*MARKKU LÄHTEENVUO, DIEGO ANTOLÍN-CONCHA, PIA VATTULAINEN,*
*ANTTI TANSKANEN, HEIDI TAIPALE, JARI TIIHONEN*

# PSYCHOPHARMACOLOGICAL TREATMENT, MORTALITY AND SUICIDE IN BIPOLAR DISORDER IN A FINNISH NATIONWIDE COHORT OF 18,018 PATIENTS

*ABSTRACT*

*Bipolar disease has been associated with high overall mortality and a marked decrease in life expectancy. Suicide is one of the most common causes of death in bipolar disorder. In recent years, use of antidepressants and anticonvulsants has increased at the expense of lithium in the treatment of this disorder. Not much "real-world" data from large inclusive cohorts is available to determine whether this switch in treatment preference could affect risk of suicide in bipolar patients. We aimed to study the risks associated with the use of pharmacological treatment on suicide and overall mortality in a nationwide cohort of Finnish patients with bipolar disorder (n=18018).*

*We studied the risk of overall and suicide mortality between 1996–2012 among all patients who had been hospitalized due to bipolar disorder in Finland (n=18018; mean follow-up time 7.2 years) using prospectively gathered nationwide databases for hospitalization and dispensed medication. The primary analysis was a Cox proportional hazards model. Analyses were adjusted for the effects of time since diagnosis, order of treatments, current use of other treatments, polypharmacy within medication group, number of hospitalizations within 2 years (indicator of inherent risk of relapse), age at index date, gender and calendar year of index date. Results are reported as hazard ratios (HRs) with 95% confidence intervals (95% CI).*

*In comparison between use and no use of medication groups reaching nominal statistical significance, use of mood stabilizers was associated with a 51% reduction in overall mortality (HR 0.49, 95% CI 0.44-0.54, p<0.001) and antidepressants with a 26% reduction in overall mortality (HR 0.74, 95% CI 0.67-0.81, p<0.0001). Use of mood stabilizers was associated with a 53% reduction in suicide mortality (HR 0.47, 95% CI 0.38-0.58, p<0.0001), whereas use of sedatives was associated with a significantly increased risk for suicide (HR 1.52, 95% CI 1.22-1.90, p=0.0002).*

*In conclusion, mood stabilizers should be considered as treatment of choice for patients with bipolar disorder who are at high risk for suicide. Use of sedatives should be avoided to the fullest extent possible.*

KEY WORDS: PSYCHOPHARMACOLOGICAL TREATMENT; BIPOLAR DISORDER; MORTALITY; SUICIDE

## INTRODUCTION

Bipolar disorder is a serious, chronic psychiatric disorder, which often leads to serious impairment and long-term symptoms, although individual disease course may vary (1). It is characterized by changes in mood and activity levels, either as elevated mood and increased energy and activity (hypomania or mania) or decreased energy and activity levels, often associated with depressive symptoms (The International Classification of Diseases, version 10, The World Health Organization). Both elevated and depressed states in bipolar disorder have been associated with an increased risk for suicidal behaviour, and indeed bipolar disorder has been regarded to carry the highest risk of suicide among major psychological disorders (2-4). Overall mortality is also increased in bipolar disorder compared with the general population, and it is thought to lead to a 9 to 20-year reduction in average lifespan (5-8). Bipolar disorder also accounts for the loss of more disability-adjusted life years than all cancers combined and is one of the most common causes of disability in the world (9). Thus, effective treatment for the disorder could lead to a greater reduction in patient suffering as well as cost to society. Long-term medication is often required to attain remission and to prevent relapse, although even with modern treatments remission rates remain low (10). Treatment regimes for bipolar disorder are varied, but medication most often used include mood stabilizers, antidepressants, antipsychotics, benzodiazepines and sedatives. However, not much data on the effects of these different medication groups in preventing suicide in bipolar patients exist, although at least one register-based study has recently studied this question in Finland with a sample of 826 bipolar patients (11). As prescription trends for bipolar disorder have shifted in recent years from the use of lithium salts towards other mood stabilizers, antipsychotics and even antidepressants, and an overall increase in the prescription of psychotropics has been noted, more research is needed to determine how this change could reflect on suicide rates, as lithium has been noted to be one of the best medications in preventing suicidal behaviour (12-15).

