TREATMENT PATTERNS, ADHERENCE AND CLINICAL OUTCOMES IN BIPOLAR DISORDER TYPE I: A SYSTEMATIC REVIEW OF OBSERVATIONAL STUDIES

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INTRODUCTION

- Bipolar disorder type I (BD-I) is characterized by at least one manic episode; major depressive episodes can occur as well, however, they are not necessary for diagnosis of BD-I.
- The primary goal of this study was to perform a systematic review of the literature on real-world data from observational studies about the treatment of bipolar disorder (BD); especially the patterns-of-care, adherence, and clinical outcomes of second-generation atypical antipsychotics (SGA).
- The secondary objectives were to describe and evaluate the types of observational studies and databases available for BD-I in the US.

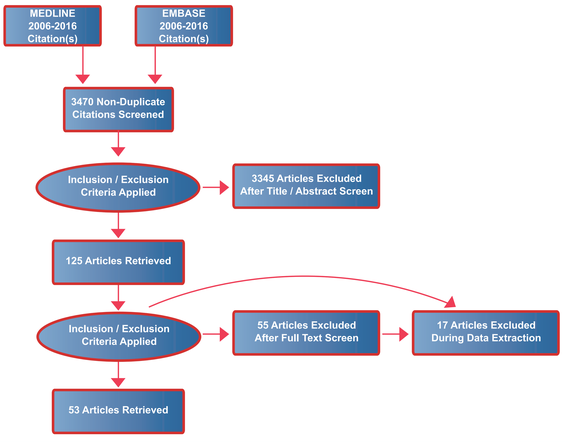
METHODOLOGY

- A systematic review was performed using MEDLINE, EMBASE; the National Health System Economic Evaluation Database (NHS EED) and the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) database.
- The search strategy was developed to include all observational studies in BD (specified in eligibility criteria) that involved at least one treatment, regardless of type, objective and quality. This strategy was robust enough to address all objective questions (patterns of care, adherence and clinical outcomes).
- The search was limited to a 10-year period (2006-2016). Inclusion criteria: original research in the US population; patients with BD-I; at least one type of therapy in use; studies of patterns of care; studies of adherence to treatment; studies of specific therapies (atypical antipsychotics) evaluating clinical outcomes.
- Exclusion criteria: sample size lower than 100 patients; safety, quality of life, heterogeneity of treatment effects, natural history, burden of disease and cost-of-illness studies; randomized controlled trials, naturalistic studies in which the intervention was determined by the study protocol; psychotherapy, social therapy, nutrition, alternative medicine and ECT (electroconvulsive therapy); studies of specific therapies other than atypical antipsychotics (i. e. studies of lithium or valproate.)

RESULTS

- A total of 53 studies were included (Figure 1). They addressed pattens of care and adherence, and also clinical outcomes.

Figure 1. PRISMA Flow Diagram



Patterns of care

- Research has shown that about 45% of patients with BD received pharmacological treatment in a 12-month period, and this proportion seemed to be consistent throughout the last decade.
- More current data estimated that SGA monotherapy was prescribed for about 45% of patients with BD as the first antimanic therapy.
- Considering all patients currently receiving medication for BD, SGAs are prescribed (as monotherapy or as a component of polytherapy) for approximately 45% to 50% of that population.
- Data on mood stabilizers (e.g.: lithium, anticonvulsants) showed that they were prescribed for 65% to 80% of patients.
- Monotherapy with an SGA was the most common approach for initial therapy, although polypharmacy was frequently used. SGA and mood stabilizer combinations were prescribed to 50% to 70% of patients during their follow-up.
- Most patients were treated according to recommendations from clinical practice guidelines. Adherence to guidelines was reported to range from approximately 50% to 83% of prescriptions.

Adherence

- Medication possession ratio (MPR), defined as the ratio of the number of doses dispensed relative to the dispensing period, was the most commonly used measure of adherence.
  - MPR ≥ 80% has been considered as a marker for appropriate adherence to therapy.
- Although some research reported extremely poor adherence rate (mean MPR of only 15% to 25% and MPR ≥80% for only 6% to 10% of patients receiving SGA), most studies reported a somewhat better adherence ranging from 40% to 60%, up to 75% MPR.
- The mean duration of SGA use ranged from 175 to 290 days over a 12-month period of observation, but persistence (defined as the time from starting an index therapy up to a time when a gap of 15 to 30 days in prescription fills occured) usually is described as around 100 days.
- Reasons for nonadherence were diverse, but the most consistent ones were:
  - younger age;
  - baseline substance use disorder;
  - higher disease burden, with a greater number of symptoms;
  - side effects as a cause for frustration;
  - comorbid anxiety or obsessive-compulsive disorder.

