Table 1. Summary Findings on Outcomes During Complex Polypharmacy in Observational Studies of Patients With BD

Authors	Study Type (n)	Main Findings
I. Bipolar Disorder		
Frye et al[1]	Retrospective review of outcomes among National Institute of Mental Health (NIMH) intramural study participants (n = 178)	Increasing numbers of medications needed to achieve remission over successive years from 1974 to 1996
Adeponle et al[2]	Cross-sectional review of 2 regional Nigerian outpatient clinics (n = 278)	92% took ≥ 2 medications; any polypharmacy in 21.1% of affective disorder patients versus 46.1% with schizophrenia
Adli et al[3]	3-month survey of German outpatient academic centers; ChronoRecord software captured a mean of 114.7 days per patient (n = 80)	93.4% received at least simple polypharmacy (mean = 3.8 medications). Most (72.5%) had bipolar I disorder (BD I); mean of 2.43 hospitalizations; 28.8% deemed disabled
Assion et al[4]	Retrospective study of 10 German clinics (n = 300)	75% took ≥ 2 medications. Antipsychotics were used in 87%–97% of individuals with bipolar disorder or schizoaffective disorder
Baek et al[5]	BD I or II patients across 10 Korean academic hospitals since 2009 (n = 1,447)	In all phases, polypharmacy picked for initial treatment in > 80% (most favored was mood stabilizer and antipsychotic). Antipsychotics prescribed in > 80% across all phases. Antidepressants were used in 15%–40%
Golden et al[6]	Longitudinal cohort study of discharges of inpatients with bipolar disorder from the Institute of Living (n = 2,712)	Complex polypharmacy more common in BP I depression (48.2%) than BP I manic (12.3%) and BP II patients and associated with being female and White and having psychotic features, comorbid borderline personality disorder, posttraumatic stress disorder, or another anxiety disorder. Lithium use not associated with complex polypharmacy
Nierenberg et al[10]	Bipolar CHOICE (Clinical Health Outcomes Initiative in Comparative Effectiveness) trial comparing adjunctive quetiapine or lithium to existing medications in adjunctive lithium recipients (n = 240)	Comparable (nonsignificantly different) rates of improvement with either augmentation; lithium better tolerated than quetiapine
Wingård et al[11]	Naturalistic 1-year follow-up after index mania using the Swedish National Registry (during 2006–2014); 5,713 hospitalizations for mania (3,772 subjects)	Among 204 subjects taking ≥ 3 medications (lithium plus divalproex plus an atypical antipsychotic), risk for medication switch, discontinuation, or rehospitalization was lower than for those taking antipsychotic monotherapies. An earlier analysis[19] showed that rehospitalization rates 1 year after an index manic episode were comparable among complex pharmacotherapy recipients and those taking fewer medications
Gonzalez-Pinto et al[12]	2-year naturalistic follow-up after index mania; Bipolar EMBLEM (European Mania in Bipolar Longitudinal Evaluation of Medication) cohort (n = 1,076)	Combination therapy groups (both simple and complex) had significantly lower rates of treatment adherence, more frequent anticholinergic use, and more tremor and sexual dysfunction than seen with olanzapine monotherapy. Monotherapy versus combination-therapy groups did not differ in time to discontinuation, improvement, or recovery
Peselow et al[14]	2-year naturalistic follow-up after index manic episode in New York Freedom from Fear Program; treatment with lithium ± divalproex ± carbamazepine (n = 1,312)	Significantly higher relapse rates at 2 years for those taking ≥ 3 medications (41.9%) or 2 mood stabilizers (43.9%) than those taking 1 mood stabilizer (22.8%)
Goldberg et al[15]	Patterns of lithium, anticonvulsants, antidepressants, and antipsychotics examined from bipolar disorder subjects entering STEP-BD (Systematic Treatment Enhancement Program for Bipisorder) in 1999–2005 (n = 4,035)	Risk of complex polypharmacy increased if subjects had ever taken an atypical antipsychotic, had ≥ 6 lifetime depressive episodes, attempted suicide, and had an annual income of $75,000 or more
Levine et al[16]	Review of 1995–1996 outpatient bipolar disorder registry (n = 457)	No differences observed in monotherapy or simple or complex polypharmacy regimens across age, sex, education, marital status; clinical outcomes not reported
Post et al[17]	Naturalistic treatment outcomes in the Stanley Bipolar Network (n = 429)	A mean of 2.98 medications was needed over 18 months to achieve remission for at least 6 months; responders took fewer antidepressants or antipsychotics than nonresponders
Weinstock et al[18]	Retrospective chart review from Brown University/Butler Hospital (n = 230)	Complex polypharmacy (≥ 4 drugs) occurred in 36% of cases. Complex polypharmacy recipients were more likely to be female and depressed, have a comorbid anxiety disorder, and have a history of a suicide attempt. No difference was found based on ethnicity or race, civil status, insurance, or history of prior hospitalizations
Kim et al[20]	Research from the Asian Psychotic Prescription Pattern for Bipolar Disorder (REAP-BD) study from 16 Asian countries (n = 348)	Simple or complex polypharmacy associated with younger age, more extensive inpatient treatment, shorter duration of untreated illness, less use of antidepressants, more use of anxiolytics, mania polarity at illness onset, and overweight/obesity