## METHODS

### *STUDY DESIGN AND DATA ACQUISITION*

Finnish databases nationwide were used to combine prospectively collected registry data in order to conduct a population-based cohort study of patients hospitalized due to bipolar disorder. The registers were used to identify the study cohort (patients hospitalized due to bipolar disorder between the years 1987 and 2012), to determine the incidence, duration and reasons for rehospitalizations, to obtain information on reimbursed medication dispensed from pharmacies (all psychotropic medications except small packages of benzodiazepines were reimbursed in this indication) and to retrieve information on causes of death. The databases and their usage have been described in more detail in our previous pharmacoepidemiological studies (16-20). In Finland, every individual has a unique identification code which makes it possible to track them even if they change their name or location of residence. All hospital treatments, deaths and prescriptions are documented in national databases. The current study included every subject (n=18018) hospitalized at least once with a bipolar disorder diagnosis (ICD-10 diagnoses F30-31, Finnish ICD-9 diagnoses 2962-2964 and 2967A) between January 1st, 1987 and December 31st, 2012, who had not been diagnosed with broadly defined schizophrenia during this time period (ICD-10: F20–29, ICD-9: 295, 2971A, 2973A, 2988A, 2989X, 3012C) and who were still alive at the start of the observation period. A total of 25860 subjects were initially identified, but 7758 were excluded due to having schizophrenia as described above, 77 excluded due to death before start of observation period and 7 excluded due to not having any follow-up time (cohort entry at the end of the observation period). Cohort entry date was set as January 1st, 1996 for subjects hospitalized due to bipolar disorder between January 1st, 1987 and December 31st, 1995, and as the first hospital discharge date for subjects hospitalized for the first time on January 1st, 1996. The cohort is described in detail in *Table 1*.

### *EXPOSURE*

The PRE2DUP method was used to define exposure and non-exposure periods for medications (17). PRE2DUP calculates current dose with a sliding average, uses package information such as number of tablets and administration intervals for injections, and takes into account stockpiling when constructing time periods of continuous use. Our previous publications on the validity of the method indicate that PRE2DUP is the most precise method currently available to estimate drug use, and it gives highly accurate drug use periods for most drug classes, especially those meant for long-term use (16-18). As variation in dose is allowed within the method, no artificial grace periods are used. Thus, the risk is attributed to the ongoing treatment(s), according to the

PRE2DUP method, for each day. Periods of cross-titration and actual polypharmacy (with two or more medications used concomitantly), not recorded in the register-based data, include somewhat more uncertainty. Antipsychotics were defined as ATC code N05A, except for N05AN01 (lithium), antidepressants as N06A, mood stabilizers as N03AF, N03AG, N03AX and N05AN01 (lithium), benzodiazepines as N05BA, and finally sedatives as N05C.

### *STATISTICAL ANALYSIS*

Two analyses were performed on the cohorts: risk association of use of medication with either mortality due to any cause or suicide, using a between-group (users and non-users) Cox proportional hazards analysis. The analyses were corrected for the effect of time since diagnosis, order of treatments, current use of other treatments and polypharmacy, number of hospitalizations within 2 years (any-cause hospitalization for overall mortality and suicidal hospitalization for suicide mortality, indicator of inherent risk of relapse), age at index date, gender and calendar year of index date. The analysis is further described in *Table 2*. A p-value of <0.01 was deemed statistically significant (due to Bonferroni correction for multiple comparisons).

### *ETHICAL CONSIDERATIONS*

The research project was approved by the Ethics Committee of the Finnish National Institute for Health and Welfare (dated December 4, 2013, 8/2013). Further permissions were granted by pertinent institutional authorities at the Finnish National Institute for Health and Welfare (permission THL/1466/6.02.00/2013), The Social Insurance Institution of Finland (34/522/2013) and Statistics Finland (TK53-305-13).

## RESULTS

The sociodemographic, clinical and treatment characteristics of the total and the incident cohorts are shown in *Table 1*. The study cohort consisted of 18018 individuals with a total observation time of 129740 person years, with a mean observation (follow-up) time of 7.2 years (range 1 day to 17.0 years). During this time period we observed a total of 2910 deaths due to any cause (~22.43 events/1000 person years), of which 477 were due to suicide (~3.68/1000 person years).

