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Conventional mood stabilizers and/or second-generation antipsychotic drugs in bipolar disorders: a population-based comparison of risk of treatment failure

Short title: **Treatment failure in bipolar disorders**

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Abstract

Background: The study compared treatment failure when using three therapeutic strategies in bipolar disorders: (i) mood stabilizers (MSs: lithium, valpromide, divalproate, carbamazepine, lamotrigine) without second-generation antipsychotics (SGAP); (ii) SGAPs (aripiprazole, olanzapine, risperidone, quetiapine) without MS; (iii) combination of MSs and SGAPs.

Methods: A historical cohort study was conducted using the French national healthcare databases in 20,086 outpatients aged 21+, newly treated with one of the three treatment strategies in 2011-2012, and diagnosed with a bipolar disorder. A composite outcome was based on indicators of treatment failure identified over 12 months: treatment discontinuation, switch or addition, psychiatric hospitalisation, suicide attempt, and death. For each strategy, the cumulative incidence of treatment failure was calculated while adjusting for covariates by propensity score weighting.

Results: A total of 8,225 patients (40.9%) were newly dispensed MSs, 9,342 (46.5%) SGAPs, and 2,519 (12.5%) both MSs and SGAPs. The one-year adjusted cumulative incidence of treatment failure was 75.7% (95%CI 74.9;76.3) in patients using MSs, 75.3% (74.6;76.0) in patients using SGAPs, and 60.5% (58.3;62.6) in patients with the combination. The adjusted difference in incidence for SGAPs compared with MSs was -0.40% (-1.4;0.6 p=0.4) in the whole population, -2.2% (-3.3; -1.2 p<0.002) in patients under 65 years and +6.7% (4.1;9.1 p<0.002) in patients 65 years and over.

Limitations: Combinations of MSs and SGAPs could not be directly compared with MS or SGAP monotherapies.

Conclusions: One-year treatment failure was high. Overall, no difference in treatment failure was observed between MS or SGAP strategy but differences might exist depending on age.

Key words

Bipolar disorder, mood stabilizer, second-generation antipsychotic, effectiveness, side event,
health claim database

Introduction

The use of second-generation antipsychotics (SGAPs) in bipolar disorders has increased dramatically in recent decades, not only to manage acute mania but also to prevent relapse, instead of conventional mood stabilizers (MSs: lithium or anticonvulsants) (Depp et al., 2008; Kessing et al., 2016; Verdoux et al., 2010). Although SGAPs are occasionally recommended as first-line monotherapy (Goodwin et al., 2016; Yatham et al., 2013), scientific knowledge does not unanimously support their extensive use, as their benefit/risk ratio when used over a long period is poorly understood (Lindstrom et al., 2017; Yatham et al., 2016).

As bipolar disorders are common, life-threatening and costly conditions and because they require very long-term treatments, the latter should have both a good proven effectiveness and a favorable safety profile. Two studies including outpatients with bipolar disorder compared the effectiveness of SGAPs and MSs in a real-life setting focusing on the risk of hospitalisation (Bauer et al., 2016; Lahtenvuo et al., 2018). In the first one, after controlling for the main confounders, the initiation of lithium or valproate monotherapies was associated with a lower likelihood of all-cause hospitalisation and of psychiatric hospitalisation than the initiation of SGAP monotherapies. As there were no differences in medical or surgical hospitalisations, these findings were probably more related to effectiveness than to safety issues. In the second one, antipsychotics were not associated with the risk of psychiatric hospitalisation, while mood stabilizers reduced this risk. Some other studies assessed the impact of products on the rate of psychiatric hospitalisation (Joas et al., 2017; Nestsiarovich et al., 2018; Wingard et al., 2017). One study did not compare products but periods when patients were medicated and periods when they were not (Joas et al., 2017). This study found that lamotrigine was associated with a decreased rate of hospitalisation due to depression, carbamazepine with a decreased rate of hospitalisation for manic episodes, quetiapine and olanzapine with lower rates of hospitalisation for both manic and depressive episodes, and

lithium and valproate with decreased rates of manic, depressive and mixed episodes. Another study combined patients with bipolar disorders and schizo-affective disorders and compared monotherapies using various products, including some that were not approved or recommended in these indications (Nestsiarovich et al., 2018). The main limitation was that hospitalisation risk could only be assessed short term, as most patients discontinued monotherapy within two months. Finally, the one-year risk of rehospitalisation was assessed in patients discharged from a hospitalisation for mania, i.e. patients with bipolar disorder type I (Wingard et al., 2017). Prescription fills of lithium, valproate, olanzapine, quetiapine and aripiprazole were only collected over the first four weeks after hospital discharge, limiting the interpretation of findings as treatment at the time of rehospitalisation was unknown.

Other studies found that, compared with MS monotherapy, combinations of MSs and SGAPs were associated with a decreased rate of relapse in the first six months of treatment but not after (Yatham et al., 2016) or of re-hospitalisation between six and twelve months after treatment initiation (Hochman et al., 2016). In the latter study, the treatment prescribed at the time of re-hospitalisation was unknown, as was adherence to treatment. Thus, the studies published to date have provided conflicting findings and have mainly focused on effectiveness, and on the risk of hospitalisation for the most part, whereas tolerance is crucial to support persistence with such long-term treatments (Vieta and Sanchez-Moreno, 2008). Investigating treatment failure based on the risk of hospitalisation allows using an objective measure but leads to underestimate safety problems, residual symptoms and relapse, particularly depressive relapse that are the most frequent.

The aim of the present study was to compare the incidence of treatment failure between three therapeutic strategies implemented in bipolar disorder using the claims database of the French national health insurance system linked to the hospital discharge database: (i) MSs without SGAPs; (ii) SGAPs approved for bipolar disorder without MSs; (iii) combination of MSs and

SGAPs. A composite outcome for treatment failure both for ineffectiveness or safety reasons was built and considered the following events: early treatment discontinuation, treatment switch, treatment addition, hospitalisation for suicide attempt, psychiatric hospitalisation, and death. A secondary objective was to compare treatment outcomes associated with the refined treatment strategies where the drugs were considered separately.

Methods

Study design and data source

A historical fixed cohort study with dynamic follow-up time was carried out in patients initiating a treatment from January 1st 2011 to December 31st 2012 for a bipolar disorder with one of the three strategies. The date of first dispensing (treatment initiation) over the study period was considered as the index date. As only patients with at least two consecutive months (56 days) of treatment were included, follow-up started after this time-lag and was pursued until the occurrence of the first outcome considered as a treatment failure marker or withdrawal from the health insurance scheme (employees and their dependents), or over 360 days of treatment in the absence of these events.

