Safety and Tolerability Associated With Second-Generation Antipsychotic Polytherapy in Bipolar Disorder: Findings From the Systematic Treatment Enhancement Program for Bipolar Disorder

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Context: Practitioners often combine 2 or more second-generation antipsychotics (SGAs) in patients with bipolar disorder, despite an absence of data to support their safety, tolerability, or efficacy.

Objective: This study sought to evaluate the safety and tolerability of SGA polytherapy compared to SGA monotherapy in bipolar disorder patients receiving open naturalistic treatment in the 22-site Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD).

Method: A longitudinal cohort of 1,958 patients who were prescribed at least 1 SGA was drawn from 4,035 bipolar patients in STEP-BD recruited between November 1999 and July 2005 and assessed at least quarterly for a mean duration of 21 months. Main outcome measures were the mean quarterly prevalence of adverse events, medical and psychiatric service usage, Global Assessment of Functioning ratings, and percentage of days spent well.

Results: Almost 10% of patients taking SGAs were prescribed SGA polytherapy. After controlling for illness onset, age, baseline illness severity, and medication load, patients prescribed SGA polytherapy, compared to monotherapy, exhibited more dry mouth (number needed to harm [NNH] = 4), tremor (NNH = 6), sedation (NNH = 8), sexual dysfunction (NNH = 8), and constipation (NNH = 11) and were almost 3 times as likely to incur more psychiatric and medical care; there was no association with greater global functioning scores or percentage of days spent well.

Conclusions: Although SGA polytherapy was fairly common in bipolar disorder, it was associated with increased side effects and health service use but not with improved clinical status or function. Thus, SGA polytherapy in bipolar disorder may incur important disadvantages without clear benefit, warranting careful consideration before undertaking such interventions.

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Bipolar disorder has a significant impact on work and interpersonal functioning[1] and gave rise to annual health care costs of over $45 billion US dollars in 1991.[2] The high health care costs are partly attributable to the expanding repertoire of medications with indications for the treatment of bipolar disorder. For example, the clinical efficacy of monotherapy with 5 second-generation antipsychotics ([SGAs]: olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole) and adjunctive (added to lithium or divalproex) therapy with 4 SGAs (olanzapine, risperidone, quetiapine, and aripiprazole) have been established in acute mania. The use of SGAs was further broadened after US Food and Drug Administration labeling indications for bipolar depression (quetiapine or olanzapine-fluoxetine combination) or maintenance treatment after an acute response in bipolar disorder (aripiprazole, olanzapine, long-acting injectable risperidone monotherapy, and adjunctive quetiapine). Enthusiasm for using SGAs in nonpsychotic affective episodes has grown in light of negative controlled data for traditional antidepressants used as adjuncts to mood stabilizers for bipolar depression[3,4] and for some anticonvulsants previously thought to have mood-stabilizing effects, such as topiramate[5] and gabapentin.[6]

Several factors appear to be associated with complex polypharmacy in bipolar disorder, such as a history of more depressive episodes and suicidality.[7] Although inadequate efficacy of current pharmacotherapy is an expected antecedent of SGA polytherapy,[8] other notable clinical and demographic parameters include male sex,[9] age (being either younger[10] or older[9]), being unmarried,[10] making greater use of mental health services,[10] having longer illness duration,[9] and having greater psychosis or agitation.[11] Additionally, an epidemiologic study has suggested that prolonged antipsychotic cotherapy often arises as a result of incomplete cross-tapers.[8]

There are no randomized trials, and little published open-label experience, of SGA polytherapy for bipolar disorder from which to inform expectations about likely benefits or adverse effects with specific combinations. Yet, the simultaneous use of 2 or more SGAs has become increasingly common in patients with serious mood disorders, regardless of the presence of psychosis. In one study of 5 statewide Medicaid programs, the annual prevalence of SGA polytherapy was 6%, and it was associated with greater drug- and nondrug–related expenditures.[12] Although SGAs have differing receptor affinities and actions, no study to date has demonstrated pharmacodynamic synergy when combining 2 or more SGAs. The limited existing data from randomized trials involving 1 versus 2 or more SGAs are based primarily on patients with treatment-resistant schizophrenia or

schizoaffective disorder,[13] with results indicating no substantial clinical advantage for combining clozapine with aripiprazole versus placebo[14] or combining clozapine with risperidone versus placebo.[15] To date, no controlled data and only very limited observational data[16] describe SGA polytherapy compared to SGA monotherapy in the treatment of bipolar disorder, despite the propensity for such regimens to be prescribed in clinical practice.