When comparing use versus non-use of certain medication groups (the risk of using a medication from a certain group or not using a medication from that group) in this patient group of bipolar patients hospitalized at least once due to bipolar disorder, differences in hazard ratios (HR) for death started to emerge.

Results for overall mortality are shown in *Table 3*. Use of benzodiazepines or sedatives was not associated with significant changes in overall mortality versus not using these medications (HR 0.98, 95% CI 0.89-1.08, p=0.69 for benzodiazepines and HR 1.09, 95% CI 0.99-1.21, p=0.07 for sedatives). Use of mood stabilizers was associated with a 51% reduction in overall mortality (HR 0.49, 95% CI 0.44-0.54, p<0.001), antidepressants with a 26% reduction in overall mortality (HR 0.74, 95% CI 0.67-0.81, p<0.0001) and antipsychotics with a 11% reduction in overall mortality (HR 0.89, 95% CI 0.81-0.98, p<0.02), although the results for antipsychotics are not statistically significant when corrected for multiple comparisons (significance level p<0.01).

Results for suicide mortality are shown in *Table 4*. Use of benzodiazepines or antipsychotics was not associated with significant change in risk for suicide (HR 1.21, 95% CI 0.97-1.51, p=0.10 for benzodiazepines and HR 1.15, 95% CI 0.91-1.43, p=0.24 for antipsychotics). Use of mood stabilizers was associated with a 53% reduction in suicide mortality (HR 0.47, 95% CI 0.38-0.58, p<0.0001). Use of sedatives and antidepressants was associated with a significantly increased risk for suicide (HR 1.52, 95% CI 1.22-1.90, p=0.0002 for sedatives and HR 1.28, 95% CI 1.02-1.61, p=0.03 for antidepressants), although the results for antidepressants are not statistically significant when corrected for multiple comparisons (significance level p<0.01).

| Covariates | Patient counts (%) |
|---|---|
| **Gender** | |
| female | 9558 (53.05%) |
| male | 8460 (46.95%) |
| **Age at cohort entry date** | |
| <30 | 3345 (18.56%) |
| 30-49 | 7121 (39.52%) |
| 50-69 | 5577 (30.95%) |
| 70 | 1975 (10.96%) |
| **Calendar year of cohort entry date** | |
| 1996-1999 | 5107 (28.34%) |
| 2000-2003 | 3102 (17.22%) |
| 2004-2007 | 4280 (23.75%) |
| 2008-2012 | 5529 (30.69%) |
| **Patients remaining in cohort after censoring hospitalization longer than 30.5 days** | |
| no | 105 (0.58%) |
| yes | 17913 (99.42%) |
| **Patients remaining in cohort after censoring hospitalization longer than 0 days** | |
| no | 141 (0.78%) |
| yes | 17877 (99.22%) |
| **Time since diagnosis at CED (years)** | |
| 0-5 | 16531 (91.75%) |
| 5-10 | 1472 (8.17%) |
| >10 | 15 (0.08%) |
| **Time since diagnosis at end of follow-up (years)** | |
| 0-5 | 7120 (39.52%) |
| 5-10 | 5357 (29.73%) |
| >10 | 5541 (30.75%) |
| **Two years history of any-cause hospitalization at cohort entry date** | |
| 0 | 1364 (7.57%) |
| 1-2 | 12129 (67.32%) |
| >2 | 4525 (25.11%) |

Table 1 (1/2): Characteristics of the study cohort.

| Covariates | Patient counts (%) |
|---|---|
| **Two years history of any-cause hospitalization at end of follow-up** | |
| 0 | 7321 (40.63%) |
| 1-2 | 6756 (37.50%) |
| >2 | 3941 (21.87%) |
| **Two years history of any psychiatric hospitalization before cohort entry date** | |
| 0 | 1777 (9.86%) |
| 1-2 | 14097 (78.24%) |
| >2 | 2144 (11.90%) |
| **Two years history of any psychiatric hospitalization at end of follow-up** | |
| 0 | 10997 (61.03%) |
| 1-2 | 5312 (29.48%) |
| >2 | 1709 (9.48%) |
| **Use of benzodiazepines during follow-up** | |
| no | 8580 (47.62%) |
| yes | 9438 (52.38%) |
| **Use of sedatives during follow-up** | |
| no | 8069 (44.78%) |
| yes | 9949 (55.22%) |
| **Use of mood stabilizers during follow-up** | |
| no | 4749 (26.36%) |
| yes | 13269 (73.64%) |
| **Use of antidepressants during follow-up** | |
| no | 4832 (26.82%) |
| yes | 13186 (73.18%) |
| **Use of antipsychotics during follow-up** | |
| no | 3413 (18.94%) |
| yes | 14605 (81.06%) |
| **Total** | **18018 (100.00%)** |

