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Original Article

Psychotropic drug prescription patterns among patients with bipolar I disorder

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Introduction: Combination treatment, rather than monotherapy, is prevalent in the treatment of subjects with bipolar disorder, probably due to the complex and phasic nature of the illness. In general, prescription patterns may be influenced by the demographic characteristics of patients as well. We evaluated prescription patterns and the influence of demographic variables on these patterns in a voluntary registry of subjects with bipolar disorder.

Methods: A subset of data from a larger voluntary registry was extracted for demographic variables and psychotropic medication use that had been reported in the month prior to registration by ambulatory, non-hospitalized subjects with bipolar I disorder in 1995/96 (n = 457).

Results: Among the thymoleptic agents, lithium was prescribed in over 50% of subjects, valproate in approximately 40%, and carbamazepine in 11% of subjects. Eighteen percent of subjects had no prescription for thymoleptic agents. Nearly one-third of all subjects were receiving antipsychotic agents, of whom two-thirds were receiving the traditional neuroleptic agents. More than half of all subjects were receiving concomitant antidepressants, of whom nearly 50% received the SSRI antidepressants and nearly 25% received buproprion. Approximately 40% of subjects received benzodiazepines. Only 18% of subjects received monotherapy, and nearly 50% received three or more psychotropic agents. In general, no associations were noted between demographic parameters including age, gender, marital or educational status, and psychotropic prescriptions.

Conclusion: Consistent with the anecdotal reports, these data confirm that combination treatment is far more common than monotherapy. Demography appears to have a minimal impact on cross-sectional prescription patterns in subjects with bipolar disorder. Given that combination treatments are the rule rather than the exception, we should strive to achieve rational, yet pragmatic, treatment guidelines and algorithms to minimize the risks while maximizing the benefits of these combination treatments for patients with bipolar disorder.

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The episodic, chronic, and phasic course of bipolar illness presents clinicians with several treatment challenges. Therefore, it is hardly surprising that the use of multiple drug therapy is the rule rather than the exception (1, 2).

Recently, expert consensus guidelines were released for the treatment of bipolar disorders (3–7). The clinical concern with the lack of a structured set of guidelines and algorithms has led to the publication of several reports by existing professional societies or the creation of organizations such as the Texas Medical Algorithm Project (TMAP) (8).

The methods to arrive at these guidelines and algorithms, by the different societies and organizations, are similar in some ways and dissimilar in

others. A comprehensive literature review by 'experts', panels of experts in subtypes of an illness, use of sophisticated polling questionnaire methods and data analyses, input from constituent organizations including professionals, patients, families, hospital, and providers, field testing, etc. have been among the methods employed. The ultimate goal for most of these guidelines is to improve patient care. However, with the lack of sufficient fundamental research-based evidence about the relative effectiveness of the various drugs used in bipolar illness, coupled with the complexities of treating a multi-phasic illness such as bipolar disorder, this seems to be a Herculean effort.

Several interacting factors including, but not limited to, patient, provider, environmental and cultural influences and drug associated factors, may influence the prescription of pharmacological treatment of bipolar patients (Table 1). These factors are interrelated, for instance, the patient's age may interact with the background and belief systems of the treating physician regarding the prescription and dosing of a specific agent (9).

Patient-dependent factors that affect prescription of treatments may include demographic characteristics such as age, gender, level of education, and marital status. Studies of drug prescriptions in psychiatric subjects, as well as in the general population, suggest that these factors may affect the prescription of drugs. For example, Hemminki (10) reported that polypharmacy of psychotropic drugs was more common among younger and older patients than in the age cohort of 51–60 year olds. Sheppard et al. (11) noted that multiple psychotropic drug prescription occurred in 39% of female patients, compared with 19% in males. Olfson and Klerman (12) reported that office-based psychiatrists tend to prescribe more antidepressants, particularly in young adult males and neurotic patients. Olfson et al. (13) reported an increase in antidepressant prescriptions by outpatient psychiatrists in 1993/94 as compared with 1985. Such an increase was noted more in young white adults with a shorter duration of illness and diagnosed with either adjustment disorders, personality disorders, or depression. Using a prescription database for the entire population of one county in Denmark, Bjerrum et al. (14) calculated the number of drugs prescribed on a random day in 1994 for several illnesses. These authors reported that more females than males consume drugs and that polypharmacy (defined as the use of two or more medications) occurred in 8.3% of the population, and that its prevalence increased with age.