Data were extracted from the claims database of the French national health insurance system (SNIIRAM, *Système National d'Information Inter-régimes de l'Assurance Maladie*) for the 2007-2013 period. This database collects all reimbursements for health care and drugs in outpatients for the whole French population, without recording the indication requiring them. The study was restricted to employees and their dependents (about 75% of the French population) for whom the available information is comprehensive. Besides healthcare use of outpatients, the database includes demographic characteristics of beneficiaries, specialty of practitioners. Medical diagnoses are available when associated with disability insurance, periods of sick leave of at least 180 days and status of “long duration disease”, an administrative status giving access to treatment free of charge for the disease concerned, but

the medical indication is not available for care and drug reimbursements in outpatients. The SNIIRAM database is linked to the hospitalisation database (PMSI, *Programme de Médicalisation des Systèmes d'Information*), which provides information on all hospital stays (duration, dates, and medical diagnoses at discharge) including stays in psychiatric hospitals. All medical diagnoses are recorded using the International Classification of Diseases, 10th edition (ICD-10). The study was approved by the French personal data protection agency (CNIL for *Commission Nationale de l'Informatique et des Libertés*). All databases used in this study contained only anonymous patient identifiers. This procedure complies with the French legislation on data protection so the study conforms to French ethical rules.

Study population

The study population met the following inclusion criteria: (i) new dispensing of MS or SGAP from January 1st 2011 to December 31st 2012; (ii) at least two consecutive months of the treatment considered (at least one dispensing in the second month after treatment initiation); (iii) age 21 years and older at index date; (iv) no dispensing of MS or SGAP during the twelve months preceding index date; (v) diagnosis of a bipolar disorder in the four years prior to index date (ICD-10 codes: F30, F31); and (vi) at least 12 months of follow-up available after index date.

As the beneficiaries' identity was not always specified in young adults (e.g. if covered by their parents' insurance), patients were included only after the age of 21. As treatment impact might vary according to age due to non-psychiatric comorbidity and age-related changes in pharmacokinetics that might lead to safety considerations in older patients, the study population was stratified according two categories: under 65 years and 65 and over (Malhi et al., 2017; Mehta et al., 2010; Sun et al., 2018). Only the first drug treatment (MS and/of SGAP) initiated over the study period was considered. Patients hospitalized for the full 12 months prior to the index date were excluded, as drug exposure during hospitalisations is not

recorded in the SNIIRAM/PMSI databases. As the follow-up started 56 days after the index date, patients who died during this 56-day period were excluded, as well as those with a psychiatric hospitalisation during this period and who were still inpatients on the 57th day after the index date.

Drug exposure

MSs and SGAPs were defined according to the World Health Organization Anatomical Therapeutic Chemical index and in accordance with market authorizations for bipolar disorder. MSs considered were lithium salts, valpromide, sodium divalproate, carbamazepine and lamotrigine. SGAPs considered were aripiprazole, olanzapine, risperidone and quetiapine. Combination of MS and SGAP was defined as the concomitant initiation of both drug classes, i.e. in the same 28-day period, with a treatment duration of more than 28 days. Lithium and anticonvulsants were considered together to contrast conventional mood stabilizers and newer second-generation antipsychotics and to enhance statistical power.

In the SNIIRAM database, there is no direct access to the dosage or duration of the prescribed treatments. Duration of exposure to each drug class (i.e. MSs and SGAPs, without distinguishing between drugs of the same class) was estimated on a daily time scale by using information on the corresponding dates of dispensing (see supplementary material for details). In France, treatments are issued for a maximum of 28 days. Therefore, for each date of dispensing, the 28 days following this date were considered as exposed (Etchepare et al., 2014; Tournier et al., 2013). If a new dispensing occurred before the end of this 28-day period, the remaining days were passed on. Moreover, as information about drug treatments dispensed during hospital stays was not available, only treatments dispensed in outpatients were considered. Treatments dispensed in the 56 days prior to hospitalisation were considered as having been pursued during the hospitalisation stay. For additional analyses, exposure was also estimated for each drug separately.

Outcomes

The following outcomes were considered as markers of a treatment failure, either related to effectiveness or to safety issues: treatment discontinuation, switch to the other drug class (i.e. from SGAs to MSs or from MSs to SGAs) or addition of a drug of the other class, psychiatric hospitalisation and hospitalisation for suicide attempt (ICD-10 codes X60-X84). They were identified over the 12 months following the index date. Recommended treatment duration is long in bipolar disorder so a dose decrease might be planned after a remission period of at least two years. However, treatment should be maintained lifelong whenever possible (Grunze et al., 2013). Therefore, a treatment cessation occurring in the 12 months after its initiation was considered as an early discontinuation and a marker of insufficient effectiveness or of disabling adverse events. Treatment discontinuation was defined by a period of more than 28 consecutive days without any exposure to MSs and/or SGAPs (Chen et al., 2013; Rascati et al., 2011). For the combination of MSs and SGAPs, only complete discontinuation of both drugs was considered for the “treatment failure” variable, i.e. more than 28 consecutive days without exposure either to MSs or to SGAPs. In this case, the follow-up was pursued after the discontinuation of one drug until the occurrence of another outcome. Partial discontinuation of one of the two drugs, i.e. more than 28 consecutive days without exposure to either MSs or SGAPs, was not considered as a marker of treatment failure as a combination might be useful only for a short period, but was described as an additional outcome. Although a 28-day period without treatment was previously used to define treatment discontinuation (Chen et al., 2013; Rascati et al., 2011), a more conservative definition, i.e. more than 56 consecutive days without exposure, was considered for a sensitivity analysis.

Two main treatment changes were considered as markers of insufficient effectiveness or adverse events, and by definition relevant only for MS or SGAP monotherapies: switch and addition. These were not considered for the “treatment failure” variable for the combination

of MSs and SGAPs. A treatment switch to the other drug class, i.e. from MS to SGAP or from SGAP to MS, occurred when (i) a second drug was dispensed after a first one within the same episode of treatment; and (ii) the overlap of both prescriptions, if any, did not exceed 28 days. Treatment addition occurred when (i) two different drug classes (MSs and SGAPs) were dispensed at the same time over a period of more than 28 days, and (ii) both drug treatments were not initiated during the same 28-day period.

Additional analyses considered treatment discontinuation or changes for each drug. The detailed algorithm for determining treatment discontinuation, switch and addition is given in supplementary materials. In order to improve the comparisons between MSs and SGAPs monotherapies and combination treatments, two sensitivity analyses were performed: (i) switch and addition were deleted from the composite variable of treatment failure for MS and SGAP monotherapies; (ii) partial discontinuation of one of the two drugs was added to the composite variable of treatment failure for combination treatment.