Table 1 (2/2): Characteristics of the study cohort.

| | | |
|---|---|---|
| **Treatment studied** | | **Drug classes:**<br>**Benzodiazepines, Sedatives, Antidepressants, Antipsychotics, Mood stabilizers** |
| **Adjusting covariates** | **Time since diagnosis** | Time since diagnosis (0-5 ,5-10,>10 years) |
| | **Order of treatment** | Order of drug classes (0-1,2,>2; cumulative number of different drug classes) |
| | **Current use of other treatments** | Current use of other drug classes (yes/no; for each drug class separately) |
| | **Polypharmacy** | Polypharmacy (yes/no; concurrent use of more than one drug class) |
| | **Number of hospitalizations within 2 years** | Number of hospitalizations due to any cause/suicide within a 2-year period (0,1-2,>2) |
| | **Age at index date** | Age at index date (<30,30-49,50-69,>70 years) |
| | **Gender** | Gender (Female/male) |
| | **Calendar year of index date** | Calendar year of index date (1996-1999,2000-2003,2004-2007,2008-2012) |

Table 2: Statistical analysis and adjusting variables.

| Covariates | HR estimate | 95% confidence interval | p-value |
|---|---|---|---|
| **Medication classes:** | | | |
| benzodiazepines | 0.98 | (0.89 - 1.08) | 0.68818 |
| sedatives | 1.09 | (0.99 - 1.21) | 0.07144 |
| mood stabilizers | **0.49** | (0.44 - 0.54) | <0.0001 |
| antidepressants | **0.74** | (0.67 - 0.81) | <0.0001 |
| antipsychotics | 0.89 | (0.81 - 0.98) | 0.01979 |
| **Gender:** | | | |
| Female | reference | reference | reference |
| Male | 1.84 | (1.71 - 1.99) | <0.0001 |
| **Age at cohort entry (years):** | | | |
| <30 | reference | reference | reference |
| 30-49 | 1.85 | (1.54 - 2.22) | <0.0001 |
| 50-69 | 3.44 | (2.87 - 4.11) | <0.0001 |
| >70 | 9.00 | (7.48 - 10.82) | <0.0001 |
| **Calendar year of cohort entry:** | | | |
| 1996-1999 | reference | reference | reference |
| 2000-2003 | 0.97 | (0.87 - 1.08) | 0.59337 |
| 2004-2007 | 0.80 | (0.71 - 0.90) | 0.00023 |
| 2008-2012 | 0.84 | (0.73 - 0.98) | 0.02439 |
| **Time since diagnosis (years):** | | | |
| 0-5 | reference | reference | reference |
| 5-10 | 1.27 | (1.09 - 1.47) | 0.00155 |
| >10 | 1.26 | (1.04 - 1.53) | 0.01876 |
| **Number of medication classes used previously:** | | | |
| 0-1 | reference | reference | reference |
| 2 | 0.90 | (0.79 - 1.04) | 0.14458 |
| >2 | 1.28 | (1.13 - 1.45 | <0.0001 |
| **Polypharmacy of medication classes:** | 0.97 | (0.84 - 1.13) | 0.70114 |
| **Number of all-cause hospitalizations within 2-year interval:** | | | |
| 0 | reference | reference | reference |
| 1-2 | 3.20 | (2.86 - 3.59) | <0.0001 |
| >2 | 9.02 | (8.05 - 10.11) | <0.0001 |

Table 3: Analysis of risk of all-cause mortality associated with use vs. no-use of medication classes. Hazard rations (HRs) still statistically significant after Bonferroni correction for multiple comparisons are bolded.