To the best of our knowledge, no study of the effect of patients' demography on patterns of psychotropic medication prescribing has been published in the English literature concerning bipolar disorder. However, there are studies highlighting the effects of age and gender on the pattern and recurrence of illness episodes. In general, several studies reported no effect of gender on the recurrence of episodes in bipolar illness (15–19). Females with bipolar disorder appear to have more severe depressive episodes as compared with males. Also, several variations in the patterns of illness course were found to be more frequent among females as compared with males, such as the depression-mania interval, an irregular course and rapid cycling (20, 21). Age-related changes have been reported in bipolar illness. In general, it is suggested that the interval between the episodes decreases with increasing age (2, 22). There are data to suggest that women are more likely to be prescribed antidepressants than antipsychotic agents, except among those who have a rapid cycling course (21). So, it may be expected that with increasing age and increased frequency of bipolar episodes, combination treatment or polypharmacy may be more common, and prescription patterns may differ among men and women.

Table 1. Factors associated with drug prescription profiles

Factor	Influences
Provider	Prior experience with drugs, belief systems, demographic factors, education, temperament, personality traits, knowledge, and expertise in illness
Patient	Age*, gender*, education*, marital status*, expectations and belief systems, former experience with drug use, personality traits (including hypochondriacal traits), sensitivity to stimuli (pain, etc.), biological factors (rapid vs. slow metabolizer), insight into illness and treatment
Illness	Onset and duration of illness, number of hospitalizations, response to therapy, severity of illness, severity of specific illness characteristics (i.e. the occurrence of suicidality, severe pain)
Sociocultural	Inpatient vs. outpatient, academic vs. private vs. institutional, insurance coverage, organizational issues, caseload and type of patients referred, access to healthcare, family or other support
Drug treatment	Efficacy, side-effect profile, interaction with other drugs, cost, risk-benefit, shape, color

* Factor measured and discussed in the current study.

The current study evaluated the association between patient factors such as age, gender, educational and marital status, and specific medications and their combinations in patients with bipolar I disorder. We also examined monotherapy versus combination treatments among these subjects.

We hypothesized that: 1) there would be no effects of gender on the prescription patterns, except perhaps that more women with bipolar illness would be prescribed antidepressants; and 2) younger patients (i.e. those ≤ 40 years of age) would have different prescription patterns than older patients (i.e. those > 40 years of age).

Methods

Starting in the Spring of 1995, a voluntary bipolar disorder case registry (the Stanley Center Bipolar Disorder Registry located in Pittsburgh, hereinafter referred to as the registry) recruited subjects with bipolar illness. The purpose was to create a representative sample of subjects with this illness in order to enable researchers to understand demographic and illness characteristics, treatment variations, pathways to treatment, and potential recruitment into clinical trails. This effort has been described in detail by Cluss et al. (23).

Briefly, after publicizing the registry efforts among consumer advocacy groups, psychiatrists, mental health providers, and other agencies, patients who were self-identified as having bipolar disorder called the registry using a local or a toll-free number. After a signed consent was returned by mail, a telephone interview was completed to gather information about demography, clinical treatment, and medical histories of the registrants. The majority of patients described in this study were interviewed with earlier versions of the questionnaire, where current mood status was not determined. Thus, we were unable to correlate an important factor associated with psychotropic prescription patterns, i.e. present mood status. A random 20% of all registered individuals completed a lengthy face-to-face interview using the Structured Clinical Interview for DSM-IV Axis I Disorders – Patient Edition (SCID) (24). Where necessary, psychiatric records and discussions with treating psychiatrists complemented the information from the SCID interview. The results of 100 such interviews confirmed that 71% had a bipolar I disorder diagnosis, 18% had a bipolar II disorder diagnosis, 1% had an 'other' bipolar disorder diagnosis, and 3% had a diagnosis of schizoaffective disorder-bipolar type, leaving only 7% who had misidentified themselves as having bipolar disorder (23).

