonlijkheidsstoornis (BPS), de antisociale persoonlijkheidsstoornis (APS) en aandachtstekortstoornis met hyperactiviteit (ADHD) bij volwassen werden er ook meetinstrumenten gebruikt om deze diagnosen te stellen.

Uit dit onderzoek bleek dat de MDQ (of aangepaste versies daarvan) geen goed screeningsinstrument is om BD beter te detecteren bij patiënten die zich aanmelden bij de verslavingszorg. De kennis die de MDQ leverde verbeterde de voorspelling dat er wel of geen BD aanwezig was niet. Wel bleek dat een negatieve score in de MDQ een goede voorspellende waarde heeft dat een patiënt geen BD heeft. Zoals we al verwachtten waren er, door de hoge prevalentie (voorkomen) van patiënten met een BPS, APS en ADHD in de verslavingszorg, veel vals positieven scores in de MDQ. Concluderend kan gezegd worden dat de MDQ hooguit een redelijk goed instrument is om een BD uit te sluiten bij patiënten die hulp zoeken bij de verslavingszorg.

Hoofdstuk 3 beschrijft een prospectieve studie waarin patiënten met een BD een jaar lang elke dag op een Life Chart (zie fig. 1, hoofdstuk 1) diverse gegevens registreerden over hun stemming (o.a. mate van de ernst van hun eventuele manische of depressieve symptomen) en welke medicatie zij gebruikten. Daarnaast noteerden zij elke dag hoeveel eenheden alcohol en cafeïne zij dronken en hoeveel sigaretten en joints zij rookten. Door prospectief onderzoek te doen, waarbij de werkelijke hoeveelheid alcohol die patiënten per dag dronken, werd geregistreerd verwachtten wij een beter inzicht te krijgen over het effect van alcohol op het beloop van BD.

De patiënten werden verdeeld in 3 groepen; zij die niet of incidenteel alcohol gebruikten, zij die gematigd (sociaal) alcohol dronken en zij die excessief alcohol gebruikten. Het aantal manische, hypomane en depressieve dagen per 4 weken, de gemiddelde ernst van de manisch, hypomane en depressieve dagen per 4 weken, het aantal manische, hypomane en depressieve episoden volgens de criteria van de DSM-IV werden o.a. als uitkomstmaten gebruikt.
Zoals wij vooraf voorspelden, waren de uitkomsten van de gematigd (sociaal) alcohol drinkende patiënten niet slechter dan die van de groep die geen of incidenteel alcohol gebruikten. Tot onze verassing bleek echter dat ook de groep patiënten die excessief alcohol gebruikten het niet slechter deed dan de twee andere groepen, zelfs als we o.a. corrigeerden voor patiënten die nu niet dronken, maar vroeger wel alcoholverslaafd waren. Onze bevindingen onderschrijven de uitkomsten van de andere studie die juist negatieve effecten vonden (zie inleiding) dus niet.

Mogelijke verklaringen voor deze bevindingen zijn: 1) dat onze groep BD patiënten minder psychiatrisch ziek waren dan de BD patiënten van de andere, vooral Amerikaanse, studies die wel negatieve effecten vonden excessief alcoholgebruik. De patiënten uit de andere studies hadden ook vaker een drugsverslaving, dat ook een negatieve invloed kan hebben op de uitkomsten. Verder zou het negatieve effect van alcohol op het beloop van BD gedurende het beloop van de DB langzaam kunnen verbleken. Een belangrijke andere verklaring voor onze bevindingen is de waarneming dat onze patiënten, in tegenstelling tot de patiënten uit de andere studies zeer trouw waren met het innemen van hun medicatie. Therapietrouw is waarschijnlijk een duidelijk beschermende factor tegen de negatieve effecten van alcohol op het beloop van BD.

In **hoofdstuk 4** wordt nader onderzoek gedaan met dezelfde groep patiënten als in hoofdstuk 3. Nu hebben wij gekeken naar het effect van het aantal eenheden alcohol per week op de verandering van stemming (depressie, gelijkmoedigheid (euthym) en manie) van patiënten in de week er na. Ook hierbij werd gebruik gemaakt van de gegevens van de Life Charts. In verband met de gedetailleerde manier van analyseren werd vooraf aangenomen dat patiënten van stemming

konden veranderen tussen gelijkmoedigheid en manie en visa versa en tussen depressie en gelijkmoedigheid en visa versa. Zie figuur 1 van hoofdstuk 4. Omdat er een verschil in uitkomst zou kunnen zijn tussen mannen en vrouwen werd het geslacht als mogelijke invloedfactor in de analyses opgenomen.
Vooraf hadden we, gebaseerd op de literatuur en onze klinische indrukken de volgende hypothesen: 1) alcoholgebruik voorspelt het optreden of verslechtering van depressieve, maar niet manische symptomen in de volgende week en 2) dat deze effecten groter zouden zijn bij mannen dan bij vrouwen.

De gevonden effecten waren beperkt. Bij vrouwen met een depressieve stemming was een hoger alcoholgebruik geassocieerd met een kortere tijd om euthym (gelijkmoedig) te worden, terwijl bij mannen die in een gelijkmoedige stemming verkeerden het hoger alcoholgebruik geassocieerd was met een langere tijd voordat zij manisch werden. De correlatie tussen het aantal eenheden alcohol per week en de gemiddelde ernst van de stemming in de volgende week was significant, maar erg klein waardoor de klinische relevantie van de gevonden uitkomsten ook erg klein is.
Onze bevindingen suggereren dat het korte termijn effect van hoger alcoholgebruik op het beloop van BD dus erg beperkt is, waardoor wij onze beide hypothesen niet konden bevestigen.