The goals of the present study were to (1) identify the prevalence of SGA polytherapy in patients with bipolar disorder, including the most frequently chosen combinations and dosages, (2) compare clinical correlates of SGA monotherapy versus polytherapy, (3) examine tolerability (adverse effects) versus global improvement (benefits) in the setting of SGA polytherapy, and (4) obtain preliminary information about functional outcomes during naturalistic treatment involving single versus multiple SGAs in a pharmacotherapy regimen. As an exploratory hypothesis, we surmised that clinical outcomes would be statistically similar for subjects whose pharmacotherapy regimens involved 1 versus 2 or more SGAs, after controlling for baseline parameters related to illness severity and cotherapies in a multivariate analysis but that medication-related adverse events would be more prevalent for those on SGA polytherapy than monotherapy.

We used aggregate data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), a collaborative 22-site effectiveness-based interventions study sponsored by the National Institute of Mental Health. Patients were recruited into STEP-BD and treated for up to 5 years according to models of expert care as informed by current practice guidelines and evidence-based literature, rather than by algorithm or randomized treatment assignment. STEP-BD sought to maximize generalizability by imposing few subject exclusion criteria, thereby providing an optimal platform for assessing moderators and mediators of outcome for typical patients who seek treatment for bipolar disorder.

METHOD

The overall design and scope of the multisite STEP-BD study has been described previously.[17] Briefly, subjects were at least 15 years old, met *DSM-IV* criteria for any type of bipolar disorder (I, II, not otherwise specified), and were recruited for participation across 22 centers in the United States between November 1999 and July 2005. Research diagnoses were made using the Mini International Neuropsychiatric Interview (MINI, Version 5.0),[18] administered by a trained master's- or doctoral-level research clinician (psychiatrist, psychologist, social worker, or psychiatric nurse). Past psychiatric history, including comorbid Axis I and Axis II diagnoses, and past treatments, was recorded from a semistructured interview (the Affective Disorders Evaluation [ADE]).[17] The mean duration of follow-up for the current group of patients was 21.3 months (SD = 0.35). All subjects provided written informed consent to participate in the study protocol, which was approved by the respective institutional review board at each of the STEP-BD study sites.

The current study focused on patients who participated in STEP-BD and were prescribed at least 1 SGA. Study exclusion criteria were kept to a minimum to optimize the generalizability of findings to patients seen with bipolar disorder under ordinary clinical conditions.

The STEP-BD Clinical Monitoring Form (CMF)[19] was used to collect data on fluctuations in mood state, functioning, medication, and adverse events. A CMF was completed for every patient visit, which was at least quarterly, during STEP-BD. The medication data recorded on the CMF were used to classify patients into SGA monotherapy or SGA polytherapy groups. The number of SGAs prescribed at each visit was averaged across visits. If a patient was prescribed more than 1 SGA on average, then the patient was classified in the SGA polytherapy group. Decisions to use 1 or more SGAs were based on the clinical judgment of the prescribing study physician, as reflective of "real-world" practice conditions rather than a protocol-based treatment assignment.

Adverse Events

The severity of adverse events was rated on the CMF for a series of adverse drug effects, including anticholinergic adverse effects (ie, constipation or dry mouth), other gastrointestinal problems (eg, diarrhea), extrapyramidal signs, headache, sedation, sexual dysfunction, tremor, and other complaints.

Health Service Use

Health service use was tracked quarterly through clinician reports of whether the patient had required additional medical or psychiatric care since the previous visit. For both medical and psychiatric visits, we used the total numbers of visits as indices of health care use during STEP-BD.