Table 2. Demography of subjects with bipolar I disorder

	n	% of total sample
General characteristics		
Number	457	100
Mean age $\pm$ SD (range in years)	40 $\pm$ 10 (18–71)	
Age $\leq$40 years	230	50.3
Age $>$40 years	227	49.7
Age $>$65 years	5	1.1
Gender: female	307	67
Gender: male	150	33
Marital status		
Single	133	29
Married	181	40
Separated and divorced	137	30
Widowed	6	1
Education		
Elementary or some high school	17	4
High school and some college	230	50
College and above	213	46

The data for the present study were extracted when the registry sample was 1486. As the registry was validated for 100 patients, selected at random, using SCID interviews based on subjects residing within a 150 mile radius of Pittsburgh (23), we limited our sample to this region, resulting in 740 subjects. We further restricted this sample to those with bipolar I disorder, and this limited the sample to 526 subjects. This sample of 526 subjects was eventually reduced to 457 subjects, based on whether they could enumerate and list their psychotropic medication use within the past month of the telephone interview. The demographic characteristics (age, gender, marital status, education levels) of these 457 subjects with bipolar I disorder are presented in Table 2.

Psychotropic medications were grouped into established (or putative) mood stabilizers including: lithium, valproate (including valproic acid too), carbamazepine, lamotrigine, gabapentin, and their combinations. Other categories of psychotropic agents included antidepressants such as tricyclic, selective serotonin reuptake inhibitors (SSRI), monoamine oxidase inhibitors (MAOI), bupropion, and more recently available antidepressants, antipsychotic agents including the first-generation neuroleptic agents, and the second-generation antipsychotic agents. Also reviewed were the prescription of anxiolytic and hypnotic agents, calcium channel blockers (as used for bipolar illness), stimulants, thyroxine, and antiparkinsonian agents.

Statistics

McNemar χ^2-tests were used to test discordance regarding the use (or lack) of one mood stabilizer exclusive of the other. χ^2-tests were used as a nonparametric test of significance for the use of a given psychotropic agent between two groups. *T*-tests were used to test significance for continuous variables. The Bonferroni correction was used to correct for multiple comparisons.

Results

Demographic data of the 457 bipolar I subjects are presented in Table 2. Most of these subjects were in treatment programs provided by health professionals, of which 82% were psychiatrists. As several classes of psychotropic drugs were involved, the results are presented separately for mood stabilizers, antidepressants, antipsychotic agents, anxiolytic or antiparkinsonian drugs, and miscellaneous drugs. Following these data is a presentation of the influence (or lack) of demographic variables on these prescription patterns, and finally the data on monotherapy versus combination treatments among these subjects are described.

Mood-stabilizer drugs

Among the 457 subjects with bipolar I disorder, nearly half (n = 229) were treated with lithium, approximately 40% (n = 182) with valproate, and only 11% (n = 52) with carbamazepine (Table 3). The McNemar χ^2-test showed that lithium and its combinations were used significantly more often as compared with valproate and its combinations, $p = 0.007$. One hundred and seventy-one subjects received lithium but no valproate, 124 subjects received valproate but no lithium, 58 subjects received both agents, and 104 subjects did not receive either of these drugs. Lithium and its combinations were used more often as compared with carbamazepine and its combinations ($p < 0.0001$).

Lithium was also the most commonly prescribed drug as thymoleptic monotherapy. Forty-one out of 88 (47%) subjects treated with monotherapy were treated with lithium alone, followed by 19 subjects who received valproate monotherapy (22%). However, and interestingly, only 18% of all subjects treated with lithium and 10% of all subjects treated with valproate received these treatments as monotherapy. Eighty-two percent of lithium-treated subjects and 90% of valproate-treated subjects with bipolar I disorder were receiving two or more medicines, and nearly one-third in each group received four or more medicines (Table 3).