Two adverse events were also considered as treatment failure: full-time psychiatric hospitalisation and hospitalisation for suicide attempt occurring after 56 days of treatment, since an earlier occurrence would likely be linked to time to efficacy onset. This information was provided by the PMSI database. The last event considered in the composite variable reflecting treatment failure was death. Death might correspond to a suicide or to an adverse event due to the treatment and, as such, to treatment failure. It was also included in the composite variable to avoid a competing risk.

Patients' and prescribers' characteristics

Like bipolar disorder diagnosis, comorbidity with other psychiatric conditions was identified in the four years prior to the index date by using medical diagnoses registered in the SNIIRAM or the PMSI databases. We considered anxiety disorders (ICD-10 codes F40, F41, F42), substance use disorders (ICD-10 codes F1) and personality disorders (ICD-10 codes

F60, F61, F62). The severity of the psychiatric conditions was assessed by the cumulative duration of psychiatric hospitalisation in the year preceding the index date (number of weeks: 0, <1, 1-4, 5-8, 9-12, >12). Co-prescription of psychotropics was defined as the dispensing of a psychotropic drug other than MSs or SGAPs at the index date: hypnotic/anxiolytic (benzodiazepines and non-benzodiazepines), sedative first-generation antipsychotics (cyamemazine, levomepromazine), non-sedative first-generation antipsychotics (FGAPs), other second-generation antipsychotics not marketed for bipolar disorder (amisulpride, clozapine) and antidepressants.

Comorbidity involving somatic conditions was also identified in the four years preceding the index date by using medical diagnoses and/or dispensing of targeted drug treatments: ischemic stroke, ischemic heart disease, heart failure, arrhythmia, high blood pressure, metabolic disorders (diabetes, dyslipidemia), chronic renal failure, dementia, Parkinson's disease and epilepsy. Four other conditions were identified in the two years preceding the index date: cancer, liver failure, hepatitis and cirrhosis.

The following demographic characteristics of patients were collected: sex, age, welfare benefit for patients under 60 years with very low income, and allowance for patients under 65 years with disabilities. The type of practice of the physician who initiated the treatment was categorized as (i) private general practitioner (GP); (ii) private psychiatrist; (iii) employed practitioner (mainly hospital practitioners, no information is available in the SNIIRAM-PMSI database on their specialty); (iv) other private specialists.

Statistical analyses

All statistical analyses were performed with SAS software, version 9.2 (SAS Institute, Inc., Cary, NC, USA). Descriptive analyses of the study population were performed according to the treatment strategy and age (under 65 and 65 and over). Then we analyzed the time to treatment failure as measured by the above listed six types of outcome. For this purpose, we

carried out competing risk analysis, as e.g. hospitalisation for suicide attempt is precluded by death and, in this study, was not of interest after treatment discontinuation, treatment switch, treatment addition or psychiatric hospitalisation. Analyzing a given type of outcome by censoring at the occurrence of another type of outcome and performing usual survival analysis would overestimate the risk of the considered type of outcome. The cumulative incidence functions were therefore estimated, one for each of the types of outcome (Austin et al., 2016; Neumann and Billionnet, 2016). For instance, the cumulative incidence of hospitalisation for suicide attempt at one year is the probability that such a hospitalisation occurs up to one year and before any other of the studied types of outcome, including treatment discontinuation or switch. Summing up these cumulative incidence functions over all types of outcome then yields 1 minus the usual survival curve for the composite outcome. First we estimated for each treatment strategy the crude the cumulative incidence functions. Second, the cumulative incidence functions were adjusted by propensity score weighting (Neumann and Billionnet, 2016). Each patient was weighted by the inverse of the probability of receiving the treatment that he/she actually received. The following covariates were retained for adjustment: demographic characteristics (sex, age in five-year groups, welfare benefit), drug use (initial prescriber, dispensing of other psychotropic drugs), substance use disorders, cumulative duration of psychiatric hospital stays during the previous year, and all somatic comorbidities listed above. Third, the adjusted difference in cumulative incidence comparing the monotherapies, SGAPs versus MSs (reference) was computed. Since two treatment changes (switch and addition) did not apply to the combination of MSs and SGAPs, combinations of MSs and SGAPs could not be directly compared with MS or SGAP monotherapies. Ninety-five per cent two-sided confidence intervals (95% CIs), both for the cumulative incidence functions and for the differences between them, were estimated using the bootstrap method. For the analyses at drug class level, percentile intervals based on 1,000

replications were calculated. For the analyses at drug level, standard normal intervals based on 100 replications were determined.

As a 28-day period without treatment might be a too short period to define treatment discontinuation, statistical analyses were repeated using a more conservative definition, i.e. more than 56 consecutive days without exposure, for a sensitivity analysis. In an additional crude analysis, each of the types of outcome under study was considered separately and the follow-up was not stopped when another type of outcome occurred before. For each treatment strategy, the number of outcomes observed during this modified 12-month follow-up was reported.

Results

Description of study population

Among the 548,439 patients having initiated a treatment with MSs and/or SGAPs over the study period, 35,626 (6.5%) had a registered diagnosis of bipolar disorder. Of them, 7,563 (21.2%) patients were excluded because they did not extend their exposure beyond initial dispensing within the first two months after treatment initiation and 95 (0.3%) other patients were excluded because they died during this period, that is, before start of follow-up. A total of 20,086 fulfilled the inclusion/exclusion criteria and were included in the study. Among these patients initiating a treatment, 8225 (40.9%) received MSs, 9342 (46.5%) SGAPs and 2519 (12.5%) a combination of MSs and SGAPs. Their mean age was 50.6 years (SD 15.7) and 33.7% were males. The main characteristics of patients are described according to treatment strategy and age in Table 1. Older patients were more likely to receive SGAPs than younger ones. As it is likely that “other prescribers” were essentially hospital psychiatrists, psychiatrists were the most frequent initial prescribers of the three therapeutic strategies in both age groups.

Treatment outcomes according to treatment strategy

Table 2 describes the treatment outcomes according to treatment strategy and age (see also Figure S1 in supplemental material). After one year, the adjusted cumulative incidence of treatment failure was 75.7% (95%CI 74.9;76.3) in patients using MSs, 75.3% (74.6;76.0) in patients using SGAPs, and 60.5% (58.3;62.6) in patients with the combination. The adjusted difference in cumulative incidence for SGAPs compared with MSs (reference) differed according to age: -0.40% (-1.4;0.6 p=0.4) in the whole population, -2.2% (-3.3;-1.2 p<0.002) in patients under 65, and 6.7% (4.1;9.1 p<0.002) in patients 65 and over. For the three treatment strategies, the first event occurring over the follow-up was the most often an early discontinuation. Treatment addition and discontinuation were slightly less frequent with SGAPs than with MSs while psychiatric hospitalisation occurred more often in the first group in the whole population and in the younger patients. In the older patients, addition was also less frequent with SGAPs than with MSs while early discontinuation, psychiatric hospitalisations and death were more frequent with SGAPs. The adjusted cumulative incidence at one year of partial discontinuation was 59.6% (95%CI 57.3-61.7) in patients with combined treatment (Table 2). Among the patients who had a partial discontinuation as first outcome, at least 17% had one of the two drugs dispensed only once and 13% only twice. The incidence of mortality was quite high as first event, particularly in the group receiving combinations.