Functional Outcome Measures

Our measure of clinical status was the mean of quarterly assessments of Global Assessment of Functioning (GAF) over the month before each pharmacotherapy visit. The estimates of monthly GAF were used because they would be less subject to variations that might occur at the time of the visit itself. Global Assessment of Functioning scores range from 1 to 100, with higher scores indicating better functioning. To assess the overall level of functioning throughout the study, we computed mean GAF scores across all STEP-BD visits. Health service use during STEP-BD was tracked quarterly through clinician reports of whether the patient had required additional medical or psychiatric care since the previous visit.

Clinical Outcome Measures

We computed an estimate of the percentage of days spent well to measure general clinical status.[20] Using clinician ratings from the ADE and CMF, patients were classified as well if (1) they were rated as "recovered" or "recovering"[17]; (2) fewer than 3 items of the Montgomery-Asberg Depression Rating Scale (MADRS)[21] had a score ≥ 4; (3) fewer than 3 items of the Young Mania Rating Scale (YMRS)[22] were

scored in the top half; (4) no serious adverse events were reported. If patients were classified as well at 2 consecutive visits, the days between those visits were classified as "well days." If a patient's status changed between 2 visits, then half of the days between visits were classified as well days. The percentage of days well was computed by dividing the total well days by the total time of enrollment in STEP-BD.

Statistical Analyses

With large samples, statistical significance can be somewhat misleading in that some comparisons may be statistically significant but not clinically meaningful. Thus, our results focus on measures of effect size for those comparisons that are significant at least at the $P < .01$ level. Between-group (ie, 1 SGA or more than 1 SGA) comparisons on dichotomous and continuous variables are presented using χ^2 and *t* tests, respectively. Because our sample size allows for relatively small effect sizes to be statistically significant, we provide Cohen *d*[23] as an effect size measure in our results. Effect sizes of 0.2 or less are considered small, around 0.5 medium, and greater than 0.8 as large. For comparisons of adverse event data, we report the number needed to harm (NNH), which is the inverse of the attributable risk, as an index of effect size. In view of the exploratory nature of this study, corrections for multiple comparisons were not applied.

We used multiple regression analyses to evaluate the extent to which SGA polytherapy versus monotherapy predicted the occurrence of adverse events, global functioning, and health service use, while including covariates described below. For each regression, we report the t statistic associated with the unique proportion of variance accounted for by SGA use and the corresponding Cohen *d*. Additional analyses according to bipolar subtype (I versus II) are reported; the "not otherwise specified" subtype was excluded because only 5 such patients with this subtype received more than 1 SGA.

Covariates

Several measures were included to control for other factors that may have influenced whether a patient received SGA polytherapy or monotherapy. Age at illness onset was included as a covariate. To control for the effects of polypharmacy, we computed a medication load index by averaging the number of psychotropic medications (first-generation antipsychotics, second-generation antipsychotics, lithium and mood-stabilizing anticonvulsants, antidepressants, and benzodiazepines) at each visit and including this number as a covariate in all analyses. Age at study entry was included as a covariate to account for health conditions associated with advancing age.

RESULTS

Sample Comparison

The characteristics of the groups of patients receiving SGA monotherapy or polytherapy are provided in Table 1. Of the 4,035 patients in STEP-BD, nearly half (1,958) of the patients were prescribed at least 1 SGA during the study. Among these patients, almost 10% (162) were prescribed SGA polytherapy. As shown in Table 1, SGA monotherapy and polytherapy recipients were remarkably similar with respect to age, sex, age at onset, number of past affective episodes, and body mass index (BMI). Bipolar I disorder patients were no more likely to receive SGA polytherapy than bipolar II disorder patients. There was a tendency for the patients in the SGA polytherapy group to be followed longer (23.7 months, SD = 1.15) than patients in the SGA monotherapy group (21.1 months, SD = 0.36), $d = 0.09$.