At the time of data collection, the number of subjects treated with lamotrigine (n = 20) and gabapentin (5) was rather small. Lithium and valproate were used in combination in about 13% of the subjects (n = 58), followed by 7% of subjects who received carbamazepine and valproate (n = 33), whereas lithium and carbamazepine and lithium and lamotrigine were combined in only 19 subjects (4%) and 3 subjects (1%), respectively. Eighteen percent of the registry subjects received no mood stabilizer at all, at least in the month prior to registration.

Table 3. The percentage of bipolar I subjects receiving monotherapy versus combination treatments distributed by primary mood stabilizer or their combinations[a,b]

Mood stabilizer	Monotherapy (%) n = 88	Two psychotropic agents (%) n = 128	Three psychotropic agents (%) n = 128	Four or more psychotropic agents (%) n = 113
Lithium (n = 229)	18	25	27	30
Valproate (n = 182)	10	21	34	35
Carbamazepine (n = 52)	0	36	31	33
Lithium and valproate (n = 58)	–	9	31	60
Lithium and carbamazepine (n = 19)	–	16	47	37
Valproate and carbamazepine (n = 33)	–	30	39	31

[a] Nearly one-half of the patients receiving mood stabilizers were also receiving antidepressant drugs, and nearly one-third of the subjects receiving mood-stabilizing agents also received antipsychotic agents. The SSRI antidepressants were the most prevalent (nearly 50%) class among antidepressants, and the first-generation antipsychotic agents were more prevalent (nearly two-thirds) than second-generation agents.

[b] Only 18% of all lithium-treated subjects and only 10% of all valproate-treated subjects received it as monotherapy.

T-test for independent samples comparing number of medications between the different mood stabilizers and its combinations shows that subjects treated with both lithium and carbamazepine received significantly more medications compared with the rest of the subjects (mean $\pm$ SD for lithium- and carbamazepine-treated subjects was 3.9 ± 1, and for the rest of the subjects was 2.5 ± 1, $t = 8.06$, $df = 1$, $p < 0.0001$, which remained significant after applying the Bonferroni correction).

Antidepressants/drugs

More than half of these subjects ($n = 261$) were treated with antidepressants and 11% ($n = 50$) received more than one antidepressant. Of subjects treated with antidepressants, nearly half ($n = 128$) received the SSRI antidepressants, and nearly a quarter received bupropion ($n = 62$). Thirty-seven subjects were treated with newer antidepressant drugs such as nefazodone and venlafaxine, whereas only six subjects were treated with the MAOI antidepressant drugs.

Antipsychotic drugs

About one-third of the subjects ($n = 146$) were treated with antipsychotic agents, only a few of them ($n = 8$) received two antipsychotic agents. Among subjects treated with antipsychotic agents, nearly two-thirds ($n = 96$) received traditional antipsychotic drugs, whereas slightly more than a third ($n = 58$) received the second-generation antipsychotic agents. At the time of the data collection, only clozapine and risperidone were commercially available of the second-generation antipsychotic agents.

Anxiolytics or antiparkinsonian agents

Nearly 40% of these subjects were treated with anxiolytic agents ($n = 179$), while less than 10% ($n = 40$) received either hypnotic or antiparkinsonian agents ($n = 38$).

Miscellaneous

A small percentage of subjects ($n = 28$) were treated with thyroid hormone, and even smaller numbers of subjects with either a calcium channel blocker ($n = 8$) or a stimulant ($n = 6$).

Demography and psychotropic medications

Table 4 describes the percentage for lithium, antidepressant, and antipsychotic treatments among groups sorted on the basis of age, gender, marital, or educational status.

χ^2-tests showed no difference between these groups in any of the demographic parameters measured, except that unmarried and separated subjects tended to receive more antipsychotic drugs as compared with married subjects ($\chi^2 = 8.04$, $df = 1$, $p = 0.0056$).