Quante et al[21]	2006 German outpatient 3-month epidemologic study (n = 306)	Combination therapy was more common in patients with mixed episodes (58%) or rapid cycling (55%) than pure-polarity phases of illness
Lyall et al[22]	Prescribing data from electronic Scottish Morbidity Records from 2009 to 2016 (n = 23,135)	Complex polypharmacy rates changed minimally from 2009 (15%) to 2016 (17%)
Baldessari et al[23]	2005 prospective study of adherence from US national data sample from 131 randomly selected prescribing psychiatrists (n = 429)	Nonadherence was rarer than with monotherapy and was associated with alcohol dependence, youth, greater affective morbidity, side effects, comorbid obsessive-compulsive disorder (OCD), and recent recovery from mania or hypomania. Unrelated factors: sex, diagnostic subtypes, other comorbidities
Baldessarini et al[24]	US national health claims from 2000 to 2004 examining polypharmacy and adherence (n = 7,406)	Initial prescriptions involved only 1 medication in 67% of patients and 2 or more in 33% of patients. At 1 year, 31% of patients received monotherapy and 32% received any polytherapy. Polypharmacy was less likely with lithium than with anticonvulsants. Anticonvulsant adherence at 1 year was greatest with lamotrigine
Bauer et al[25]	Self-reported daily medication analysis over 6 months (n = 450)	75% took stable simple or complex polypharmacy. About half of stable polypharmacy patients took an antidepressant. No pattern found between stable drug combinations
Bauer et al[26]	Self-reported mood and medication adherence over 6 months (n = 312)	No significant association between adherence and daily number of medications versus pills. Subjects with lower adherence took smaller doses of mood stabilizers
Bjørklund et al[27]	Cohort study from annual cross-sectional examination of medication use (1995–2012) in the Danish Psychiatric Central Research Register (n = 20,618)	Simple or complex polypharmacy increased significantly from 1997 (55.7%) to 2012 (61.0%) except in patients over age 70 years. The proportion receiving lithium, typical antipsychotics, and benzodiazepines/sedatives decreased. The proportion receiving antidepressants, atypical antipsychotics, and anticonvulsants increased. The proportion of patients on treatment with antidepressants decreased from 20.5% in 1997 to 12.1% in 2012, and monotherapy decreased from 47.7% to 23.9%
Garver et al[28]	Retrospective claims database (1998–2004) comparing racial differences in polypharmacy (n = 1,113)	More Black individuals received ≥ 2 medications from different classes (41.1% compared to 34.7%) and switching or concomitant medications than non-Black individuals
Jaracz et al[29]	Chart review of discharges from 5 psychiatric facilities in Poland (n = 127)	Considering only mood stabilizers, second-generation antipsychotics, and lamotrigine, 61% of patients took 2, 21.3% took 3, and 1 took 4 medications. Mood stabilizer + atypical antipsychotic was the most common simple polypharmacy (48%). No association between polypharmacy and age, duration of illness, and global improvement
Peh and Tay[30]	Record review of two private outpatient practices in Singapore from 1999 to 2003 (n = 121)	46% received combinations of mood stabilizers, antipsychotics, and antidepressants. 34% incurred a delayed correct diagnosis by > 2 years
Sachs et al[31]	Cross-sectional assessment of personality features and polypharmacy in consecutive patients from Massachusetts General Hospital bipolar clinic (n = 89)	Low openness, low extraversion, and low conscientiousness may be associated with increased psychotropic medication use
Kupfer et al[32]	Cohort study within the Stanley Center Bipolar Disorder Registry (Pittsburgh) (1995–1999) (n = 2,839)	More than a third took complex polypharmacy; half had attempted suicide
Fung et al[33]	Secondary analysis of adult bipolar disorder participants in the Bipolar CHOICE trial (n = 482)	Complex polypharmacy found in 43% and associated with nonadherence but not greater side effect burden. 16% of complex polypharmacy recipients achieved remission. Remission was less likely in those with poor adherence, comorbid social or generalized anxiety disorder, or BD I vs II diagnoses
Adachi et al[34]	Cross-sectional nationwide survey of 176 Japanese outpatient clinics (MUSUBI) (n = 3,130)	Patients took a mean of 3.5 ± 0.8 medications. Number of drugs was associated with poor social adjustment, psychiatric comorbidities, and duration of illness
II. Bipolar Depression		
Greil et al[13]	Observational cross-sectional prescription data from European psychiatric hospitals in inpatients from 1994 to 2009 (n = 2,231)	81.3% received antidepressants (7.8% as monotherapy), 57.9% antipsychotics, 50.1% anticonvulsants, 47.5% tranquilizers, and 34.6% lithium. Use over time decreased with lithium and increased for anticonvulsants, antipsychotics, and tranquilizers; was stable for antidepressants; and increased for quetiapine, lamotrigine, and valproate
Howland[35]	Cross-sectional assessment of depressed inpatients with bipolar disorder at Pittsburgh Western Psychiatric Institute and Clinic (n = 69)	Polypharmacy more common among patients with psychosis; antidepressant use observed in about half of depressed bipolar patients