Table 1. Sample Description and Predictors of SGA Monotherapy Versus SGA Polytherapy in Patients With Bipolar Disorder

Variable	1 SGA (n = 1,796)	>1 SGA (n = 162)
Age, mean (SD), y	40.3 (12.7)	38.8 (12.5)
Male sex, proportion	0.41	0.40
White, proportion	0.91	0.86
Age at onset, mean (SD), y	16.2 (3.5)	16.2 (3.7)
Bipolar disorder subtype, proportion		
Type I	0.71	0.83
Type II	0.23	0.13
NOS	0.05	0.03
No. of manic episodes, mean (SD)	4.3 (1.7)	4.4 (1.7)
No. of depressive episodes, mean (SD)	4.6 (1.6)	4.5 (1.8)
YMRS score at entry, mean (SD)	7.1 (6.9)	9.1 (7.5)
MADRS score at entry, mean (SD)	17.1 (11.0)	19.7 (11.9)
GAF score over 1 mo prior to entry, mean (SD)	58.6 (12.5)	55.3 (14.3)
History of suicide attempt, proportion	0.41	0.44
History of psychosis, proportion	0.44	0.45
Alcohol use disorder, proportion	0.10	0.06
Substance use disorder, proportion	0.13	0.11
BMI, mean (SD), kg/m^2	28.8 (7.0)	28.6 (6.8)

Abbreviations: BMI = body mass index, GAF = Global Assessment of Functioning, MADRS = Montgomery-Asberg Depression Rating Scale, NOS = not otherwise specified, SGA = second-generation antipsychotic, STEP-BD = Systematic Treatment Enhancement Program for Bipolar Disorder, YMRS = Young Mania Rating Scale.

Baseline Measures

Although a comparison of means of baseline measures and demographics does not reveal any appreciable differences between the SGA monotherapy and SGA polytherapy groups, we performed a logistic regression in which SGA therapy (monotherapy or polytherapy) was treated as the dependent measure and the sample characteristics listed in Table 1 were included as predictors. There was no evidence that any demographic or baseline variable was a statistically significant predictor of SGA polytherapy (all *P* values > .10). Thus, insofar as baseline measures characterize illness severity and potential confounding factors, none of these variables was associated with SGA polytherapy.

The prevalence of comorbid personality disorders among participants in STEP-BD was low, with only 4.7% of patients in the SGA monotherapy group receiving an Axis II diagnosis compared with 5.7% of patients in the SGA polytherapy group ($P > .05$). The frequency with which patients were diagnosed with personality disorders did not significantly differ between the SGA polytherapy group and the SGA

Table 2. Prevalence of Adverse Events Throughout STEP-BD for Entire Sample

Event	1 SGA (n = 1,796), Proportion	>1 SGA (n = 162), Proportion	NNH
Constipation	0.10	0.19	11
Diarrhea	0.11	0.14	33
Dry mouth	0.28	0.52	4
Extrapyramidal signs	0.02	0.06	25
Headache	0.29	0.32	33
Sedation	0.33	0.45	8
Sexual dysfunction	0.19	0.31	8
Tremor	0.27	0.45	6

Abbreviations: NNH = number needed to harm, SGA = second-generation antipsychotic, STEP-BD = Systematic Treatment Enhancement Program for Bipolar Disorder.

Table 3. Average Medical and Psychiatric Service Use and Global Assessment of Functioning[a] Throughout STEP-BD[b]

Bipolar Subtype	Measure	1 SGA	>1 SGA	Cohen *d*
Total sample	Service use	n = 1,749	n = 158	
	General medical treatment	2.2 (3.6)	4.0 (5.8)	0.26
	Psychiatric treatment	2.4 (5.0)	7.1 (11.1)	0.44
	Functional measure			
	GAF over past mo	62.3 (8.3)	60.4 (7.6)	0.14
	Clinical measure			
	Percent of days well	66.9 (25.2)	59.3 (25.4)	0.18
Bipolar I disorder	Service use	n = 1,249	n = 131	
	General medical treatment	2.0 (3.4)	3.6 (5.7)	0.26
	Psychiatric treatment	2.1 (4.7)	6.4 (10.0)	0.46
	Functional measure			
	GAF over past mo	63.6 (8.6)	60.4 (7.7)	0.15
	Clinical measure			
	Percent of days well	67.2 (25.7)	59.9 (25.5)	0.16
Bipolar II disorder	Service use	n = 406	n = 22	
	General medical treatment	2.8 (4.2)	6.0 (6.4)	0.33
	Psychiatric treatment	3.1 (5.6)	10.2 (15.6)	0.49
	Functional measure			
	GAF over past mo	63.0 (7.4)	62.0 (5.6)	0.06
	Clinical measure			
	Percent of days well	66.2 (23.2)	54.6 (23.7)	0.27