Clinical Outcomes

- Clinical outcomes were defined as any therapy benefit for the patient directly linked to the disease, not regarding safety, resource use or costs.
- The main outcomes evaluated addressed hospitalization: risk and rate of hospitalization, time to hospitalization and length of hospitalization.
- A total of 19 studies were included and subdivided in two groups: studies clearly designed to obtain the value of a single SGA and studies that evaluated the SGA class (Tables 1 and 2).

Table 1. Studies designed to obtain the value of a single SGA

First author, year (ref.)	Study type and Source	Study overview	Main Results
Järbrink, 2009 (2)*	RDA, Premier Perspective™ Inpatient Hospital Database	Premier Perspective™ Inpatient Hospital Data	Quetiapine XR significantly reduced length of hospitalization on patients with BD (0.23 days, p<0.001)
Locklear. 2013 (3)	RDA, HealthCore Integrated Research Database	N=3,049. Patients with BD. Quetiapine XR vs quetiapine IR. Treatment patterns, healthcare resource use, and costs.	Differences were found in patterns of care and dosing but not in health care resource use and costs
Locklear. 2014 (4)	RDA, Premier Perspectives™ inpatient hospital Database	N=30,429. Patients with schizophrenia and BD (separate analysis). Quetiapine XR vs quetiapine IR. Hospitalization length and costs.	Length of stay statistically lower with quetiapine XR. No significant differences in costs among the groups.
Bonafede, 2015 (5)	RDA, Truven Health Analytics MarketScan Hospital Drug Database	N=3,088. Patients with BD-I. Quetiapine XR vs quetiapine IR. Hospitalization length.	No statistically significant differences between groups. By excluding an outlier, XR has longer length of hospitalization
Kreys, 2013 (6)	RDA, Acute psychiatric hospital in an academic medical center	N=336. Patients with BD. Aripiprazole vs. quetiapine. Treatment continuation and hospital readmission.	No statistically significant differences in continuation and 30-day hospital readmission.
Kim, 2009 (7)	RDA, Ingenix I3/LabRx claim data	N= 6,262. Patients with BD. Aripiprazole vs other adjunctive SGAs. Time to hospitalization.	Patients using aripiprazole as adjunctive therapy had longer time to hospitalization in comparison to the other adjunctive SGA.
Kim, 2011 (8)	RDA, Ingenix I3/LabRx claim data	N= 7,169. Patients with BD. Aripiprazole vs other SGAs (monotherapy or adjunctive to MS. 1-year risk of hospitalization and cost.	Risk of hospitalization: Aripiprazole < ziprasidone, quetiapine and olanzapine. Total health care cost: aripiprazole < ziprasidone and quetiapine.
Ulcickas Yood, 2010 (9)	RDA, 3 claims databases (KPNC, HealthCore Integrated Research Network and Henry Ford Health System)	N=20,489. Patients with schizophrenia and BD. Aripiprazole vs other SGAs. Incidence of suicide events.	No statistically significant differences between aripiprazole and other SGAs.
Brooks, 2011 (10)*	Naturalistic observational study, STEP-BD	N=282. Patients with BD. Ziprasidone. Adherence to ziprasidone in adjunctive therapy	Ziprasidone had low nonadherence rate (4%). Profiles linked to nonadherence were not found.
Chitnis, 2015 (11)	RDA, Truven MarketScan® / Encounters Database and Truven Medicare Supplemental Coordination of Benefits Database	N=1,403. Patients with BD-I. Asenapine. Impact of asenapine on healthcare utilization and costs.	Initiation of asenapine significantly decreased the length of hospitalization.
Signorovitch, 2011 (12)*	RDA, Medicaid	Patients with schizophrenia and BD. Assess the short-term impact of police change in Florida (classified olanzapine as non-preferred)	There was a great discontinuation of olanzapine which increased hospitalization and ER visits (difference statistically significant).
Zhu, 2007 (13)	RDA, PharMetrics Integrated Database	N=1,516. Patients with BD. Olanzapine vs quetiapine and risperidone. Patterns of care and costs	Olanzapine was more likely to be used as monotherapy for BD. Annual healthcare costs of olanzapine and risperidone were similar (considerably lower than quetiapine or ziprasidone).

