Acta Psychiatrica Scandinavica

Acta Psychiatr Scand 2014: 130: 388–396

DOI: 10.1111/acps.12308

ACTA PSYCHIATRICA SCANDINAVICA

Risk factors of cycle acceleration in acutely admitted patients with bipolar disorder

Finseth PI, Morken G, Malt UF, Andreassen OA, Vaaler AE. Risk factors of cycle acceleration in acutely admitted patients with bipolar disorder.

Objective: To identify risk factors associated with cycle acceleration (CA), that is, progressive decrease in duration of syndrome-free intervals between affective episodes, in acutely admitted patients with bipolar disorder (BD).
Method: All patients (n = 210) with BD I (67%) and BD II (33%) (DSM-IV) acutely admitted to a hospital serving a catchment area were compared in retrospect with regard to a positive or negative history of CA. Putative risk factors of CA with a P-value <0.05 in uni-variate tests were secondly entered into a logistic regression model.
Results: The logistic regression model was statistically significant (P < 0.0001) and explained between 45.3% and 60.5% of the variance of CA status. 83.7% of the cases were correctly classified with a sensitivity of 87.2% and a specificity of 80.4%. Unique significant risk factors of CA were increasing severity of affective episodes (odds ratio (OR) = 28.8), BD II (OR = 3.3), hypomanic/manic episode induced by an antidepressant and/or alcohol (OR = 3.3), and female gender (OR = 3.1).
Conclusion: The clinical factors associated with CA may help targeting patients with BD with a course aggravation, and are in line with previously reported neuropathological processes of illness progression.

P. I. Finseth[1,2], G. Morken[1,3], U. F. Malt[4,5], O. A. Andreassen[6,7], A. E. Vaaler[1,2]

[1]Department of Neuroscience, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway, [2]Østmarka Psychiatric Department, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway, [3]Department of Research and Development, Psychiatry, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway, [4]Institute of Clinical Medicine, University of Oslo, Oslo, Norway, [5]Department of Psychosomatic Medicine, Oslo University Hospital - Rikshospitalet, Oslo, Norway, [6]NORMENT, Institute of Clinical Medicine, University of Oslo, Oslo, Norway, and [7]KG Jebsen Centre for Psychosis Research, Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway

Key words: bipolar disorder; in-patient; cycle acceleration; risk factors

Per Ivar Finseth, Østmarka Psychiatric Department, St Olavs Hospital, Pb 3008, Lade, 7441 Trondheim, Norway. E-mail: per.i.finseth@ntnu.no

Clinical trial registration: Trial registry name: ClinicalTrials.gov. Identification number: NCT00201526. URL: http://clinicaltrials.gov/ct2/show/NCT00201526?term=morken&rank=1.

Accepted for publication June 4, 2014

Significant Outcomes

- Significant risk factors of cycle acceleration were increasing severity of affective episodes, Bipolar disorder II, hypomanic/manic episode induced by an antidepressant and/or alcohol, and female gender.

Limitations

- The conclusions are limited due to the definition of cycle acceleration based on self-report and the naturalistic cross-sectional retrospective study design.
- The risk factors of cycle acceleration may not be representative for other clinical populations than acutely admitted Bipolar disorder patients.

Introduction

Bipolar disorder (BD) is characterized by recurrent episodes of depression and hypomania/mania (1). BD is one of the leading causes of disability worldwide (2), and the functional decline correlates with increasing rates of recurrence (3). Recurrence rates are required to evaluate the prognosis and treatment of individual patients with BD (4). Cycle acceleration (CA), defined as progressive decrease in duration of syndrome-free intervals during the course of illness, is an unequivocally negative outcome demonstrated in several studies (5–7). Among different measures of recurrence, CA and potential risk factors associated to it are essential targets for assessing and identifying course aggravation of BD (8).

Predictors or causes of CA are sparsely known, and several reviews have stated a general underrecognition of CA in BD (9, 10). It is unclear whether CA is a natural clinical course in a subset of patients with BD, an adverse event of treatment interventions, or a combination of these. CA is somewhat correlated to rapid cycling, which is defined by four or more affective episodes in a 12-month period (11), but an important difference is the lack of an acceleration or progression criterion in the definition of rapid cycling. In a recent report, Baldessarini et al. found no general trend of CA in a sample of patients with BD I (12). However, they estimated that approximately 40% of their patients had an accelerating progressive illness and noted that these were of special interest to be evaluated for biological, clinical, and treatment response differences. Another study suggested that CA is associated with current Axis - I comorbidity (13). A large Danish case register study identified CA in 25–35% of patients with BD during their initial hospitalizations in the course of their illness, where the estimates varied with different computational methods (7). In this study, female gender was a significant predictor of CA, while marital status and age at first admission were not. Yet another study detected CA in 52% of consecutive treatment resistant BD in-patients (6). However, the factors underlying CA development are still unknown, and CA has not been investigated in a catchment area based emergency ward sample.