[a]Global assessment of functioning over the month prior to visit.
[b]Values are presented as mean (SD).
Abbreviations: GAF = Global Assessment of Functioning, SGA = second-generation antipsychotic, STEP-BD = Systematic Treatment Enhancement Program for Bipolar Disorder.

monotherapy group. Although the diagnosis of borderline personality disorder was slightly more frequent in patients prescribed SGA monotherapy (4.6%) than those prescribed SGA polytherapy (2.3%), this difference was not statistically significant ($\chi^2_1 = 2.9$, $P > .05$).

Adverse Events

The prevalence of adverse events in patients who were prescribed SGAs is provided in Table 2. Except for extrapyramidal signs, all adverse events were more common in patients receiving SGA polytherapy compared to those receiving SGA monotherapy. All of these differences were statistically significant at $P < .001$. The NNH values are provided in Table 2 for additional clinical context. The adverse effects with the greatest differential prevalence were dry mouth, tremor, sedation, and sexual dysfunction (NNH ranging from 4 to 11). Diarrhea, constipation, and headache were associated with SGA polytherapy to a lesser degree.

The findings in Table 2 suggest substantive disadvantages associated with the use of SGA polytherapy in bipolar disorder, but it is possible that SGA polytherapy was used for patients with more severe forms of bipolar disorder. Moreover, some adverse effects, such as tremor, could reflect years of use of psychotropic medications in older patients. To control for these possibilities, we performed multiple regression analyses that examined the relation of SGA group to number of adverse events, while covarying age at study entry, age at illness onset, and total number of psychotropic medications. The results of these analyses closely paralleled the pattern of results in Table 2. This finding suggests that age at study entry, age at illness onset, and medication load did not account for the observed differences between SGA monotherapy and polytherapy.

SGAs have well-documented effects on weight gain and metabolic function. STEP-BD did not track metabolic changes during the study, but weight was recorded on the CMF, and height was recorded in the ADE, so that BMI could be calculated at each visit. Initially, we performed regression analyses in which type of SGA therapy, age at illness onset, age, and number of psychotropic medications were used to predict the mean BMI over the course of the study and the mean rate of change of each patient's BMI. There were no statistically significant relations among any of the predictors and BMI or the rate of change of BMI for patients prescribed SGA monotherapy or polytherapy. The models yielded virtually identical results when carried out within the bipolar I and II disorder subsets.

Health Service Use

Presumably the prescription of a second SGA was performed with the intent to improve clinical status and, consequently, decrease the need for additional treatment. However, SGA polytherapy was associated with increased use of medical services, as shown in Table 3. Patients receiving SGA polytherapy used almost twice as much additional medical treatment and nearly 3 times as much additional psychiatric treatment compared to patients receiving SGA monotherapy.

Regression analyses confirmed that SGA polytherapy had an independent association with medical ($d = 0.26$) and psychiatric service use ($d = 0.44$), even when the effects of age, illness duration, and other psychotropic medications are accounted for. The effect sizes were approximately equal for both bipolar I and II disorders.

Global Assessment of Functioning

Second-generation antipsychotic polytherapy was associated with slightly poorer global functioning, although the associated effect size was small. The mean GAF score for patients receiving SGA polytherapy was 60.4, (SD = 7.6) and 62.3 (SD = 8.3) for those receiving SGA monotherapy,

Table 4. Combination Dosing of Second-Generation Antipsychotics (SGAs)[a]

SGA	Olanzapine	Risperidone	Quetiapine	Ziprasidone	Aripiprazole
Olanzapine	10	16/3	12/240	12/80	14/19
Risperidone	…	2	3/243	3/93	2/18
Quetiapine	…	…	269	263/98	449/16
Ziprasidone	…	…	…	92	69/13
Aripiprazole	…	…	…	…	16

[a]Dosages are in mg/d. Combination dosages for medications in the far left column are to the left of the forward slash and for co-medications in the top row are to the right of the forward slash. Single numbers on the diagonal represent dosages as monotherapy.