Monotherapy versus combination treatments

Less than 20% of the subjects received one psychotropic medication and 28% received two psychotropic agents. More than 50% of subjects took three or more psychotropic agents and 25% received four or more psychotropic drugs. No difference was found between subjects taking one, two, three, four, and more psychotropic medications for any of the demographic variables including age

Table 4. The percentage of prescriptions for the three major psychotropic drugs among patients classified on the basis of age, gender, education, and marital status

	No. of subjects	Li[1] (%) (n = 229)	AD[2] (%) (n = 261)	AP[3] (%) (n = 146)
Total	457	50	57	32
Age $\leq$40 years	230	52	57	33
Age >40 years	227	48	58	31
Male	150	53	53	31
Female	307	49	59	33
Educational level: some college or less	244	46	61	34
Educational level: college or above	213	55	53	30
Single/separated/widowed	276	53	56	40
Married	181	46	59	24[4]

[1] Lithium.
[2] Antidepressant drugs.
[3] Antipsychotic agents.
[4] Statistically significantly fewer married patients were likely to receive antipsychotic agents as compared with single, separated or widowed subjects ($\chi^2 = 8.04$, $df = 1$, $p < 0.005$).
Comment: In general, there were no statistically significant differences among the three major psychotropic drug classes on the basis of the patient demographic characteristics noted above.

(≤ 40 vs. > 40 years), gender, educational level, and marital status. Table 5 describes the percentage of subjects using mood stabilizers and their combinations among these same groups. The χ^2-test showed no statistically significant differences between these groups receiving treatments for bipolar disorder based on any of the demographic parameters noted above.

Discussion

The observations and conclusions of this paper have to be tempered by the recognition that the sample consisted of subjects volunteering to be included in a registry at a tertiary medical center. It may be speculated that this might bias the sample towards patients with either more severe or refractory forms of illness, which may necessitate polypharmacy. Those patients who have a less severe form of the illness, or those who remit with the first mood-stabilizing treatment they receive, may be less inclined to participate in a registry. However, this registry was comprised of nearly all subjects who had completed high school and nearly half had a college education, so altruistic motives may have been another reason to participate. Also, a history of medical problems may be associated with greater or lesser use of psychotropic drugs, since they may interact with other medication or be contraindicated in some conditions.

The discussion first focuses on the demographic characteristics of the present sample and compares it with those reported in the literature. Then, we discuss the patterns of psychotropic agents used for these subjects and compare monotherapy versus combination treatments. Finally, we discuss the influence of age, gender, marital, and educational status of the study subjects on these prescription patterns.

Homogeneity of the group

The current study presents data for a relatively homogenous group of bipolar I subjects, excluding those subjects with bipolar II, schizoaffective-bipolar type or other diagnoses. This strategy may be of importance, as data comparing bipolar I to bipolar II patients suggest that those with bipolar I disorder may have different biological and genetic matrices, clinical course, and response to treatment (20, 25–31).

Age, gender, marital status, and education

The mean age of our subjects was 40 years (range 18–71). Other studies (31, 32) found the age of bipolar subjects in hospital clinics or inpatients were similar to those reported in the present study. About half of our subjects were less than 40 years, and the other half were above this age, whereas only 1% of the subjects were above 65 years. The elderly may be under-represented in this sample due to the selection process of the voluntary registry, or a more ominous alternate explanation, such as a higher risk for early death due to suicide, accidental death, or cardiovascular or respiratory diseases in this population (33–35).

Table 5. The percentage of bipolar I subjects receiving mood stabilizers or their combinations classified on the basis of age, gender, education, and marital status[1]

	No. of subjects	Li (%) (n = 229)	Val (%) (n = 182)	Car (%) (n = 52)	Li & Val (%) (n = 58)	Val & Car (%) (n = 33)
Total	457	50	40	11	13	7
Age ≤ 40 years	230	52	41	10	13	6
Age > 40 years	227	48	38	12	12	8
Male	150	53	43	11	14	6
Female	307	49	38	12	12	8
Educational level: some college or less	244	46	40	10	11	7
Educational level: college or above	213	55	39	13	15	8
Single/separated/widowed	276	53	39	12	13	6
Married	181	46	41	10	12	8

[1] Only combinations of mood stabilizers reported in 20 or more patients are presented in this table.
Li = Lithium; Val = divalproex sodium and valproic acid; Car = carbamazepine.