There is a growing body of evidence implicating progressive neuropathological processes in the development of CA (14). These are in line with observations that originate back to Kraepelin who described a natural course of BD with progressively increasing frequency of episodes in some patients (5). His theory was later comprised in the kindling hypothesis of BD, involving a sensitization of affective episodes leading to shorter euthymic intervals as a function of episode numbers (15). A review of kindling and recurrence rates in BD supported that kindling-like phenomena occurred in a subgroup of patients with BD, and proposed that these may be characterized by a rapid cycling course, current or past use of antidepressants (AD), and early age at onset of illness (16). The role of AD in BD is highly debated (17), most notably the discussion on induction of mania. However, there is limited knowledge whether AD or other psychopharmacological agents may induce CA (8). Some reports have described AD-induced CA in BD (18–23), but to what extent this occurs, remains uncertain (24).

Aims of the study

The aim of the current study was to identify risk factors associated with cycle acceleration in a cohort of acutely admitted patients with bipolar disorder from one catchment area.

Material and methods

Setting

The Østmarka Psychiatric Department, St. Olavs Hospital, Trondheim University Hospital, Norway, has a catchment area of 212 000 inhabitants ≥18 years of age. Norwegian acute psychiatric services are public and available to everyone free of charge. All patients with acute psychiatric conditions in the catchment area are admitted to this department. Acute admission to other psychiatric hospitals occurs only when inhabitants temporarily reside outside of the catchment area. The department is a partaker in The Bipolar Research And Innovation Network – Norway (Nor-BRAIN) (25, 26).

Patients

Consecutive patients acutely admitted to the hospital from November 2002 through June 2009 suffering from current mania, mixed episode, or depression were diagnosed with the Structured Clinical Interview for DSM-IV (SCID-I) by two of the authors (GM and AEV) (27, 28). These two psychiatrists had undergone a structured SCID-I training programme before the inclusions started. The diagnoses were confirmed in a weekly consensus meeting with participation from at least two senior psychiatrists, of whom at least one personally had examined the patient. All patients with

BD I or II (DSM-IV) were asked to participate. The number of patients refusing inclusion was not registered, but in a retrospective approximation they counted <2% of all consecutively admitted patients with BD. Patients were asked to participate in the study when they were considered to be able to give an informed consent, and they were included only once. The only exclusion criterion was a non-proficiency in English or Norwegian.

Ethics

Written, informed consent was obtained from all the included patients. The study was approved by The Regional Committee for Research Ethics, Central Norway.

Assessments

The patients were interviewed with a Norwegian adaptation of the Network Entry Questionnaire (NEQ) developed by the Bipolar Collaboration Network (29, 30). The NEQ ratings were conducted by a specially trained research nurse or one of the psychiatrists (GM or AEV). The NEQ has 48 items covering a wide range of demographic and clinical factors describing the course of the illness. This included a retrospective assessment of all current and previous medication the patient has taken for treatment of BD. CA was assessed by asking the patients to disclose whether they had exhibited progressive decrease in duration of syndrome-free intervals in the course of their illness. From this, CA was solely based on the patients' own judgement and was registered dichotomously (yes/no). Alcohol and substance use disorders, history of psychosis, and social and occupational functioning between episodes the past year, were defined as recently described by Finseth et al. (31). Measures of education and disability pension were defined as described by Schoeyen et al. (26). Early age at onset of BD is a well known predictor of poor outcome (32), and was defined as debut of first affective episode ≤18 years based on self-report (33). Long-term pharmacological treatment was defined as continuous use of at least one medication against BD (AD, anticonvulsant, antipsychotic or lithium) for ≥12 months prior to the index episode.

Statistics

The patients were divided into two groups with regard to history of CA or not, termed CA and Non-CA. Risk factors and pharmacological treatment likely to affect recurrence of new affective episodes were analyzed between the two groups. The total number of patients with index mixed episode was low (7 in the CA group and 4 in the Non-CA group). In the statistical procedures, we chose to merge these with index episode mania, as in this setting (Emergency ward), patients with mixed episode were generally admitted due to symptoms of mania. Hypomania/mania induced by an AD and hypomania/mania induced by alcohol were analyzed both separately and combined. This combination was also utilized in a recent report from our research group, where the combined variable of AD-induced and/or alcohol-induced affective episodes revealed a significantly stronger association to suicide attempt versus the separate variables (31). The rationale for this combination was to assess patients at risk of experiencing hypomanic/manic episodes induced by biological substances (34).