$d = 0.14$. A regression analysis covarying age, age at illness onset, and number of psychotropic medications indicated that SGA polytherapy had a small ($d = 0.15$) negative association with mean GAF scores over the course of STEP-BD. When the analyses of global function were broken down by bipolar subtype, it appears that the negative association between SGA polytherapy and functioning was even smaller for bipolar II disorder patients ($d = 0.06$) than it was for patients with bipolar I disorder ($d = 0.15$).

Finally, we examined the relations between GAF and adverse effects over the course of the study by using GAF as the dependent measure and adverse effects as predictors, while covarying age, age at illness onset, and number of psychotropic medications. None of the adverse effects had a statistically significant relation with GAF in these regressions (P values > .05). Thus, the lower GAF scores of the SGA polytherapy group do not appear to be attributable to an increase in adverse effects.

Clinical Status

The percentage of days well during participation in STEP-BD served as the measure of clinical status. As shown in Table 3, SGA polytherapy was associated with a lower percentage of days well for the sample overall even in a regression analysis covarying age, age at illness onset, and number of psychotropic medications ($d = 0.18$). When the regression analyses were performed with the same covariates, the same pattern of results obtained for patients with bipolar I or II disorder. The effect size measures suggest that the association between SGA polytherapy and percentage of days well was somewhat stronger for bipolar II disorder ($d = 0.27$) than for bipolar I disorder ($d = 0.16$).

Patterns of SGA Prescription

As demonstrated in Table 4, SGAs were more often dosed at higher levels in SGA polytherapy compared to SGA monotherapy. For example, the mean olanzapine dose in monotherapy was 10 mg, but it ranged from 12 to 16 mg when used in combination with other SGAs. Quetiapine dosage in conjunction with aripiprazole (449 mg) was nearly double its dosage when used as SGA monotherapy (269 mg). Unfortunately, the CMF did not allow us to determine what degree of quetiapine may have been deliberately prescribed at low dosages to capitalize on its side effect of sedation. For example, low (eg, 25–50 mg) doses of quetiapine may have been administered at bedtime to attenuate insomnia, with the hope that there might be some additional affective benefit during the daytime.

CONCLUSIONS

The use of SGAs in bipolar disorder has increased, especially because such agents have demonstrated efficacy in bipolar depression,[24,25] acute mania, mood stabilization,[26–28] acute agitation, and psychosis. Nearly half of over 4,000 patients enrolled in STEP-BD were treated with an SGA, and of those patients, almost 10% received SGA polytherapy. The varied indications of SGAs in bipolar disorder—and the absence of guidelines for combination therapy—highlight a substantial deficiency of evidence to inform clinical practice for physicians considering the use of SGA polytherapy.

Although one might presume that the decision to prescribe multiple SGAs reflects greater illness severity,[29] we did not detect any differences in illness severity between the SGA monotherapy and polytherapy groups as indexed by number of manic or depressive episodes, illness duration, scores on clinical measures at study entry, and prevalence of comorbid diagnoses. The relations of SGA polytherapy with increased adverse effects, lower global functioning, and fewer days well persisted when controlling for factors that could be proxies for illness severity.

Our hypothesis that SGA polytherapy would be associated with increased adverse events was borne out for a wide range of events measured on the CMT. Importantly, the effect sizes associated with the differences between the SGA monotherapy and SGA polytherapy groups were moderate to large, which suggests a meaningful impact on the adverse events recorded for the sample. The increased occurrence of adverse effects was not guaranteed, as adding a second SGA with overlapping receptor activity (eg, antihistaminic) does not necessarily increase the occurrence of related side effects. Thus, it is possible that the increases in adverse effects can reflect both overlapping and nonoverlapping receptor affinities of the SGAs.