Two-thirds of the sample were females. In general, it is agreed that there are equal proportions of men and women among patients with bipolar I disorder. Kessler et al. (36) reported epidemiological data on 29 bipolar I patients diagnosed using DSM-III-R criteria from the National Comorbidity Survey. Lifetime prevalence of bipolar disorder was estimated to be 0.47% in women and 0.42% in men. Vieta et al. (31) found 55% of females and 45% of males, in a sample of 38 bipolar subjects attending a university hospital clinic. Lish et al. (37) surveyed members of the National Depressive and Manic Depressive Association who had bipolar disorder. These authors report that 63% of the subjects were female. There is an excess of women in the present study as compared with the equal gender prevalence of bipolar disorder I in the general population. However, it has been reported that female patients (whether bipolar or schizophrenic) tend to report their illness earlier and tend to be more compliant with medication treatment (20, 38) and so this may explain the preponderance of females in a voluntary registry.

The majority of the patients were single, separated, or divorced in the present study. Previous authors reported a high proportion of unmarried subjects in this disorder (39, 36). In contrast to Kessler et al. (36), a large proportion of our subjects had received their college degree or had completed a high school education. Kessler reported 'caseness' to be negatively related to education among his subjects. However, it is possible that educated people are more likely to call a voluntary registry leading to a selection bias.

Mood-stabilizer treatment

More than half a century after lithium was first introduced as a treatment for bipolar illness, this drug still has a pivotal role in the treatment of this disorder. The present study suggests lithium to be the most frequently prescribed drug, whether alone or in combination therapy, followed by sodium valproate. The relatively small percentage of patients treated with lithium monotherapy (18%) may be disappointing. A similar number (26%) was reported by Harrow et al. (40) in a naturalistic follow-up study of bipolar patients recovering from mania and by Sachs et al. (41) (26%) in an unselected bipolar patient sample receiving a variety of maintenance treatments. One may speculate that this might reflect the bias of the voluntary registry with subjects who are not readily responsive to treatments and are looking for alternative treatments. However, Vonig et al. (42), surveying long-term treatment in hospitalized patients, reported that between the years 1980 and 1985, only 11% of the patients were treated with lithium alone in 1980, none during 1981–1983, 7% in 1984, and none in 1985. In contrast, Silverstone et al. (43) prospectively studied two representative samples of bipolar I patients for 2 years, noting that 57 out of 120 patients (48%) were treated with lithium alone.

Eighteen percent of the patients received no mood stabilizer at all, and worryingly two-thirds of this group were receiving antidepressant agents. This group is also at greater risk for precipitation of hypomania or manic episodes and possibly cycle acceleration (44, 45). Higher numbers were reported by Markar and Mander (46). These authors conducted a retrospective naturalistic study of 83 bipolar patients recovering from mania. Forty-one received prophylactic lithium and 42 received no prophylactic mood stabilizer. In a study with similar design, Harrow et al. (40) reported that 55% of 73 discharged manic patients, followed for 1 year, were not receiving mood stabilizers. Sachs et al. (41), in another naturalistic study, reported that 10 out of 100 bipolar patients, followed for 1 year, did not receive any treatment and 27 did not receive mood stabilizers. Interestingly, no difference in outcome measures was found in the last three studies between patients receiving lithium and those not receiving lithium (or any other mood stabilizer). Maj et al. (47) reported that 27.9% of patients enrolled in lithium treatment were not on lithium 5 years after starting this treatment, despite adequate follow-up. Possible explanations for not receiving mood-stabilizing agents may include, among others, a less severe illness with infrequent episodes, lack of tolerability to mood-stabilizer treatment, non-adherence to treatment while they registered voluntarily, or lack of response to mood-stabilizing agents.