When considering each type of outcome separately without stopping the follow-up when another type of outcome occurred (Table 2), patients ≥ 65 with SGAPs (with or without MSs) were at higher risk of death. Psychiatric hospitalisation was also more frequent in patients treated only with SGAPs and hospitalisation for suicide attempt was lower in patients with a combined treatment.

When considering individual drugs separately (Table 3), early discontinuation without switch was by far the most frequent first event over the follow-up, as for drug classes. Lamotrigine had the lowest rate of treatment failure, mainly because early discontinuation as first event was less frequent with it. Conversely, risperidone had the highest rate of treatment failure with frequent early discontinuations, switches and mortality. Lithium had the highest rate of addition (as first event), the lowest rate of switch and the second lowest rate of psychiatric hospitalization. The most frequent treatment additions and switches as first event during follow-up are shown in Table 4. More than 58% of additions included valproate or valpromide and more than 24% included two SGAPs. Conversely, addition of one MS to another and switches from one MS to another were rare.

Sensitivity analyses

Among the 6466 patients who discontinued their treatment within the 180 days after initiation, 1613 (24.9%) were dispensed MSs and/or SGAPs in the 28 days following the treatment discontinuation, respectively. Most of them (n=1345; 83.4%) were dispensed the same drug treatment. When considering more than 56 consecutive days without exposure instead of 28 days to define treatment discontinuation, the adjusted cumulative incidences of treatment discontinuation and treatment failure were reduced. Treatment failure occurred in 64.8 % (95%CI 64.0-65.6) of patients with MSs, 67.4% (95%CI 66.7-68.2) of patients with SGAPs and 50.8% (95%CI 48.6-53.0) of patients with a combination. The adjusted cumulative incidence of early treatment discontinuation was 37.0% (95%CI 36.1-37.8) with MSs, 38% (95%CI 37.3-38.) with SGAPs, and 28.4% (95%CI 26.4-30.2) with a combination. Discontinuation was significantly more frequent with SGAPs than with MSs with an adjusted difference in cumulative incidence equal to 2.6% (95%CI 1.5-3.7; p<0.002).

When switch and addition were deleted from the composite variable of treatment failure for MS and SGAP monotherapies, differences with combination treatments were only slightly

reduced: treatment failure occurred in 70.3% (95%CI 69.5-71.1) of patients with MSs, 71.6% (95%CI 70.9-72.3) of patients with SGAPs and 60.5% (58.4-62.9) of patients with a combination (Table S6). When partial discontinuation of one of the two drugs was added to the composite variable of treatment failure for combination treatment, treatment failure was significantly more frequent with combination treatment than with MSs and SGAPs monotherapies: treatment failure occurred in 75.7% (95%CI 74.9-76.3) of patients with MSs, 75.3% (95%CI 74.6-76.0) of patients with SGAPs and 86.9% (85.4-88.2) of patients with a combination (Table S7). Partial discontinuation occurred in 59.6% (95%CI 57.3-61.7) of patients receiving a combination treatment. Treatment failure with combination was more frequent in patients aged 21-64 years (87.9%; 95%CI 86.4-89.4) than in patients aged 65 and over (82.6%; 95%CI 78.5-86.3).

Discussion

This study conducted on a large nationwide-representative sample highlights four important points. First, a monotherapy for bipolar disorder was more frequently initiated with SGAPs than with MSs. Second, the rate of treatment failure was very high in all age groups and for all therapeutic strategies. Third, based on the outcomes considered, SGAPs did not perform better than MSs in the whole study population and were even worse in the sensitivity analyses. They were slightly more effective than MSs in younger patients, but less effective in older ones. Fourth, mortality was quite high in all age groups and for all therapeutic strategies, particularly in older patients treated with SGAPs or a combination.

These findings should be considered in the light of some methodological limitations. First, as treatment switches and additions were relevant only for monotherapies, combinations of MSs and SGAPs could not be directly compared with MS or SGAP monotherapies. Conversely, as early discontinuation involved the discontinuation of both drugs, this outcome was likely to be less frequent in the combination group than in the monotherapy groups. Therefore,

additional analyses were performed to provide further knowledge. In the first one, treatment switch and addition were not considered as outcome and, in the second one, partial discontinuation was considered as additional outcome for the combined treatment outcome. Furthermore, patients treated using combinations of MSs and SGAPs might present with more severe disorders than those receiving one of these drug classes (drug channeling bias). Second, the healthcare insurance database did not provide clinical information such as severity of the disorder, treatment dosage or duration. The method used to estimate the duration of treatment was used previously (Chen et al., 2013; Etchepare et al., 2014; Rascati et al., 2011; Tournier et al., 2013) and a sensitivity analysis was performed by considering more than 56 consecutive days without exposure instead of 28 days to define treatment discontinuation. Third, a limitation is that dispensing might not necessarily correspond to actual and complete drug ingestion. However, this putative information bias was minimized by the inclusion of patients still exposed in the second month after treatment initiation. Due to this design choice, very early treatment failure was not investigated in the first two months after treatment initiation. Fourth, treatment durations might have been overestimated, since we considered that the treatment was continued during hospital stays. Conversely, a first dispensing after the hospital stay might not correspond to an actual treatment initiation. The study outcomes consisted of events *a priori* related to a worsening of the psychiatric condition and of treatment changes that might also be linked to practice habits, e.g. treatment switches. However, switches from MSs to SGAPs or from SGAPs to MSs very likely resulted from ineffectiveness or the occurrence of an unacceptable adverse effect. Treatment changes by psychiatrists were previously shown to be risk factors for an earlier relapse in bipolar patients, as well as discontinuations by patients (Simhandl et al., 2014). The procedure used to ascertain the diagnosis of bipolar disorder might have led to over-representing the sickest

patients. Finally, owing to the observational nature of the data, residual confounding cannot be excluded.