| Covariates | HR estimate | Confidence interval | p-value |
|---|---|---|---|
| **Medication classes:** benzodiazepines | 1.21 | (0.97 - 1.51) | 0.09774 |
| sedatives | **1.52** | (1.22 - 1.90) | 0.00020 |
| mood stabilizers | **0.47** | (0.38 - 0.58) | <0.0001 |
| antidepressants | 1.28 | (1.02 - 1.61) | 0.03041 |
| antipsychotics | 1.15 | (0.91 - 1.43) | 0.23775 |
| **Gender:** | | | |
| Female | reference | reference | reference |
| Male | 2.08 | (1.73 - 2.52) | <0.0001 |
| **Age at cohort entry (years):** | | | |
| <30 | reference | reference | reference |
| 30-49 | 0.86 | (0.65 - 1.13) | 0.26866 |
| 50-69 | 0.82 | (0.61 - 1.10) | 0.18685 |
| >70 | 0.22 | (0.12 - 0.41) | <0.0001 |
| **Calendar year of cohort entry:** | | | |
| 1996-1999 | reference | reference | reference |
| 2000-2003 | 0.75 | (0.58 - 0.96) | 0.02310 |
| 2004-2007 | 0.45 | (0.34 - 0.60) | <0.0001 |
| 2008-2012 | 0.45 | (0.33 - 0.62) | <0.0001 |
| **Time since diagnosis (years):** | | | |
| 0-5 | reference | reference | reference |
| 5-10 | 0.79 | (0.54 - 1.14) | 0.19971 |
| >10 | 0.65 | (0.37 - 1.14) | 0.13171 |
| **Number of medication classes used previously:** | | | |
| 0-1 | reference | reference | reference |
| 2 | 1.51 | (0.99 - 2.31) | 0.05585 |
| >2 | 3.03 | (2.05 - 4.48) | <0.0001 |
| **Polypharmacy of medication classes:** | 1.09 | (0.76 - 1.56) | 0.63275 |
| **Number of suicidal hospitalizations within 2 year interval:** | | | |
| 0 | reference | reference | reference |
| >0 | 1.86 | (0.26 - 13.40) | 0.53929 |

Table 4: Analysis of risk of suicide mortality associated with use vs. no-use of medication classes. Hazard rations (HRs) still statistically significant after Bonferroni correction for multiple comparisons are bolded.

## DISCUSSION

To our knowledge, this is the first comprehensive Finnish nationwide study on the risk correlations for use of psychotherapeutics and overall mortality and suicide in bipolar patients hospitalized at least once due to their disorder. A previous study in Finland has evaluated the risks for medication use versus mortality rates in a cohort of 826 bipolar patients hospitalized due to previous suicide attempt (11). The main results of our study are well in line with the previous smaller study, and indicate that use of mood stabilizers is associated with the lowest risk for overall and suicide mortality in bipolar patients. Use of antidepressants was also associated with a reduced risk for overall mortality, whereas use of sedatives was associated with an increased risk for suicide mortality.

Although our study was comprehensive, which is one of the key strengths of this study, any results obtained should be interpreted with caution. The study population included only Finns, so while the results are very much valid inside Finland they might not be generalizable to other countries. Also, as mortality and suicide are one-time events, more advanced within-individual analyses could not be performed, and so confounding by factors inherent to the contributing individuals (such as genetics or degree of illness) could not be controlled for. However, especially for one-time events, the overall change in the prevalence of these events as time goes by needs to be corrected for, as was recently shown in a large register-based study exploring the temporal trends in suicide mortality in depression patients in Finland between 1991 and 2014 (21). We used information on time since diagnosis, age at index date and calendar year of index date to try to correct for different temporal trends. Between-group analyses are often also fraught with residual confounding due to selection bias, which arises from the fact that patients most mildly ill often use less or no medication, whereas patients with more pronounced symptoms and severe course of disease often have more medication prescribed. As this study compares the use of a certain medication group to non-use of the same medication group, the results could also be influenced by protopathic bias. This is a form of bias which arises when medications are often added when the patient experiences a worsening of his/her symptoms. Thus, the medications in use at time of death might not have contributed to the mortality event, but rather have been initiated too late to have been able to stop it. This protopathic bias can be controlled for by excluding time periods right after initiation of new treatments, but doing so would markedly decrease the number of suicide events available for analysis, as suicides are often completed during or right after hospitalization (22) when medications are also often initiated. Also, as this study is based on information gained from registers, no data on clinical variables, such as smoking or alcohol use or substance abuse, were obtained or available for analysis.