Thyroid hormone

The majority of patients receiving thyroid hormone were also receiving lithium. Less than 10% of all patients receiving lithium received thyroid hormone replacement. In the literature, 5–35% of lithium-treated patients showed clinical and laboratory abnormalities consistent with hypothyroidism (20, 48).

Antidepressant use in bipolar subjects

Overall, mania responds to treatment much more readily than bipolar depression (4), and this may be one reason for the excessive use of antidepressants in this condition. However, there are serious problems with switches to hypomania or mania or cycle acceleration associated with antidepressant use (45). There are considerable risks for these subjects, although not all agree with this position (44).

Buproprion

This antidepressant is less likely to induce cycling (49), although this conclusion is based on one small controlled study. If these results are confirmed by larger double-blind studies, these registry data concerning buproprion usage are encouraging. Similar results were found by Zarate et al. (50), where 894 out of 3829 (23%) hospitalized bipolar subjects received buproprion.

MAOIs

In spite of reasonably good efficacy data regarding MAOI antidepressants in bipolar depression (51, 52), especially in the anergic subtype, these agents were used rarely in our sample for bipolar depression. Zarate et al. (50) found a higher percentage (19%) of MAOI use, but it should be noted that these were hospitalized bipolar subjects in a treatment setting with special emphasis for bipolar disorder. Perhaps the dietary restrictions have resulted in a low acceptance of MAOI antidepressants among patients and physicians alike.

Bipolar subjects and antipsychotic agents

Previous studies (53–55) have shown that over 50% of bipolar subjects were receiving antipsychotic agents 6 months after discharge from a hospital. However, the use of antipsychotics in this disorder is not without risk. Bipolar and unipolar subjects may be more prone to EPS and tardive dyskinesia as compared with patients with schizophrenia (56, 57). So, the chronic use of traditional antipsychotic agents with bipolar subjects is troublesome. Today, it appears more reasonable to prescribe the second-generation antipsychotic agents in the acute and maintenance phase of bipolar disorder. It must be borne in mind that when these data were collected, clozapine and risperidone were the two second-generation antipsychotic agents commercially available in the United States. Recent marketing data suggest nearly 20–25% of all prescriptions written for olanzapine, risperidone, and quetiapine are for subjects with bipolar disorder. Two controlled trials involving risperidone and olanzapine for acute mania have been reported in the recent literature. A small study ($n = 45$), comparing risperidone (6 mg/day), haloperidol (10 mg/day) and lithium (800–1200 mg/day) as monotherapy for acute mania, noted equal efficacy for the three agents with no switches to hypomania or mania (58). A large ($n = 139$) multi-site-controlled comparison of olanzapine with placebo for acute mania noted a response of 48.6% for olanzapine compared with 24.2% for placebo ($p < 0.004$) (59). Clozapine has been used in several open trials with response rates that are impressive for treatment-resistant or refractory bipolar manic (60, 61), mixed or depressed patients. Clozapine has also been used for bipolar subjects with a rapid cycling course (61, 62) or for those who have neuroleptic-induced dystonias and dyskinesias (60, 63) Frye et al. (64) suggest that clozapine may have greater antimanic than antidepressant properties. So, it is likely that the second-generation antipsychotic agents such as risperidone, olanzapine, and quetiapine will be used more extensively for acute mania, and clozapine will be reserved for those subjects who are treatment-resistant or refractory, or intolerant to the first-line newer medications. However, no data as yet have been reported suggesting that atypical antipsychotics have a role in the maintenance treatment of bipolar disorder. This should be emphasized, since there is yet no existing evidence that long-term dopaminergic blockade by atypical antipsychotic agents in bipolar patients carries minimal risk for tardive dyskinesia.