Categorical variables were analysed with chi-square tests. Continuous variables with normal distribution were analysed with a *t*-test for independent samples. A Mann–Whitney test was used when assumptions of normal distribution were not adequately met. The alpha level was set to <0.05. We did not correct for multiple comparisons but included all variables with $P < 0.05$ in the logistic regression analysis.

All variables from the univariate analysis with $P < 0.05$, together with gender and duration of illness, were entered as independent variables into a stepwise logistic regression model with CA as the dependent variable. As recommended when conducting regression models, gender was also included (35), although it did not meet the criterion of $P < 0.05$. Due to clinical overlap and high intercorrelations between some independent variables, there were certain exceptions from the selection of variables: Rapid cycling was excluded due to the partial overlap with CA per definition, as we wanted to identify the unique predictors of CA. Time from first affective episode to any medication was excluded due to strong correlation with early age at onset, which has also been shown before (25, 36). Duration of illness was included instead of age at inclusion, as this was considered more adequate to control for due to the longitudinal quality of CA. Hospitalizations due to mania were per definition occurring only in BD I, and lifetime diagnosis of psychosis was strongly correlated to BD I (13% of BD II patients and 63% of BD I patients with lifetime diagnosis of psychosis respectively). We thus repeated the univariate analysis between CA and lifetime diagnosis of psychosis for the BD I patients only, with a non-significant result. From this, we concluded that the variables

lifetime diagnosis of psychosis and number of hospitalizations due to mania were better explained by the variance of BD subtype, and they were therefore omitted from the regression model. All covariates were entered in one block with the backward stepwise method as this was an explorative analysis.

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS Statistics) version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 210 patients entered the study. Of them were 112 women (53.3%). 143 patients (68.1%) were diagnosed with BD I and 67 (31.9%) with BD II. Mean age at inclusion for the total sample was 43 ± 14 (SD) years. 100 patients (47.6%) reported CA in the course of their disorder.

Descriptive analyses of sociodemographic features, psychiatric morbidity, psychopharmacological treatment and course of illness between the CA and Non-CA groups are shown in Table 1 and Table 2.

Clinical factors associated with CA

CA was more frequent in patients with BD II ($P < 0.0001$) as well as in patients with index episode depression ($P = 0.002$). In an analysis of CA and BD subtype in the subsample of patients with index episode depression, there was a non-significant trend of more CA among patients with BD II (per definition index episode depression), than in patients with BD I (CA in BD II 66.2% vs. BD I 33.8%, $\chi^2 = 3.78$, df = 1, $P = 0.052$). A higher number of hospitalizations due to mania ($P < 0.0001$) and a life-time diagnosis of psychosis ($P < 0.0001$) were both negatively associated with CA, while the number of hospitalizations due to depression did not differ between the groups.

The CA group was characterized by a higher proportion of individuals with early age at onset of BD ($P = 0.002$) and a longer delay from onset of BD to first medication against affective symptoms ($P < 0.0001$), but not with duration of illness. The CA group had significantly higher number of suicide attempts ($P = 0.022$). However, the latter association was no longer significant in a separate logistic regression model between CA and number of suicide attempts with duration of illness added as a covariate only.

Hypomanic/manic episode induced by AD and/or alcohol was significantly more frequent in the CA group ($P = 0.003$), while the isolated variables hypomanic/manic episode induced by AD, and hypomanic/manic episode induced by alcohol alone were not significantly associated with CA. Patients in the CA group had significantly more prior trials with AD's ($P < 0.0001$) and anxiolytics/hypnotics ($P = 0.027$). Long-term use, i.e. ≥12 months, of at least one current psychopharmacological agent was negatively associated with CA ($P = 0.032$). Except these findings, there were

Table 1. Characteristics of acutely admitted bipolar disorder patients with and without cycle acceleration