Our results indicate that, as a therapeutic group, mood stabilizers are associated with the lowest risk of any-cause and suicide mortality in bipolar patients. With respect to previous findings by ourselves and others (12, 13, 15, 20, 23-27) and the new findings presented here, these medications should be considered as first choice for bipolar patients requiring hospitalization for their disorder, not only to prevent rehospitalization, but also mortality. Patients at a high risk for suicide should be especially considered for treatment with mood stabilizers. However, when considering a patient for this group of medication, their side-effect profile and tolerability should also be taken into consideration.

It would also seem clear in light of our current findings that the use of sedatives should be avoided where possible, as their use was associated with an increased risk for suicide. As this study is of an observational nature, no direct causation can be drawn from the data, and one explanation could be that patients using sedatives suffer from sleep disorders and are thus at a higher risk for suicide and mortality, and at least part of the risk association shown here comes from the effect of the sleep disorder rather than the use of sedatives. If this were the case, one would also expect to see the same association with other medication groups with sedative properties often used to treat sleep disorders, such as benzodiazepines or antipsychotics. However, this association did not surface in this study. Lending credence to the risk associated with use of sedatives is the fact that an increased risk for overall mortality has previously been reported by other groups for the use sedatives (28-30), although our study did not find such an association. Use of sedatives has been associated with an increased risk for an excess of death at night (31), excess of infection (32) and chronic obstructive pulmonary disease (33), excess of specific cancers, such as lung and oesophagus (34), as well as an excess of suicide death (35) (36).

Although use of benzodiazepines for bipolar patients has previously been associated with a higher risk for rehospitalization (20), suicide mortality (28) as well as overall mortality (29), we did not find an association for significantly increased risk for overall or suicide mortality in this study. An explanation could be that this study was underpowered to detect changes in risk for benzodiazepine use, as the number of suicides was rather low even in this

large cohort, since use of benzodiazepines seemed to be associated with a non-significant trend towards an increased risk. The difference may also arise from different definitions of benzodiazepines between the studies, for example, our definition of "sedatives" also included some benzodiazepines commonly used as hypnotics. Further studies are required to obtain further information on this subject. However, as data on the harmful effects of long-term benzodiazepine use are becoming more and more prominent, great care should be taken when prescribing these medications by making sure they remain in use for only as long as absolutely necessary.

In conclusion, one of the major shortcomings of this study is that data on treatment effectiveness were only analysed on a group-wise level. As individual medications inside medication groups can have markedly different effects, translating these results into clinical practice is difficult. Some inferences can be made, however, as the use of mood stabilizers in this Finnish cohort of patients with bipolar disorder was associated with the lowest risk for all-cause mortality and suicide mortality, and as these medications have also previously been associated with lowest risk of rehospitalization due to mental disorder, they would seem to be the obvious first choice to be considered for the treatment of bipolar disorder. In this study, use of sedatives was associated with an increased risk for suicide mortality, and should thus be avoided in patients at a high risk for suicide.

Authors:

*Markku Lähteenvuo*, MD, PhD
*Diego Antolín-Concha*, MD
*Pia Vattulainen,* MSc
*Antti Tanskanen*, PhLic
*Heidi Taipale*, PhD
*Jari Tiihonen,* MD, PhD

Affiliations:

University of Eastern Finland, Department of Forensic Psychiatry, Niuvanniemi Hospital, Finland (*Lähteenvuo, Antolín-Concha, Tanskanen, Taipale, Tiihonen*)
Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden (*Tanskanen, Taipale, Tiihonen*)
National Institute for Health and Welfare, Impact Assessment Unit, Helsinki, Finland (*Tanskanen*)
School of Pharmacy, University of Eastern Finland, Kuopio, Finland (*Taipale*)
EPID Research Oy, Espoo, Finland (*Vattulainen*)

Correspondence to:

Jari Tiihonen, MD, PhD, professor, Department of Clinical Neuroscience, Karolinska Institutet, Byggnad R5, S-17176 Stockholm, Sweden. E-mail: *jari.tiihonen@ki.se*

References:

1. Saunders KE, Goodwin GM. *The course of bipolar disorder.* Adv Psychiatr Treat 2010; 16: 318–328.

2. Costa Lda S, Alencar ÁP, Nascimento Neto PJ, dos Santos Mdo S, da Silva CG, Pinheiro Sde F, Silveira RT, Bianco BA, Pinheiro RF Jr, de Lima MA, Reis AO, Rolim Neto ML. *Risk factors for suicide in bipolar disorder: a systematic review*. J Affect Disord 2015; 170: 237–254.