On the other hand, this study has many strengths. It was a large-scale, almost nationwide, cohort study. Thanks to its design, time-related biases and especially an immortal time bias were avoided. In addition, as the outcomes might compete with each other, we estimated the cumulative incidence functions, one for each type of outcome, by using a competing risk approach that allows for a deeper understanding of the treatment failure dynamics (Austin et al., 2016). Furthermore, in order to minimize prescription channeling bias, we used propensity score weighting to adjust for numerous relevant covariates.

A striking finding of this study is the high mortality rates observed over the first year of treatment. These estimates should be compared with annual mortality rates available for France (INED). The annual mortality rate in our whole study population (2.4%; mean age 50.6 years) was higher than the annual mortality rate in France for the 70-79 age group, which was 1.97% in 2015. Similarly, the mortality rate observed in patients aged ≥ 65 treated with SGAPs (8.5%; mean age 75.5) or a combination of MS and SGAP (7.1%; mean age 73.4) was higher than the annual mortality rate for the 80-89 age group in the French population, i.e. 6.1%. Moreover, the rate of hospitalisation for suicide attempt in the whole population (3.3%) was 20-fold the French national annual rate (18.3/10,000 in 2011) (InVS, 2014). These findings underline the severity of bipolar disorders, even when diagnosed and treated, and the need to optimize general health care management for these patients (Crump et al., 2013).

This severity is to be seen in the context of another important finding of the present study: the high rate of treatment failures. Treatment failed in three patients out of four (treatment change, discontinuation, relapse or death) over the first year and half of all patients discontinued treatment without any switch. This result is consistent with previous studies on adherence and persistence to treatments for bipolar disorder. In a study conducted in Taiwan,

the average medication possession ratio was very low for all treatment strategies (Chang et al., 2016). Another study conducted in the USA showed that most bipolar patients treated with antipsychotics discontinued treatment without restarting any antipsychotic treatment (Chen et al., 2013). This high rate of treatment failure was also consistent with the fact that among the new users included in the study (defined as not having been treated for one year) about a third had already been treated before this one-year period by MS or SGAP therapies. This raises concern regarding treatment adherence and continuity of care in bipolar patients, which might be linked to the high rate of coprescribed psychotropic drugs at baseline, including antidepressants in four patients out of ten.

This study suggests that SGAPs fail more often than MSs in older patients. Their effectiveness has already been questioned (Moro and Carta, 2014; Tsai et al., 2011; Yatham et al., 2016; Zupancic, 2011) and their safety profile gives cause for concern, whatever the age group but particularly in older people. Their adverse metabolic effects have been underlined in numerous studies (Chaggar et al., 2011; Coryell, 2009; Tournier et al., 2012). These risks are anything but trivial in bipolar patients who already have to cope with higher rates of early mortality, mainly due to cardiovascular causes (Carlborg et al., 2015; Crump et al., 2013). Older patients could also be exposed to an increased risk of cerebrovascular mortality (Jackson et al., 2015) and the impact of SGAPs on cognitive functions is poorly understood (Cullen et al., 2016). Conversely, some MSs, particularly lithium, might present some advantages: effectiveness maintained over the long-term (Geddes et al., 2010; Simhandl et al., 2014{Coryell, 2009 #8}), reduction of impulsivity (Hayes et al., 2016; Jones et al., 2011), of cognitive disturbances (Kessing et al., 2010; Sabater et al., 2016), of suicidal behaviours and of all-cause mortality (Toffol et al., 2015). As lamotrigine has also been shown not to have deleterious effects on cognitive functions, it might be preferable to prescribe these drugs in older people.

This nationwide cohort study based on claims data shows that treatment failure was high in bipolar patients during the first year after initiation of MS or/and SGAP monotherapy, irrespective of age groups. Overall, no difference in one-year treatment failure was observed between monotherapy of MS or SGAP but differences were suggested for certain types of treatment failure outcome and depending on age. Other strategies that foster adherence and persistence, such as psychoeducation or cognitive remediation, should also be strongly promoted.

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Table 1. Characteristics of study population according to age and treatment strategy

	Population aged 21 to 64 years (n=16224)							Population aged 65 years and over (n=3862)							Whole population						
	MS (n=6775 41.8%)		SGAP (n=7268 44.8%)		MS and SGAP (n=2181 13.4%)		P	MS (n=1450 37.5%)		SGAP (n=2074 53.7%)		MS and SGAP (n=338 8.8%)		P	MS (n=8225 40.9%)		SGAP (n=9342 46.5%)		MS and SGAP (n=2519 12.5%)		P
	n	%	n	%	n	%		n	%	n	%	n	%		n	%	n	%	n	%	
Age (mean, SD)	45.2	10.6	45.2	11.0	42.6	11.3	<0.001	74.4	7.0	75.5	7.2	73.4	6.9	<0.001	50.3	15.0	51.9	16.3	46.8	15.0	
Sex (male)	2349	34.7	2615	36.0	825	37.8	<0.05	380	26.2	489	23.6	105	31.1	<0.01	2729	33.2	3104	33.2	930	36.9	<0.01
Welfare benefit	861	14.2	1057	16.3	371	18.4	<0.001								861	14.2	1057	16.3	371	18.4	<0.001
Allowance for disabilities	630	9.3	1159	15.9	268	12.3	<0.001	22	1.5	44	2.1	10	3.0		652	7.9	1203	12.9	278	11.0	
Prescriber							<0.001							<0.001							<0.001
Private general practitioner	1370	20.2	946	13.0	235	10.8		430	29.7	640	30.9	56	16.6		1800	21.9	1586	17.0	291	11.6	
Private psychiatrist	2105	31.1	2153	29.6	402	18.4		320	22.1	425	20.5	32	9.5		2425	29.5	2578	27.6	434	17.2	
Other private specialist	106	1.6	67	0.9	33	1.5		38	2.6	48	2.3	10	3.0		144	1.8	115	1.2	43	1.7	
Employed practitioner	3194	47.1	4102	56.4	1511	69.3		662	45.7	961	46.3	240	71.0		3856	46.9	5063	54.2	1751	69.5	
Psychiatric comorbidity																					
Anxiety disorders	1302	19.2	1495	20.6	345	15.8	<0.001	340	23.4	520	25.1	62	18.3	<0.05	1642	20.0	2015	21.6	407	16.2	<0.001
Substance use disorders	2130	31.4	2229	30.7	634	29.1		181	12.5	233	11.2	46	13.6		2311	28.1	2462	26.4	680	27.0	<0.05
Personality disorders	1856	27.4	2363	32.5	614	28.2	<0.001	285	19.7	434	20.9	49	14.5	<0.05	2141	26.0	2797	29.9	663	26.3	<0.001

Table 1. Characteristics of study population according to age and treatment strategy (continued)