		Cycle acceleration		Non-Cycle Acceleration			
	Total N*	*n* = 100	47.6%	*n* = 110	52.4%	Statistic†	*P*-value
Socio-demographic features							
Gender, *n* (%)							
Female	210	60	60	52	47	3.41	0.065
Male		40	40	58	53		
Age, mean ± SD		41	±14	44	±14	−1.89	0.061
Education, some college plus, n (%)	210	29	29	41	37	1.61	0.20
Disability pension, *n* (%)	210	48	48	52	47	0.01	0.92
Own children, *n* (%)	210	62	62	70	64	0.06	0.81
Married or cohabitating, *n* (%)	204	30	31	42	39	1.54	0.21
Psychiatric morbidity							
Bipolar disorder I or II, n (%)							
BD I	210	56	56	87	79	12.9	<0.0001
BD II		44	44	23	21		
Index episode, *n* (%)							
Depression	210	65	65	48	44	9.62	0.002
Mania or mixed		35	35	62	56		
Alcohol and/or substance use disorder, lifetime, *n* (%)	210	28	28	29	26	0.07	0.79
Diagnosis of psychosis, lifetime, *n* (%)	210	34	34	65	59	13.2	<0.0001

*Statistical analyses were performed for the subsamples in this column due to missing data in some variables.

†Statistic: Contingency tables (χ^2) and Independent samples *t*-test (t).

SD, Standard deviation; BD, Bipolar disorder.

Table 2. Psychopharmacological treatment and course of illness in acutely admitted bipolar disorder patients with and without cycle acceleration

		Cycle acceleration		Non-Cycle acceleration			
	Total N*	*n* = 100	47.6%	*n* = 110	52.4%	Statistic†	*P*-value
Current psychopharmacological treatment							
Total number of current psychopharmacological agents, median (IQR)‡	207	3	2–3	3	2–3	−0.29	0.77
Current antidepressant, *n* (%)	210	29	29	30	27	0.08	0.78
Current antipsychotic, *n* (%)	210	54	54	69	63	1.64	0.20
Current anticonvulsant, *n* (%)	210	78	78	73	66	3.51	0.06
Current lithium, *n* (%)	210	12	12	17	16	0.53	0.47
Current anxiolytic/hypnotic, *n* (%)	210	46	46	45	41	0.55	0.46
At least one psychopharmacological agent ≥12 months, *n* (%)	210	22	22	39	36	4.60	0.032
Prior psychopharmacological treatment							
Total number of prior psychopharmacological agents, median (IQR)‡	210	2.5	1–5	3	1–4	−0.88	0.38
Number of prior antidepressants, median (IQR)‡	210	1	0–2	0	0–1	−3.94	<0.0001
Number of prior antipsychotics, mean (IQR)‡·§	210	0.77	0–1	1.16	0–2	−1.95	0.051
Number of prior anticonvulsants, median (IQR)‡	210	0	0–0	0	0–1	−1.06	0.29
Ever prior Lithium, *n* (%)	210	17	17	27	24.5	1.80	0.18
Number of prior anxiolytics/hypnotics, mean (IQR)‡·§	210	0.84	0–1	0.45	0–1	−2.21	0.027
Course of illness							
Number of hospitalizations due to depression, median (IQR)‡	190	1	1–2	1	0–2	−1.25	0.21
Number of hospitalizations due to mania, median (IQR)‡	190	0	0–1	1	0–3	−3.66	<.0001
Duration of illness (years), mean ± SD¶	205	24	±14	21	±15	1.37	0.17
Early age of onset (<19 years), any affective symptoms, *n* (%)	207	68	68	50	47	9.54	0.002
Years from first affective episode to any medication, median (IQR)‡	192	13	5–20	9	0–14	−3.72	<0.0001
Number of suicide attempts (0->4), median (IQR)‡	209	2	1–2	1	1–2	−2.28	0.022
Increasing severity of affective episodes, *n* (%)	203	87	90	26	25	87.2	<0.0001
Rapid cycling, *n* (%)	209	22	22	10	9.1	6.93	0.008
Social and occupational functioning between episodes the past year, median (IQR)‡	209	3.2	2–4	2.8	2–4	−2.52	0.012
Hypomanic/manic episode induced by AD and/or alcohol, *n* (%)	207	34	35	18	17	9.07	0.003
Hypomanic/manic episode induced by AD, *n* (%)	204	15	16	8	7	3.43	0.064
Hypomanic/manic episode induced by alcohol, *n* (%)	206	22	22	13	12	3.70	0.054

*Statistical analyses were performed for the subsamples in this column due to missing data in some variables.

†Statistic: Contingency tables (χ^2), Mann–Whitney (z for two groups) and Independent samples *t*-test (t).

‡Mann–Whitney test.

§The mean is shown due to equal median values.

¶Independent samples *t*-test.

IQR, Inter quartile range; SD, Standard deviation; AD, Antidepressant.

no other differences in current or prior medication, and total numbers of prior and current psychopharmacological agents were indifferent between the CA and Non-CA groups.