An increase in adverse events has important implications for the use of SGA polytherapy in the treatment of bipolar disorder. Increased adverse events are associated with diminished quality of life[30] and poorer medication adherence.[31,32] Indeed, if the increased adverse events had a clinically meaningful effect on psychiatric care, one would expect the SGA polytherapy group to exhibit an increased use of psychiatric services, which we observed. It is possible that the increased use of psychiatric care represented increased illness severity, but such an explanation does not account for the observation that the SGA polytherapy group exhibited greater use of medical care than did the monotherapy group, even after controlling statistically for age. The reason for increased use of medical services is unclear, though other researchers have reported an increased risk for metabolic syndrome during SGA polytherapy versus monotherapy, as mediated by BMI and age.[33] Although we did not have measures to

assess metabolic syndrome, we did not find evidence of an association between BMI, age, and SGA polytherapy.

Our finding that higher doses of SGAs were given in polytherapy than in monotherapy may partially explain the increased prevalence of adverse events. Interestingly, the tendency we observed for clinicians to prescribe higher doses of SGAs in polytherapy than in monotherapy is consistent with studies of diagnostically heterogeneous patients receiving antipsychotic polytherapy.[11,34] An observational study of patients receiving olanzapine monotherapy or olanzapine in combination with mood stabilizers or antipsychotics reported increased side effects in the combination-therapy group.[16]

We found that SGA polytherapy was associated with slightly lower global functioning scores over the study. This finding is consistent with a study of acute psychiatric inpatients with various diagnoses that did not detect significant differences in rates of clinical improvement in those taking 1 versus 2 or more antipsychotics[34] and a study of bipolar disorder patients taking olanzapine monotherapy or combination therapy.[16] Our findings provide evidence that SGA polytherapy is associated with substantive disadvantages, and they are strengthened by the large sample size and the fact that the patient population is generally representative of bipolar disorder patients seen in clinical practice; although, there is some evidence that participants in STEP-BD were of a higher socioeconomic status and had a lower rate of substance use disorders than would be expected.[35]

The reasons physicians prescribed SGA polytherapy in the present sample were unclear, given that patients reported increased adverse events, increased health care usage, and decreased clinical benefit. Some SGA polytherapy may represent protracted and unfinished cross-tapering of medications, as has been suggested by Sernyak and Rosenheck.[8] However, our observation of higher SGA doses in combination than in monotherapy regimens would not support this hypothesis in all instances. Previous research has revealed that prescribers can frequently cite a target symptom when questioned about the use of antipsychotic polytherapy.[8] Data from the CMF did not allow for such a fine-grained analysis in the present study group.

Another possible explanation for SGA polytherapy may bear less on illness severity than chronicity, or the persistence of low-grade symptoms or incomplete responses that could prompt clinicians to combine agents in hope of their alleviation. Insofar as subsyndromal symptoms involving mood, anxiety, cognition, or other psychopathology features in bipolar disorder are common, yet relatively understudied with respect to optimal therapeutic approaches,[36] the use of SGA combinations may represent an effort by practitioners to address a highly prevalent but unmet clinical need. Notably, the observed higher mean SGA dosages among polytherapy than among monotherapy SGA recipients would suggest that residual symptoms were likely not usually the consequence of underdosing or suboptimization of a first SGA.

It is important to identify illness characteristics that might differentiate SGA polytherapy from monotherapy recipients under ordinary treatment conditions before undertaking randomized comparisons of outcome in these 2 groups. Herein lies an important finding of the current study, in that neither baseline illness severity nor symptom ratings were significant predictors of treatment group membership. The greater prevalence of medication-related adverse drug effects, with no appreciable advantage in terms of functional outcome with polytherapy despite baseline similarities, suggests that SGA polytherapy may be unlikely to improve functional outcome in bipolar disorder. A prospective controlled trial would be needed to affirm this preliminary observation, although the present findings are consistent with other controlled data from the literature on schizophrenia and schizoaffective disorder suggesting little benefit from adding a second SGA to clozapine after an inadequate clozapine response.[13]