	Population aged 21 to 64 years (n=16224)							Population aged 65 years and over (n=3862)							Whole population						
	MS (n=6775 41.8%)		SGAP (n=7268 44.8%)		MS and SGAP (n=2181 13.4%)		p	MS (n=1450 37.5%)		SGAP (n=2074 53.7%)		MS and SGAP (n=338 8.8%)		p	MS (n=8225 40.9%)		SGAP (n=9342 46.5%)		MS and SGAP (n=2519 12.5%)		p
	n	%	n	%	n	%		n	%	n	%	n	%		n	%	n	%	n	%	
Psychiatric hospitalisation weeks in previous year							<0.001							<0.001							<0.001
0	3190	47.1	3056	42.0	432	19.8		830	57.2	1172	56.5	109	32.2		4020	48.9	4228	45.3	541	21.5	
<1	328	4.8	355	4.9	60	2.8		23	1.6	36	1.7	5	1.5		351	4.3	391	4.2	65	2.6	
1-4	1789	26.4	2065	28.4	787	36.1		271	18.7	366	17.6	106	31.4		2060	25.0	2431	26.0	893	35.5	
5-8	780	11.5	918	12.6	492	22.6		170	11.7	218	10.5	68	20.1		950	11.6	1136	12.2	560	22.2	
9-12	324	4.8	368	5.1	185	8.5		65	4.5	103	5.0	25	7.4		389	4.7	471	5.0	210	8.3	
>12	364	5.4	506	7.0	225	10.3		91	6.3	179	8.6	25	7.4		455	5.5	685	7.3	250	9.9	
Co-prescription of psychotropic drugs	5468	80.7	5769	79.4	1784	81.8	<0.05	1127	77.7	1564	75.4	271	80.2		6595	80.2	7333	78.5	2055	81.6	<0.001
Anxiolytic	3650	53.9	4072	56.0	1122	51.4	<0.001	726	50.1	1023	49.3	162	47.9		4376	53.2	5095	54.5	1284	51.0	<0.01
Hypnotic	2467	36.4	2706	37.2	864	39.6	<0.05	543	37.4	758	36.5	138	40.8		3010	36.6	3464	37.1	1002	39.8	<0.05
Antidepressant	3031	44.7	3133	43.1	491	22.5	<0.001	663	45.7	961	46.3	89	26.3	<0.001	3694	44.9	4094	43.8	580	23.0	<0.001
Other SGAP	326	4.8	107	1.5	19	0.9	<0.001	38	2.6	8	0.4	0		<0.001	364	4.4	115	1.2	19	0.8	<0.001
Sedative FGAP	1037	15.3	1225	16.9	424	19.4	<0.001	165	11.4	208	10.0	40	11.8		1202	14.6	1433	15.3	464	18.4	<0.001
Non-sedative FGAP	363	5.4	697	9.6	106	4.9	<0.001	114	7.9	270	13.0	23	6.8	<0.001	477	5.8	967	10.4	129	5.1	<0.001
MS 5 to 2 years before	2662	39.3	2269	31.2	840	38.5	<0.001	622	42.9	503	24.3	103	30.5	<0.001	3284	39.9	2772	29.7	943	37.4	<0.001
SGAP 5 to 2 years before	1711	25.3	3027	41.6	840	38.5	<0.001	318	21.9	668	32.2	81	24.0	<0.001	2029	24.7	3695	39.6	921	36.6	<0.001

Table 1. Characteristics of study population according to age and treatment strategy (continued)

	Population aged 21 to 64 years (n=16224)							Population aged 65 years and over (n=3862)							Whole population						
	MS (n=6775 41.8%)		SGAP (n=7268 44.8%)		MS and SGAP (n=2181 13.4%)		p	MS (n=1450 37.5%)		SGAP (n=2074 53.7%)		MS and SGAP (n=338 8.8%)		p	MS (n=8225 40.9%)		SGAP (n=9342 46.5%)		MS and SGAP (n=2519 12.5%)		p
	n	%	n	%	n	%		n	%	n	%	n	%		n	%	n	%	n	%	
History of somatic conditions																					
Ischemic stroke	50	0.7	42	0.6	7	0.3		56	3.9	90	4.3	5	1.5	<0.05	106	1.3	132	1.4	12	0.5	<0.001
Ischemic heart disease	170	2.5	175	2.4	30	1.4	<0.01	169	11.7	289	13.9	49	14.5		339	4.1	464	5.0	79	3.1	<0.001
Heart failure	85	1.3	102	1.4	18	0.8		123	8.5	189	9.1	27	8.0		208	2.5	201	3.1	45	1.8	<0.001
Arrhythmia	149	2.2	189	2.6	30	1.4	<0.01	223	15.4	352	17.0	56	16.6		372	4.5	541	5.8	86	3.4	<0.001
High blood pressure	1051	15.5	1132	15.6	234	10.7	<0.001	787	54.3	1204	58.1	179	53.0	<0.05	1838	22.3	2336	25.0	413	16.4	<0.001
Diabetes	386	5.7	462	6.4	90	4.1	<0.001	281	19.4	451	21.7	65	19.2		667	8.1	913	9.8	155	6.2	<0.001
Dyslipidemia	741	10.9	818	11.3	137	6.3	<0.001	480	33.1	713	34.4	115	34.0		1221	14.8	1531	16.4	252	10.0	<0.001
Chronic renal failure	38	0.6	58	0.8	7	0.3	<0.05	68	4.7	128	6.2	14	4.1		106	1.3	186	2.0	21	0.8	<0.001
Dementia	36	0.5	66	0.9	8	0.4	<0.01	204	14.1	476	23.0	44	13.0	<0.001	240	2.9	542	5.8	52	2.1	<0.001
Parkinson's disease	23	0.3	26	0.4	3	0.1		81	5.6	135	6.5	7	2.1	<0.01	104	1.3	161	1.7	10	0.4	<0.001
Epilepsy	365	5.4	514	7.1	62	2.8	<0.001	148	10.2	142	6.8	17	5.0	<0.001	513	6.2	656	7.0	79	3.1	<0.001

MS: mood stabilizer, SGAP: second-generation antipsychotic marketed for bipolar disorder; FGAP: first-generation antipsychotic

Table 2. Treatment outcomes and adjusted difference in cumulative incidence for SGAPs vs MSs at one year after treatment initiation according to age and treatment strategy group (in % with 95% confidence intervals)