3. Ösby U, Brandt L, Correia N, Ekbom A, Sparén P. *Excess mortality in bipolar and unipolar disorder in Sweden*. Arch Gen Psychiatry 2001; 58: 844–850.

4. Pompili M, Gonda X, Serafini G, Innamorati M, Sher L, Amore M, Rihmer Z, Girardi P. *Epidemiology of suicide in bipolar disorders: a systematic review of the literature.* Bipolar Disord 2013; 15: 457–490.

5. Miller C, Bauer MS. *Excess mortality in bipolar disorders.* Curr Psychiatry Rep 2014; 16: 499.

6. Crump C, Sundquist K, Winkleby MA, Sundquist J. *Comorbidities and mortality in bipolar disorder: a Swedish national cohort study.* JAMA Psychiatry 2013; 70: 931–939.

7. Medici CR, Videbech P, Gustafsson LN, Munk-Jørgensen P. *Mortality and secular trend in the incidence of bipolar disorder.* J Affect Disord 2015; 183: 39–44.

8. Hayes JF, Miles J, Walters K, King M, Osborn DP. *A systematic review and meta-analysis of premature mortality in bipolar affective disorder.* Acta Psychiatr Scand 2015; 131: 417–425.

9. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015; 386: 743–800.

10. Perlis RH, Ostacher MJ, Patel JK, Marangell LB, Zhang H, Wisniewski SR, Ketter TA, Miklowitz DJ, Otto MW, Gyulai L, Reilly-Harrington NA, Nierenberg AA, Sachs GS, Thase ME. *Predictors of recurrence in bipolar disorder: primary outcomes from the Systematic Treatment Enhancement Program for Bipolar Disorder* (STEP-BD). Am J Psychiatry 2006; 163: 217–224.

11. Toffol E, Hätönen T, Tanskanen A, Lönnqvist J, Wahlbeck K, Joffe G, Tiihonen J, Haukka J, Partonen T. *Lithium is associated with decrease in all-cause and suicide mortality in high-risk bipolar patients: A nationwide registry-based prospective cohort study.* J Affect Disord 2015; 183: 159–165.

12. Song J, Sjölander A, Joas E, Bergen SE, Runeson B, Larsson H, Landén M, Lichtenstein P. *Suicidal behavior during lithium and valproate treatment: a within individual 8-year prospective study of 50,000 patients with bipolar disorder.* Am J Psychiatry 2017; 174: 795–802.

13. Collins JC, McFarland BH. *Divalproex, lithium, and suicide among Medicaid patients with bipolar disorder.* J Affect Disord 2008; 107: 23–28.

14. Carlborg A, Ferntoft L, Thuresson M, Bodegard J. *Population study of disease burden, management, and treatment of bipolar disorder in Sweden: a retrospective observational registry study.* Bipolar Disord 2015; 17: 76–85.

15. Kessing LV, Hellmund G Geddes JR Goodwin GM, Andersen PK. *Valproate v. lithium in the treatment of bipolar disorder in clinical practice: observational nationwide register-based cohort study.* Br J Psychiatry 2011; 199: 57–63.

16. Tanskanen A, Taipale H, Koponen M, Tolppanen AM, Hartikainen S, Ahonen R, Tiihonen J. *Drug exposure in register-based research: an expert-opinion based evaluation of methods.* PLoS One 2017; 12: e0184070.

17. Tanskanen A, Taipale H, Koponen M, Tolppanen AM, Hartikainen S, Ahonen R, Tiihonen J. *From prescription drug purchases to drug use periods: a second generation method (PRE2DUP)*. BMC Med Inform Decis Mak 2015; 15: 21.

18. Taipale H, Tanskanen A, Koponen M, Tolppanen AM, Tiihonen J, Hartikainen S. *Agreement between PRE2DUP register data modeling method and comprehensive drug use interview among older persons.* Clin Epidemiol 2016; 8: 363–371.