Bipolar subjects and benzodiazepines

The extensive use of these agents in the present data set may speak either to the extent of polypharmacy or the lack of adequate control of the episodes or the comfort level of physicians in prescribing these agents. However, worryingly, among 93 subjects with lifetime bipolar spectrum disorders who completed a SCID interview (23) to validate this registry, nearly 56% had comorbid substance abuse or dependence where the extensive use of these agents could raise problematic clinical issues. Interestingly, another explanation for the extensive use of benzodiazepines may reside in the fact that almost 20% of this registry population (23) had comorbid panic disorder, and 10% had post-traumatic disorder where these agents are used as treatment. Additionally, certain benzodiazepines are suggested to have antimanic effects in add-on treatment (65, 66) or as monotherapy in comparison with lithium (67), or placebo (68), suggesting yet another use of these agents.

Polypharmacy or combination treatments

Less than 20% of bipolar patients received monotherapy and over 80% received two or more medicines, of whom nearly 50% received three or more medicines. Among the entire group, nearly 25% were taking four or more medications. As compared with a general county population in Denmark (14), the bipolar subjects in this registry

had a nearly 8-fold increase in the rate of receiving two or more medications. On the one hand, the use of polypharmacy is risky due to drug–drug interactions, increased side-effect burdens, increased cost, and lack of adherence. On the other hand, these data may address the complex nature of the disorder, and that subsets of patients are less responsive to monotherapeutic regimens (1, 2). In agreement with Post et al. (2) and Sachs (1), Denicoff et al. (69) in a 2-year, randomized, cross-over study, reported that response to lithium or carbamazepine monotherapy is up to 33%, while response to the combination of these two is 55%. There are also data that suggest that a subset of patients responding initially to lithium may acquire lithium refractoriness (70–72). However, Coryell et al. (73) have reported otherwise among subjects who discontinue lithium. The high prevalence of combination treatment in this disorder attests to both the complexity of the illness and to the limitations of existing treatments, suggesting that the current mood-stabilizing agents do not meet the 'ideal' criteria of helping all phases (hypomania, mania, mixed, depressed) or as prophylaxis for most patients. These attributes point towards the need for development of new treatments and to the methodological challenges in undertaking such an enterprise. If the background rate of combination treatment is as high as indicated by these data, a significant impact of this can be anticipated on future clinical trials of maintenance therapy in bipolar disorder.

Demography and medication use

The identification of possible relationships among patient-dependent demographic variables such as age, gender, educational, and personal status on the one hand and patterns of psychotropic drug administration on the other in bipolar patient population is not a mere intellectual exercise. First, such analysis may assist in reflecting the practice of psychotropic drug prescriptions in 'real life' situations as opposed to similar data obtained from research studies, treatment guidelines and textbooks. Second, the acquisition of such data may enable a judgmental evaluation of the differences between treatment recommendations based on controlled studies, and the practice carried out in the uncontrolled routine care of these patients. Third, based upon such evaluations the planning of educational programs and the creation of appropriate but pragmatic treatment, recommendations can occur in the context of continuing medical education, practice guidelines, and treatment algorithms (8).

Interestingly, analysis of the present data reveals, in contrast to psychiatric outpatient clinics (12, 13) and findings in the realm of general medical practice (14), that no bias towards specific demographic variables such as age, gender, educational, or marital status is apparent. This is an encouraging finding, especially as we were concerned that bipolar women subjects may be more likely to receive antidepressants and thus possibly be at greater risk for switches to mania and/or rapid cycling. It must be noted that we chose a bipolar I cohort, and the findings may have been different if bipolar II subjects were included. Another limiting factor for this data set is its cross-sectional nature. However, contrary to our hypothesis, there was no statistically significant excess of antidepressant use among bipolar women.

In summary, these cross-sectional data suggest combination treatments are very common rather than rare, reflecting the complex and phasic course of bipolar disorder. These data also reflect that available thymoleptic agents are not entirely satisfactory to treat the different phases of the illness or the subtypes of bipolar illness as monotherapeutic agents. Combination treatments bring with them complexities for treatment, for instance, risks such as drug interactions, adverse effects and toxicity, decreased adherence, increased monitoring, etc. So, until we have agents that meet most of the ideal mood-stabilizing criteria, we should strive for rational yet pragmatic guidelines and algorithms for combination treatments in the treatment of bipolar disorder to minimize the risk and maximize the benefits for subjects with this illness.

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