The CA group reported more increasing severity of affective episodes ($P < 0.0001$) and more rapid cycling than the Non-CA group ($P = 0.008$). During the past 12 months before inclusion to the study, the CA group reported a worse level of social and occupational functioning between affective episodes ($P = 0.012$).

Multi-variate analysis revealed independent effect of several CA risk factors

The statistically significant variables from the logistic regression model are presented in Table 3. The final step of the backward stepwise logistic regression model was statistically significant with χ^2 (df = 6, $n = 196$) = 118.3, $P < 0.0001$. It explained between 45.3% (Cox and Snell R square) and 60.5% (Nagelkerke R square) of the variance of CA status. There was a reasonable sensitivity and specificity, as 83.7% of the cases were correctly classified with a sensitivity of 87.2% and a specificity of 80.4%. None of the variables had a variance inflation factor above 2, which was small and supported a low risk of multicollinearity in the model. The predictors that made a unique significant contribution were (in order of decreasing odds ratio): increasing severity of affective episodes, BD II, hypomanic/manic episode induced by an AD and/or alcohol, and female gender.

Discussion

The present study identifies risk factors related to CA in a cohort of acutely admitted patients with BD, including severity of affective episodes, BD II, hypomanic/manic episode induced by an AD and/or alcohol, and female gender. These results are in line with previous findings of patients with BD

Table 3. Significant risk factors from the final step of the logistic regression model based on risk factors with *P*-value <0.05 in the univariate analysis

	B	Wald	*P*-value	Exp(B)	95% CI for Exp (B) Lower	Upper
Increasing severity of affective episodes	3.36	51.41	<0.0001	28.81	11.50	72.20
BD type II (vs I)	1.20	6.04	0.01	3.31	1.27	8.61
Hypomanic/manic episode induced by AD and/or alcohol	1.19	5.62	0.02	3.29	1.23	8.79
Female gender	1.13	5.95	0.01	3.08	1.25	7.63
Constant	−4.60	33.36	<0.0001	0.010		

CI, confidence interval; BD, bipolar disorder; AD, antidepressant.

with rapid cycling (37), but have to our knowledge only sparsely been studied in relation to the quality of acceleration of subsequent episodes included in the definition of CA. Thus, the current risk factors may be useful in assessing a progressive course of BD as well in providing clinical entities for future studies of progressive pathways of recurrence in BD.

Sociodemographic features were indifferent between the CA and Non-CA groups, except female gender being a risk factor of CA in the logistic regression model. Female gender was, however, not significantly associated with CA in the univariate analysis, which may have been due to suppressor effects of unknown confounders in the univariate analysis, or by more precise estimation of gender as a predictor in the logistic regression model due to the presence of another strong predictor in the model (38). The association between CA and female gender is concordant with findings in the Danish case register study (7). The causative relation between CA and female gender has never been investigated, but it is known that also rapid cycling is more common in women than in men (39). Reproductive hormones, higher rates of hypothyroidism, and possible differences in response or exposure to mood stabilizers and antidepressants have been hypothesized to account for the increased risk of rapid cycling in women (40). Further studies are needed to identify the underlying cause of the association between female gender and CA.

CA was correlated with patient-reported increasing severity of the disorder in the logistic regression model, which has also been demonstrated before (6). This indicates that assessment of CA gives important information of the longitudinal development of BD. It may seem contradictory that CA was associated with increasing severity of the disorder, while not with disability pension. One possible explanation to this is the relatively long duration of illness in both groups in this study, which is known to be associated with unemployment (41). It should be noted that the CA group still reported a worse social and occupational functioning between affective episodes the year prior to study inclusion, however only in the univariate analysis.

CA was associated with a diagnosis of BD II. This was further explained in the univariate analysis where CA was associated with index episode depression and negatively associated with number of hospitalizations due to mania. Together, this indicates that CA is a clinical phenomenon more likely to occur in BD patients with a depressive dominance, and might be the reason why CA could not be identified in a follow-up of patients with BD I in a recent report (12). Another possible explanation could be different strategies of pharmacological treatment of BD I vs. BD II.

Our findings of alcohol and/or AD association with CA are in line with the hypothesis that AD and alcohol are involved in stimulating initial affective episodes in a subgroup of patients who later develop a sensitized pattern of spontaneous episodes with a decrease in duration of syndrome-free intervals (15, 42). This view has been supported by clinical findings that AD exposure predicts long-term mood instability in patients with BD and loss of AD efficacy after repeated exposures (43–46). The findings could also be in line with the kindling hypothesis (16). This supports the view that BD is a progressive illness, at least in a subgroup of severely affected patients, such as included in the current study. However, these clinical observations are in contrast to experimental animal evidence suggesting neuroprotective properties of AD (47). AD induction of hypomania/mania alone was not significantly associated with CA, which may be a result of the relatively low frequency of hypomania/mania induced by AD and the small sample size and thus statistical power in the current study. Future studies to determine the direction of the association between CA and AD treatment are warranted, advocating for longitudinal studies of the role of AD treatment and alcohol use in development of CA in BD.