19. Tiihonen J, Tanskanen A, Hoti F, Vattulainen P, Taipale H, Mehtälä J, Lähteenvuo M. *Pharmacological treatments and risk of readmission to hospital for unipolar depression in Finland: a nationwide cohort study.* Lancet Psychiatry 2017; 4: 547–553.

20. Lähteenvuo M, Tanskanen A, Taipale H, Hoti F, Vattulainen P, Vieta E, Tiihonen J. *Real-world effectiveness of pharmacologic treatments for the prevention of rehospitalization in a Finnish nationwide cohort of patients with bipolar disorder.* JAMA Psychiatry 2018; 75: 347–355.

21. Aaltonen KI, Isometsä E, Sund R, Pirkola S. *Decline in suicide mortality after psychiatric hospitalization for depression in Finland between 1991 and 2014.* World Psychiatry 2018; 17: 110–112.

22. Olfson M, Wall M, Wang S, Crystal S, Liu SM, Gerhard T, Blanco C. *Short-term suicide risk after psychiatric hospital discharge*. JAMA Psychiatry 2016; 73: 1119–1126.

23. Miura T, Noma H, Furukawa TA, Mitsuyasu H, Tanaka S, Stockton S, Salanti G, Motomura K, Shimano-Katsuki S, Leucht S, Cipriani A, Geddes JR, Kanba S. *Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis.* Lancet Psychiatry 2014; 1: 251–259.

24. Severus E, Taylor MJ, Sauer C, Pfennig A, Ritter P, Bauer M, Geddes JR. *Lithium for prevention of mood episodes in bipolar disorders: systematic review and meta-analysis.* Int J Bipolar Disord 2014; 2: 15.

25. Hayes JF, Marston L, Walters K, Geddes JR, King M, Osborn DPJ. *Lithium vs. valproate vs. olanzapine vs. quetiapine as maintenance monotherapy for bipolar disorder: a population-based UK cohort study using electronic health records.* World Psychiatry 2016; 15: 53–58.

26. Simhandl C, König B, Amann BL. *A prospective 4-year naturalistic follow-up of treatment and outcome of 300 bipolar I and II patients.* J Clin Psychiatry 2014; 75: 254–262.

27. Joas E, Karanti A, Song J, Goodwin GM, Lichtenstein P, Landén M. *Pharmacological treatment and risk of psychiatric hospital admission in bipolar disorder.* Br J Psychiatry 2017; 210: 197–202.

28. Dodds TJ. *Prescribed benzodiazepines and suicide risk: a review of the literature*. Prim Care Companion CNS Disord 2017; 19: 16r02037.

29. Weich S, Pearce HL, Croft P, Singh S, Crome I, Bashford J, Frisher M. *Effect of anxiolytic and hypnotic drug prescriptions on mortality hazards: retrospective cohort study.* BMJ 2014; 348: g1996.

30. Kriegbaum M, Hendriksen C, Vass M, Mortensen EL, Osler M. H*ypnotics and mortality: partial confounding by disease, substance abuse and socioeconomic factors?* Pharmacoepidemiol Drug Saf 2015; 24: 779–783.

31. Kripke DF, Garfinkel L. *Excess nocturnal deaths related to sleeping pill and tranquilliser use*. Lancet 1984; 1(8368): 99.

32. Obiora E, Hubbard R, Sanders RD, Myles PR. *The impact of benzodiazepines on occurrence of pneumonia and mortality from pneumonia: a nested case-control and survival analysis in a population-based cohort.* Thorax 2012; 68: 163–170.

33. Chung WS, Lai CY, Lin CL, Kao CH. *Adverse respiratory events associated with hypnotics use in patients of chronic obstructive pulmonary disease: a population-based case-control study.* Medicine (Baltimore) 2015; 94: e1110.

34. Kao CH, Sun LM, Liang JA, Chang SN, Sung FC, Muo CH. *Relationship of zolpidem and cancer risk: a Taiwanese population-based cohort study*. Mayo Clin Proc 2012; 87: 430–436.

35. Park TW, Saitz R, Ganoczy D, Ilgen MA, Bohnert AS. *Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case–cohort study.* BMJ 2015; 350: h2698.

36. Kripke DF. *Mortality risk of hypnotics: strengths and limits of evidence.* Drug Saf 2016; 39: 93–107.