There are several limitations to this study. First, the nonrandomized, noncontrolled design precludes causal inferences about the outcomes of SGA polytherapy versus SGA monotherapy. While efforts were made to control for illness severity within a multiple regression model, it remains possible that other unmeasured aspects of illness severity may have affected the observed associations. Second, data regarding adherence with the prescribed medication regimen was not systematically available, limiting the ability to assess the degree to which patients were nonadherent to SGA polytherapy and may therefore have incurred more extensive service utilization or prescriptions for higher medication dosages. Third, the GAF is a global measure based on clinician impressions; had more highly structured measures been employed, our findings regarding changes in clinical status may have differed. Finally, the lack of serial laboratory monitoring did not permit us to explore the extent to which SGA poly therapy may have been associated with metabolic dysregulation. The latter consideration is of particular importance in light of previous findings by Correll et al[33] suggesting that SGA polytherapy is associated with an increased prevalence of metabolic syndrome across disorders.

The present study, based on a large, naturalistic sample of patients diagnosed with bipolar disorder, suggests that SGA polytherapy is associated with substantial disadvantages, ranging from increased adverse events to increased health service usage to decreased functioning. Clearly, randomized controlled trials are needed to definitively assess SGA polytherapy compared to SGA monotherapy, but in the interim, the substantial disadvantages of the former ought to be carefully considered by clinicians considering such interventions.

Drug names: aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), divalproex (Depakote), gabapentin (Neurontin and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), olanzapine/fluoxetine combination (Symbyax), quetiapine (Seroquel), risperidone (Risperdal), topiramate (Topamax), ziprasidone (Geodon).

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Potential conflicts of interest: **Dr Brooks** is on the speakers' bureaus of Eli Lilly, Bristol-Myers Squibb, Pfizer, and AstraZeneca. **Dr Goldberg** is on the speakers' bureaus for AstraZeneca, Eli Lilly, GlaxoSmithKline, and Pfizer and is on the Scientific Advisory Board for Eli Lilly. In the past 12 months, **Dr Ketter** has received grant/research support from AstraZeneca, Cephalon, Eli Lilly, and Pfizer; is a consultant to Bristol-Myers Squibb, Dainippon Sumitomo, GlaxoSmithKline, Merck, and Sepracor; has received lecture honoraria from AstraZeneca and GlaxoSmithKline; and his spouse (Nzeera Ketter, MD) is an employee and stock shareholder of Johnson & Johnson. **Dr Calabrese** has received has received grant/research support from Abbott, AstraZeneca, Eli Lilly, GlaxoSmithKline, and Janssen; has been an advisory board member for Abbott, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, Johnson & Johnson, and OrthoMcNeil; and has been involved in CME activities with AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, and Johnson & Johnson. **Dr Bowden** receives research funding from Abbott, Bristol-Myers Squibb, Elan, GlaxoSmithKline, Janssen, Lilly Research, NIMH, Parke Davis, R. W. Johnson Pharmaceutical Institute, Smith Kline Beecham, and Stanley Medical Research Foundation; serves on the speakers bureaus for Abbott, AstraZeneca, GlaxoSmithKline, Janssen, Lilly Research, and Pfizer; and serves as a consultant to Abbott, GlaxoSmithKline, Janssen, Lilly Research, Sanofi Synthelabo, and UCB Pharma. **Dr Thase** has provided scientific consultation to AstraZeneca, Bristol-Myers Squibb, Cephalon, Cyberonics, Eli Lilly, Forest, GlaxoSmithKline, Janssen, MedAvante, Neuronetics, Novartis, Organon, Seprecor, Shire, Supernus, and Wyeth-Ayerst; has been a member of the speakers' bureaus for AstraZeneca, Bristol-Myers Squibb, Cyberonics, Eli Lilly, GlaxoSmithKline, Organon, Sanofi Aventis, and Wyeth-Ayerst; has equity holdings in MedAvante; receives royalty income from American Psychiatric Publishing, Guilford Publications, Herald House, and W. W. Norton; has provided expert testimony for Jones Day and Philips Lyttle, LLP, and Pepper Hamilton LLP; and his wife is employed as the senior medical director for Advogent. **Dr Miklowitz** does not have any conflicts of interest to disclose.

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