Onze bevindingen komen overeen met de bevindingen is hoofdstuk 3, waarbij wij beperkter gebruik hebben gemaakt van zeer gedetailleerde data analyses. Mogelijke verklaringen worden besproken, waarbij weer de hoge therapietrouw aan medicatie een belangrijke verklaring kan zijn voor de gevonden resultaten. Het is dus zeer belangrijk dat patiënten therapietrouw zijn aan hun medicatie om negatieve effecten van (excessief) alcoholgebruik te voorkomen.

De EMBLEM studie wordt in **hoofdstuk 5** besproken. Deze studie betrof een grote Europese studie (14 landen) waaraan meer dan 3500 patiënten met een acute manie deelnamen. Patiënten werden regulier door hun psychiaters voor hun acute manie behandeld en zij werden 52 weken lang gevolgd. Het doel van dit onderzoek was om onze bevindingen uit hoofdstuk 3 te verifiëren. Hiertoe werden de patiënten verdeeld in drie groepen: geen alcoholgebruik, gematigd

(sociaal) alcoholgebruik (d.w.z. geen problematisch gebruik) en problematisch/ excessief alcoholgebruik (alcoholverslaving).

Na correctie voor de sociodemografische verschillen tussen de patiënten van de drie groepen, bleek dat er na 12 en na 52 weken geen verschillen waren tussen de drie groepen in de ernst van de manisch, depressieve, psychotische en algehele bipolaire ziekte symptomen. Ook als we alle patiënten (uit de groep niet drinkende en gematigd drinkende patiënten) die vroeger alcoholverslaafd waren geweest uit de analyses verwijderden vonden wij geen significante verschillen in uitkomst tussen de drie groepen. Wanneer wij een nadere analyse deden met die patiënten uit de drie groepen die gedurende een jaar een stabiel alcoholgebruikspatroon behielden, vonden wij weer dat er na 12 weken geen verschil in de ernst van de symptomen was tussen deze subgroepen. Echter, na 52 weken waren er wel significante uitkomstverschillen tussen de groep problematische alcoholgebruikers en de geen alcohol gebruikende groep en de gematigd alcohol gebruikende groep. Dit significante verschil gold zowel voor de ernst van de manische en als de algehele bipolaire ziekte symptomen, maar niet voor de ernst van de depressieve en psychotische symptomen. Verklaringen voor deze uitkomsten worden besproken en komen grotendeels overeen met de verklaringen van het onderzoek van hoofdstuk 4. Een verklaring voor het verschil met de studie uit hoofdstuk 3 is waarschijnlijk de waarneming dat de therapietrouw aan de voorgeschreven medicatie in de EMBLEM groepen veel lager was dan de therapietrouw van de patiënten in de studie van hoofdstuk 3. Opnieuw conclude(e)r(d)en wij dat therapietrouw waarschijnlijk een belangrijke verzachtende factor is bij de negatieve effecten van alcoholgebruik op het beloop van de bipolaire stoornis.

In **Hoofdstuk 6** worden de resultaten van alle studies kort samengevat en mogelijke verklaringen voor de gevonden resultaten besproken. De MDQ blijkt geen goed screeningsinstrument te zijn om bij patiënten, die zich aanmelden in de verslavingszorg, bipolaire stoornissen op te sporen, wel om deze uit te sluiten. Er worden suggesties gedaan hoe een screeningsinstrument als de MDQ verbeterd zou kunnen worden.

De meest opmerkelijke bevinding van de ADS en de EMBLEM studies is dat het gebruik van gematigd, maar ook van excessief alcoholgebruik geen negatieve invloed heeft op het beloop van bipolaire stoornissen. Dit is volstrekt in tegenspraak met de resultaten van andere, vooral Amerikaanse studies, die juist wel verschillende negatieve effecten van alcohol op het beloop van bipolaire stoornissen vonden. Onze belangrijkste verklaring is dat goede therapietrouw aan medicatie een beschermende rol speelt tegen eventuele negatieve effecten van alcohol op het beloop van bipolaire stoornissen. Aanbevelingen voor toekomstig onderzoek worden gedaan.

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CURRICULUM VITAE

(Summary in Dutch)

Jan van Zaane werd op 16 augustus 1950 geboren te Holwierde (gemeente Bierum). In 1968 haalde hij zijn HBS-B diploma aan de Willem II HBS te Tilburg. In Amsterdam studeerde hij van 1968 tot 1977 geneeskunde aan de Universiteit van Amsterdam (UvA). Daarna specialiseerde hij zich in de huisartsengeneeskunde (1978, UvA) en psychiatrie (1990, PZ Vogelenzang / De Geestgronden, opleider Peter Bierenbroodspot). Sindsdien is hij als psychiater werkzaam bij GGZ InGeest (voorheen PZ Vogelenzang en de Geestgronden). Gaande weg heeft hij zich gespecialiseerd op het gebied van bipolaire stoornissen en is hij nu lid van de Academische Werkplaats Bipolaire stoornissen van GGZ InGeest / VUmc. Hij heeft jaren deel uitgemaakt van de het bestuur van de LithiumPlusWerkGroep en het kenniscentrum Bipolaire stoornissen (KenBiS).