	Whole study population			Aged 21 to 64 years				Aged 65 and over				
	MS (n=8225)	SGAP (n=9342)	Difference SGAPs vs MSs	MS and SGAP (n=2519)	MS (n=6775)	SGAP (n=7268)	Difference SGAPs vs MSs	MS and SGAP (n=2181)	MS (n=1450)	SGAP (n=2074)	Difference SGAPs vs MSs	MS and SGAP (n=338)
Treatment failure† (%)	75.7 (74.9-76.3)	75.3 (74.6-76.0)	-0.4 (-1.4;0.6) p=0.5	60.5 (58.3-62.6)	77.7 (77.0-78.5)	75.5 (74.7-76.3)	-2.2 (-3.3;-1.2) p<0.002	62.9 (60.6-65.4)	67.7 (65.8-69.6)	74.5 (72.9-75.9)	6.7 (4.1;9.1) p<0.002	49.5 (43.0-56.1)
Early discontinuation‡	50.6 (49.8-51.5)	49.1 (48.3-49.9)	-1.5 (-2.6;-0.3) p=0.02	40.2 (38.1-42.3)	52.3 (51.5-53.3)	48.4 (47.5-49.3)	-3.9 (-5.2;-2.7) p<0.002	43.7 (41.4-46.3)	44.0 (42.0-45.9)	51.8 (50.3-53.6)	7.8 (5.3;10.4) p<0.002	25.3 (18.8-31.7)
Switch	3.5 (3.2-3.8)	3.8 (3.5-4.1)	0.3 (-0.1;0.7) p=0.2		3.7 (3.4-4.1)	4.3 (3.9-4.6)	0.5 (0.0;1.1) p=0.03		2.8 (2.2-3.5)	2.0 (1.5-2.5)	-0.8 (-1.6;0.0) p=0.06	
Addition	7.0 (6.6-7.5)	4.1 (3.8-4.4)	-2.9 (-3.5;-2.4) p<0.002		7.3 (6.8-7.8)	4.5 (4.2-4.9)	-2.8 (-3.3;-2.2) p<0.002		6.0 (5.0-6.9)	2.4 (1.9-2.9)	-3.6 (-4.7;-2.5) p<0.002	
Psychiatric hospitalisation§	11.9 (11.4-12.4)	15.6 (15.0-16.2)	3.6 (2.4;4.4) p<0.002	16.8 (15.0-18.5)	12.1 (11.5-12.7)	16.2 (15.5-16.8)	4.0 (3.2;5.0) p<0.002	17.0 (15.0-18.9)	11.3 (10.0-12.5)	13.1 (11.9-14.2)	1.8 (0.1;3.4) p=0.04	15.6 (10.7-20.8)
Hospitalisation for suicide attempt§	1.5 (1.3-1.7)	1.4 (1.2-1.6)	-0.1 (-0.3;0.2) p=0.6	1.6 (1.1-2.1)	1.7 (1.5-2.0)	1.5 (1.3-1.8)	-0.2 (-0.5;0.1) p=0.2	1.8 (1.2-2.4)	0.3 (0.1-0.6)	0.7 (0.4-1.1)	0.4 (-0.1;0.8) p=0.1	1.2 (0.0-2.5)
Death§	1.1 (0.9-1.3)	1.4 (1.2-1.5)	0.3 (0.0;0.5) p=0.03	1.9 (1.2-2.6)	0.6 (0.4-0.7)	0.6 (0.5-0.7)	0.1 (-0.01;0.2) p=0.6	0.4 (0.2-0.6)	3.3 (2.5-4.2)	4.5 (3.8-5.2)	1.2 (0.1;2.3) p=0.04	7.4 (4.1-11.0)

Table 2. Treatment outcomes according to age and treatment strategy and adjusted difference in cumulative incidence for SGAPs vs MSs at one year after treatment initiation (in % with 95% confidence intervals) (continued)

	Whole study population				Aged 21 to 64 years				Aged 65 and over			
	MS (n=8225)	SGAP (n=9342)	Difference SGAPs vs MSs	MS and SGAP (n=2519)	MS (n=6775)	SGAP (n=7268)	Difference SGAPs vs MSs	MS and SGAP (n=2181)	MS (n=1450)	SGAP (n=2074)	Difference SGAPs vs MSs	MS and SGAP (n=338)
Other outcomes												
Partial discontinuation				59.6 (57.3- 61.7)				60.3 (57.9- 62.8)				56.4 (49.4- 62.8)
Treatment mean duration before failure (m, SD)	151.3 (77.5)	147.8 (77.0)		169.9 (79.7)	150.9 (76.8)	146.3 (76.9)		169.5 (79.7)	153.8 (80.7)	153.0 (77.3)		173.5 (80.7)
Psychiatric hospitalisation§¶	20.3	25.2		23.1	21.0	27.0		23.6	16.6	19.1		20.1
Hospitalisation for suicide attempt§¶	3.5	3.5		2.3	4.0	4.1		2.5	1.1	1.3		1.2
Death§¶	1.8	3.0		1.8	1.0	1.4		1.0	5.7	8.5		7.1

†: adjusted cumulative incidence in first twelve months of treatment, only first of all possible events was taken into account; ‡: considering only complete discontinuation for combinations MS + SGAP; §: after 56 days of treatment; ¶: crude proportion, over twelve months of follow-up, without stopping when another type of outcome occurred;

MS: mood stabilizer, SGAP: second-generation antipsychotic marketed for bipolar disorder

Table 3. Adjusted cumulative incidence of outcomes at one year after treatment initiation according to drug and age group (in % with confidence intervals)