Although not significantly associated with CA in the logistic regression model, it should be commented on some of the associations between CA and psychopharmacological treatment. The negative association between CA and use of at least one current psychopharmacological agent for at least 12 months could be the result of protective effects of long-term pharmacological treatment for some patients, but may as well be a selected group of

patients where the disorder requires fewer needs to initiate change in medication. The association between CA and that of currently using an anticonvulsant might be a result of the clinicians being aware of CA in these patients, and unlikely to be caused by anticonvulsants *per se*. The CA group had significantly more trials with AD, and anxiolytics and hypnotics. These findings might be linked to the depressive dominance in patients with CA, but this study does not allow us to conclude on the direction of these associations.

The CA frequency of 47.6% in our acute ward sample is in line with the NIMH-study with severely ill patients resistant for conventional treatment (6), but higher than the Danish care register study which conservatively assessed intervals between hospitalizations only (7). However, our study design does not allow us to make claims about the absolute frequency of CA as the assessments were based on self-report, which is subject to recall bias and possibly inflated reporting due to the influence of the current affective episode.

This study has some strengths and limitations. All acutely admitted patients from one catchment area were evaluated for inclusion. The sample is representative, but may not be generalizable to other clinical settings. A limitation in this study is the definition of CA, which was based solely on the patient's own judgement and not on the more preferably objective recordings of cycle evolution over time with a standardized life-chart method. It is also possible that the self-report data were influenced by a recall bias related to the current affective episode at inclusion. Consequently this may have altered the patient's self-report of CA by confusing CA with other reasons to increase of illness severity, possibly inflating the CA frequency among patients included with a current depressive episode. It is however unlikely that a recall bias of CA should systematically skew the specific findings of risk factors associated with CA. In this case, the effect of recall bias would more likely result in type II error. We are limited by the naturalistic, retrospective design to conclude on the direction of the associations, and there may be unknown confounding factors not accounted for in the present analysis. Specifically, we cannot make inferences about the direction of effect between CA and hypomanic/manic episode induced by AD and/or alcohol. If hypomanic/manic episode induced by AD and/or alcohol preceded CA, it may be the result of a biological vulnerability of switching between mood states in some patients. This finding may add to further understanding of neuroprogressive pathways of recurrence in BD (14). However, it is also possible that patients with CA due to a more depressive dominance of their disorder were treated more frequently with AD, resulting in a higher accumulated chance of AD-induced hypomania/mania. The possibility that CA is an intrinsic naturally occurring course in some patients as noted in the prepharmacological era (5), meaning it would occur independently of pharmacological treatment, is impossible to correct for due to ethical considerations.

In conclusion, in this naturalistic, retrospective study, we found that severity of affective episodes, BD II, hypomanic/manic episode induced by an AD and/or alcohol, and female gender are associated with CA. These putative risk factors of CA may help targeting patients with BD with a course aggravation, and they are in line with previously proposed neuropathological processes of illness progression. The directions of cause for these risk factors need to be identified in longitudinal studies, preferably differentiating subgroups of BD and grade of severity for the broader understanding of CA.

Acknowledgements

The authors would like to thank Gunn E. Folden, MSc, Østmarka Psychiatric Department, St. Olavs Hospital, Trondheim University Hospital, Norway. G. E. Folden helped in data collection and was funded by her institution. The authors also thank patients for their participation in the study, and the health professionals who facilitated their work.

Declaration of interest

Per Ivar Finseth received a research grant from the Liaison Committee between the Central Norway Regional Health Authority (RHA) and the Norwegian University of Science and Technology (NTNU) and a travel grant from BMS. Arne E. Vaaler reports no conflict of interests. Gunnar Morken reports no conflict of interests. Ole A. Andreassen has received speaker's honorarium from GSK, Lundbeck and Otsuka. Ulrik F. Malt has received speaker's honorarium for lecturing about antidepressant drugs and related topics from psychiatric organizations in Norway and Sweden; from School of Pharmacy, University of Oslo and manufacturers of most antidepressants drugs marketed in Norway. All authors other than Per Ivar Finseth were funded by their respective institutions. The funding sources had no influence on study design, collection, analysis, interpretation of data, writing the report, nor on the decision to submit the report for publication.