*XR: Extended release. IR: immediate release. SGA: second generation (atypical) antipsychotic. FGA: first generation (typical) antipsychotic. MS: mood stabilizers. RDA: Retrospective Database Analysis. *Available only in abstract. **When there was no information regarding sponsoring it was classified as unidentified, 0 meaning that the study can be not sponsored or sponsored but we could not access information (e.g.: abstracts).*

Table 2. Studies that evaluated the SGA class

First author, year (ref.)	Study type and Source	Study overview	Main Results
Chen,2014 (14)	RDA, Medicaid Analytic eXtract (MAX)	N=7,423. Patients with BD. SGA vs MS. Hospital admission, discontinuation and augmentation.	Comparable outcomes in hospitalization. Lower discontinuation and augmentation with SGA.
Gianfrancesco, 2007 (15)	RDA, PharMetrics Integrated Database	N=10,037. Patients with BD and mania. SGA monotherapy vs FGA. Hospitalization rates.	Olanzapine had significantly lower hospitalization rates vs risperidone and quetiapine. No other differences found.
Yerevanian 2007 (16)	RCR, Veterans Administration (VEGLAHS)	N=405. Patients with BD and schizoaffective. SGA monotherapy vs SGA plus MS vs MS. Effects on suicidal behavior.	SGA mono or combined therapy was associated with higher risks of suicidal behavior compared to MS monotherapy.
Koek 2012 (17)	RCR, Veterans Administration (VEGLAHS)	N=405. Patients with BD and schizoaffective. SGA or FGA as monotherapy or plus MS. Rates of suicidal behavior.	Monotherapy: Higher rates of suicidal behavior for FGA class vs each SGA or SGA class. Combined to MS: no differences among each SGA or FGA vs SGA.
Lang, 2010 (18)**	RDA, PharMetrics database	N=12,100. Patients with BD-I. Antipsychotics. Risk of AC and PR hospitalization.	27.9% had AC and 25.4% PR hospitalization. Nonadherence to antipsychotics associated with significantly greater risk of PR hospitalization.
Mehta, 2012 (19)	RDA, Medical Analytic eXtract	N=8,424. Patients with BD. SGA monotherapy vs MS monotherapy. Adherence, persistence and time to hospitalization	Differences found only in one measure of persistence: time to augmentation was higher in SGA group.
Post, 2016 (20)	Mixed type (RCT/observational), Stanley foundation network	N=429. Patients with BD. All therapies. Patterns of drugs utilization and outcomes by group of poor prognosis factor (PPF).	SGA group: more used in BD-I than BD-II, and more used in US than Europe, although with lower success rates (15.8% vs. 31.0%) Least success in rapid cycling, >20 episodes and patents with more than 3 PFFs.

*AC: all-cause and PR: psychiatric-related (referring to cause of hospitalization). FGA: first generation (typical) antipsychotic. MS: mood stabilizers. PPR: poor prognosis factor. RDA: Retrospective Database Analysis. RCR: Retrospective Chart Review. SGA: second generation (atypical) antipsychotic. .*Available only in abstract. **Available only in poster. ***When there was no information regarding sponsoring it was classified as unidentified, meaning that the study can be not sponsored or sponsored but we could not access information (e.g.: abstracts).*

DISCUSSION

- Bipolar disorder (including BD-I) is a chronic condition, and clinical practice guidelines recommended treatments for both acute episodes and as a maintenance therapy for prevention of relapses. However, only 45% of the patients received treatment.
- There were several limitations observed in the research addressing patterns of treatment for BD.
  - Most studies described only data about BD as a broadly defined condition, with few specifically addressing BD-I.
  - Most studies covered a wide time span, including periods in which some antipsychotics have just been approved by the FDA, which limited our observation of a reliable assessment of more current medication choices.
  - Moreover, there were no data addressing each treatment phase (i.e., acute episode or maintenance therapy).
  - Finally, there were scarce data on prevalence of long-acting injectable (LAI) antipsychotic prescription and adherence or persistence patterns for these agents.
- The main type of analyses was retrospective claims database and very few chart reviews were detected. Claims analyses bring valuable information but lack clinical details that can hinder the investigation of outcome drivers and identification of confounding variables.
- Most common SGAs had at least one publication, however, for risperidone injectable, no study met the eligibility criteria.

CONCLUSION

- Observations from real-world evidence are essential components in economic models development and the decision-making process. This review showed which patterns-of-care are adopted in clinical practice for the treatment of patients with BD (including those with BD-I) as well as adherence and clinical outcomes studied.

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