	Mood stabilizers***					Second-generation antipsychotics***			Combination	
	Lithium	Valpromide	Divalproate	Carbamazepi	Lamotrigine	Olanzapine	Aripiprazole	Risperidone	Quetiapine	
	ne									
Patients aged 21-64	n=823	n=1,805	n=3,058	n=402	n=607	n=1,977	n=2,275	n=1,647	n=1,252	n=2,378
Treatment failure†	80.6 (78.2-83.1)	77.1 (75.5-78.8)	83.2 (82.1-84.3)	79.5 (76.5-82.6)	70.9 (67.5-74.3)	81.6 (80.2-83.0)	79.1 (77.7-80.5)	84.1 (82.7-85.6)	74.4 (72.0-76.7)	74.7 (73.1-76.4)
Discontinuation‡	50.2 (46.9-53.5)	48.1 (46.0-50.2)	55.1 (53.8-56.3)	44.1 (39.5-48.7)	34.0 (30.4-37.6)	42.5 (40.8-44.3)	46.2 (44.7-47.8)	52.2 (50.0-54.3)	39.8 (37.4-42.1)	39.3 (37.3-41.3)
Switch	7.6 (5.8-9.4)	8.6 (7.5-9.7)	7.9 (7.2-8.6)	12.5 (9.6-15.4)	11.4 (8.7-14.0)	13.5 (12.3-14.8)	11.0 (10.1-12.0)	12.4 (10.9-13.8)	12.0 (10.5-13.5)	15.5 (13.9-17.1)
Addition	10.1 (8.2-12.0)	6.3 (5.4-7.2)	7.4 (6.6-8.1)	8.5 (6.0-10.9)	9.6 (7.6-11.7)	8.8 (7.8-9.9)	5.7 (4.8-6.5)	4.8 (3.9-5.8)	4.9 (3.8-5.9)	3.8 (2.9-4.7)
Psychiatric hospitalisation§	11.1 (9.4-12.8)	11.7 (10.3-13.2)	10.7 (9.9-11.6)	12.0 (8.7-15.3)	14.0 (11.3-16.7)	14.3 (13.0-15.6)	14.9 (13.8-16.0)	13.1 (11.9-14.4)	15.7 (13.8-17.6)	14.3 (13.0-15.6)
Hospitalisation for suicide attempt§	1.2 (0.6-1.8)	1.7 (1.2-2.3)	1.7 (1.2-2.1)	2.4 (0.8-4.0)	1.3 (0.6-2.0)	1.8 (1.3-2.3)	1.0 (0.7-1.2)	1.1 (0.6-1.5)	1.6 (1.0-2.2)	1.7 (1.1-2.2)
Death§	0.4 (0.1-0.8)	0.7 (0.3-1.0)	0.5 (0.3-0.7)	0.1 (0.0-0.2)	0.6 (0.0-1.4)	0.6 (0.3-0.9)	0.3 (0.1-0.5)	0.6 (0.4-0.9)	0.4 (0.2-0.7)	0.2 (0.1-0.3)

Table 3. Adjusted cumulative incidence of outcomes at one year after treatment initiation according to drug and age group (in % with confidence intervals)
(continued)

Patients aged 65+	n=128	n=454	n=583	n=107	n=165	n=507	n=326	n=1,027	n=197	n=368
Treatment failure†	82.0 (73.2-90.8)	62.8 (58.1- 67.4)	74.8 (71.9- 77.7)	73.2 (60.6- 85.8)	61.3 (46.5- 76.2)	65.3 (61.6- 69.0)	73.8 (68.9- 78.8)	82.6 (78.4- 86.7)	73.1 (62.6- 83.6)	58.9 (53.- 64.6)
Discontinuation‡	64.7 (52.1-77.2)	36.2 (32.4- 40.0)	47.3 (44.1- 50.4)	57.6 (45.1- 70.0)	33.2 (21.3- 45.1)	35.7 (31.3- 40.1)	42.1 (36.4- 47.9)	57.1 (45.3- 68.9)	44.9 (36.1- 53.7)	26.6 (20.0- 33.1)
Switch	6.0 (0.9-11.1)	5.6 (3.4-7.7)	6.1 (4.5-7.7)	2.5 (0.0-6.7)	3.8 (0.5-7.1)	5.4 (3.7-7.1)	5.6 (3.6-7.6)	3.9 (2.5-5.3)	3.6 (2.0-5.1)	6.3 (4.3-8.4)
Addition	3.6 (0.0-9.9)	5.9 (3.9-8.0)	7.5 (5.9-9.1)	1.4 (0.0-2.7)	10.4 (2.8- 18.0)	6.0 (4.0-7.9)	5.8 (3.2-8.4)	3.3 (2.1-4.5)	6.8 (0.0-15.2)	2.8 (0.6-4.9)
Psychiatric hospitalisation§	5.4 (0.0-11.0)	11.5 (9.3- 13.8)	10.1 (8.3- 12.0)	10.5 (3.5- 17.5)	9.5 (3.8-15.1)	13.7 (11.1- 16.4)	14.9 (11.1- 18.7)	13.2 (0.0- 30.6)	15.6 (9.8- 21.5)	14.8 (10.6- 18.9)
Hospitalisation for suicide attempt§	0.3 (0.0-0.9)	0.0 (0.0-0.0)	0.4 (0.0-0.8)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.9 (0.1-1.6)	1.1 (0.0-2.2)	0.4 (0.1-0.6)	0.0 (0.0-0.0)	1.0 (0.0-2.2)
Death§	2.0 (0.0-6.0)	3.5 (1.6-5.5)	3.5 (2.1-4.9)	1.3 (0.0-4.2)	4.5 (0.7-8.2)	3.7 (2.3-5.1)	4.3 (1.4-7.1)	4.6 (3.3-6.0)	2.2 (0.0-6.0)	7.4 (2.0-12.8)

†: adjusted cumulative incidence in first twelve months; only first of all possible events taken into account; ‡: considering only complete discontinuation for combinations MS + SGAP; §: after 56 days of treatment; ¶: in monotherapy; MS: mood stabilizer, SGAP: second-generation antipsychotic marketed for bipolar disorder

Table 4. Most frequent additions of treatment (>1.0% among 1206 patients with an addition) and switches of treatment (>1.0% among 1983 patients with a switch) as first treatment outcome over follow-up (n; %)

Initial drug	lithium	valpromide	valproate	lamotrigine	olanzapine	aripiprazole	risperidone	quetiapine
Added drug								
lithium			13; 1.1%			13; 1.1%		
valpromide					15; 1.2%	17; 1.4%		
valproate					50; 4.1%	41; 3.4%	33; 2.7%	20; 1.7%
lamotrigine			13; 1.1%					
olanzapine		26; 2.2%	47; 3.9%					
aripiprazole	20; 1.7%	29; 2.4%	76; 6.3%	17; 1.4%	63; 5.2%		18; 1.5%	13; 1.1%
risperidone		31; 2.6%	45; 3.7%					
quetiapine	18; 1.5%	19; 1.6%	52; 4.3%	22; 1.8%	29; 2.4%	24; 2.0%		

Table 4. Most frequent additions of treatment (>1.0% among 1206 patients with an addition) and switches of treatment (>1.0% among 1983 patients with a switch) as first treatment outcome over follow-up (n; %) (continued)

Subsequent drug							
lithium		29; 1.5%					
valpromide		39; 2.0%			22; 1.1%	22; 1.1%	
valproate	56; 2.8%		20; 1.0%	42; 2.1%	47; 2.4%	28; 1.4%	29; 1.5%
lamotrigine	21; 1.1%	26; 1.3%			24; 1.2%		
olanzapine		32; 1.6%			45; 2.3%	52; 2.6%	
aripiprazole	29; 1.5%	53; 2.7%		93; 4.7%		57; 2.9%	48; 2.4%
risperidone		22; 1.1%		51; 2.6%	35; 1.8%		
quetiapine		45; 2.3%		53; 2.7%	62; 3.1%	35; 1.8%	

Carbamazepine was deleted as not concerned either by addition or switch.