References

1. Angst J, Gamma A, Sellaro R, Lavori PW, Zhang H. Recurrence of bipolar disorders and major depression. A life-long perspective. Eur Arch Psychiatry Clin Neurosci 2003;**253**:236–240.
2. Whiteford HA, Degenhardt L, Rehm J et al. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet 2013;**382**:1575–1586.

3. Goldberg JF, Garno JL, Harrow M. Long-term remission and recovery in bipolar disorder: a review. Curr Psychiatry Rep 2005;**7**:456–461.
4. Haghighat R. Lifelong development of risk of recurrence in depressive disorders. J Affect Disord 1996;**41**:141–147.
5. Kraepelin E. Manic-depressive insanity and paranoia, 8th edn. Edinburgh: ES Livingstone, 1921.
6. Roy-Byrne P, Post RM, Uhde TW, Porcu T, Davis D. The longitudinal course of recurrent affective illness: life chart data from research patients at the NIMH. Acta Psychiatr Scand Suppl 1985;**317**:1–34.
7. Kessing LV, Mortensen PB, Bolwig TG. Clinical definitions of sensitisation in affective disorder: a case register study of prevalence and prediction. J Affect Disord 1998;**47**:31–39.
8. Berk M, Ng F, Dodd S, Goldberg JF, Malhi GS. Do we need to flick the switch? The need for a broader conceptualization of iatrogenic course aggravation in clinical trials of bipolar disorder. Psychiatry Clin Neurosci 2010;**64**:367–371.
9. Harel EV, Levkovitz Y. Effectiveness and safety of adjunctive antidepressants in the treatment of bipolar depression: a review. Isr J Psychiatry Relat Sci 2008;**45**:121–128.
10. Licht RW, Gijsman H, Nolen WA, Angst J. Are antidepressants safe in the treatment of bipolar depression? A critical evaluation of their potential risk to induce switch into mania or cycle acceleration. Acta Psychiatr Scand 2008;**118**:337–346.
11. Dunner DL, Patrick V, Fieve RR. Rapid cycling manic depressive patients. Compr Psychiatry 1977;**18**:561–566.
12. Baldessarini RJ, Salvatore P, Khalsa HM, Imaz-Etxeberria H, Gonzalez-Pinto A, Tohen M. Episode cycles with increasing recurrences in first-episode bipolar-I disorder patients. J Affect Disord 2012;**136**:149–154.
13. McElroy SL, Altshuler LL, Suppes T et al. Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. Am J Psychiatry 2001;**158**:420–426.
14. Berk M, Kapczinski F, Andreazza AC et al. Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. Neurosci Biobehav Rev 2011;**35**:804–817.
15. Post RM. The status of the sensitization/kindling hypothesis of bipolar disorder. Curr Psychos Ther Rep 2004;**2**:135–141.
16. Ghaemi SN, Boiman EE, Goodwin FK. Kindling and second messengers: an approach to the neurobiology of recurrence in bipolar disorder. Biol Psychiatry 1999;**45**:137–144.
17. Tondo L, Baldessarini RJ, Vazquez G, Lepri B, Visioli C. Clinical responses to antidepressants among 1036 acutely depressed patients with bipolar or unipolar major affective disorders. Acta Psychiatr Scand 2013;**127**:355–364.
18. Fava GA, Offidani E. The mechanisms of tolerance in antidepressant action. Prog Neuropsychopharmacol Biol Psychiatry 2011;**35**:1593–1602.
19. Yerevanian BI, Koek RJ, Mintz J, Akiskal HS. Bipolar pharmacotherapy and suicidal behavior Part 2. The impact of antidepressants. J Affect Disord 2007;**103**:13–21.
20. Wehr TA, Goodwin FK. Do antidepressants cause mania? Psychopharmacol Bull 1987;**23**:61–65.
21. Altshuler LL, Post RM, Leverich GS, Mikalauskas K, Rosoff A, Ackerman L. Antidepressant-induced mania and cycle acceleration: a controversy revisited. Am J Psychiatry 1995;**152**:1130–1138.
22. Ghaemi SN, Rosenquist KJ, Ko JY, Baldassano CF, Kontos NJ, Baldessarini RJ. Antidepressant treatment in bipolar versus unipolar depression. Am J Psychiatry 2004;**161**:163–165.
23. Joffe RT, Macqueen GM, Marriott M, Robb J, Begin H, Young LT. Induction of mania and cycle acceleration in bipolar disorder: effect of different classes of antidepressant. Acta Psychiatr Scand 2002;**105**:427–430.
24. Goodwin FK, Jamison KR. Manic-depressive illness: bipolar disorders and recurrent depression, 2nd edn. New York: Oxford University Press, 2007.
25. Morken G, Vaaler AE, Folden GE, Andreassen OA, Malt UF. Age at onset of first episode and time to treatment in in-patients with bipolar disorder. Br J Psychiatry 2009;**194**:559–560.
26. Schoeyen HK, Birkenaes AB, Vaaler AE et al. Bipolar disorder patients have similar levels of education but lower socio-economic status than the general population. J Affect Disord 2011;**129**:68–74.
27. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th edn. Washington, DC: American Psychiatric Association, 1994.
28. First MB, Spitzer RL, Gibbon M, Williams JBW. Structured clinical interview for DSM-IV - patient version. New York, NY: American Psychiatric Press, 1997.
29. Post RM, Nolen WA, Kupka RW et al. The Stanley Foundation Bipolar Network. I. Rationale and methods. Br J Psychiatry Suppl 2001;**41**:s169–s176.
30. Suppes T, Leverich GS, Keck PE et al. The Stanley Foundation Bipolar Treatment Outcome Network. II. Demographics and illness characteristics of the first 261 patients. J Affect Disord 2001;**67**:45–59.
31. Finseth PI, Morken G, Andreassen OA, Malt UF, Vaaler AE. Risk factors related to lifetime suicide attempts in acutely admitted bipolar disorder inpatients. Bipolar Disord 2012;**14**:727–734.
32. Drancourt N, Etain B, Lajnef M et al. Duration of untreated bipolar disorder: missed opportunities on the long road to optimal treatment. Acta Psychiatr Scand 2013;**127**:136–144.
33. Post RM, Luckenbaugh DA, Leverich GS et al. Incidence of childhood-onset bipolar illness in the USA and Europe. Br J Psychiatry 2008;**192**:150–151.
34. Goldberg JF, Whiteside JE. The association between substance abuse and antidepressant-induced mania in bipolar disorder: a preliminary study. J Clin Psychiatry 2002;**63**:791–795.
35. Ghaemi SN. A clinician's guide to statistics and epidemiology in mental health: Measuring truth and uncertainty. New York, NY: Cambridge University Press, 2009.
36. Leverich GS, Post RM, Keck PE Jr et al. The poor prognosis of childhood-onset bipolar disorder. J Pediatr 2007;**150**:485–490.
37. Bauer M, Beaulieu S, Dunner DL, Lafer B, Kupka R. Rapid cycling bipolar disorder–diagnostic concepts. Bipolar Disord 2008;**10**:153–162.
38. Hosmer DW Jr, Lemeshow S, Sturdivant RX. Applied logistic regression. Hoboken, NJ: John Wiley & Sons, 2013.
39. Suppes T, Dennehy EB, Gibbons EW. The longitudinal course of bipolar disorder. J Clin Psychiatry 2000;**61**:23–30.
40. Leibenluft E. Women and bipolar disorder: an update. Bull Menninger Clin 2000;**64**:5–17.
41. Marwaha S, Durrani A, Singh S. Employment outcomes in people with bipolar disorder: a systematic review. Acta Psychiatr Scand 2013;**128**:179–193.

42. Kilzieh N, Akiskal HS. Rapid-cycling bipolar disorder. An overview of research and clinical experience. Psychiatr Clin North Am 1999;**22**:585–607.
43. Strejilevich SA, Martino DJ, Marengo E et al. Long-term worsening of bipolar disorder related with frequency of antidepressant exposure. Ann Clin Psychiatry 2011;**23**: 186–192.
44. Amsterdam JD, Shults J. Does tachyphylaxis occur after repeated antidepressant exposure in patients with Bipolar II major depressive episode? J Affect Disord 2009;**115**: 234–240.
45. Ghaemi SN, Ostacher MM, El-Mallakh RS et al. Antidepressant discontinuation in bipolar depression: a Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) randomized clinical trial of long-term effectiveness and safety. J Clin Psychiatry 2010;**71**: 372–380.
46. Post RM, Leverich GS, Altshuler LL et al. Relationship of prior antidepressant exposure to long-term prospective outcome in bipolar I disorder outpatients. J Clin Psychiatry 2012;**73**:924–930.
47. Dodd S, Maes M, Anderson G, Dean OM, Moylan S, Berk M. Putative neuroprotective agents in neuropsychiatric disorders. Prog Neuropsychopharmacol Biol Psychiatry 2013;**42**:135–145.