# Original Article

# Illness characteristics and their association with prescription patterns for bipolar I disorder

***Introduction:*** The present study explores the relationships among psychotropic medications, illness-related parameters, patient demography, suicidality, and levels of functioning in a voluntary bipolar case registry.

***Methods:*** Four hundred and fifty-seven subjects with bipolar I disorder were selected from a voluntary registry for subjects with bipolar illness. Demographic characteristics, psychotropic medications, age at onset of illness, duration of illness, number of hospitalizations, the ability to live independently, employment and driving status as well as the history of suicidal attempts were obtained through a structured phone interview.

***Results:*** Subjects treated with antidepressants had a shorter duration of illness, while patients treated with antipsychotic drugs had an earlier onset of illness. The number of hospitalizations for mania was fewer among patients taking a combination of lithium and carbamazepine as compared to patients not receiving them, while subjects taking neuroleptics had more hospitalizations as compared to subjects not receiving them. The number of psychotropic agents prescribed correlated positively with the number of hospitalizations for depressive episodes. Curiously, no correlations were found between the types of psychotropic agents prescribed and the levels of functioning or a history of suicidal attempts. Interestingly, our results suggest that more than half of the subjects were unable to live independently or to work due to their illness. Also, more than 50% of the subjects had at least one suicidal attempt, the majority occurred during depressive episodes.

***Conclusions:*** Our results suggest that subjects with bipolar I disorder have high rate of suicidal attempts and may have serious functional impairments.

**Joseph Levine[a,b,c],**
**KN Roy Chengappa[a,b,c],**
**Jaspreet S Brar[a],**
**Samuel Gershon[a,b] and David**
**J Kupfer[a,b]**

[a] Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, [b] Stanley Center for the Innovative Treatment of Bipolar Disorder, [c] Special Studies Center at Mayview State Hospital, USA

Corresponding author: KN Roy Chengappa, MD, Western Psychiatric Institute and Clinic, Stanley Center for the Innovative Treatment of Bipolar Disorder, 3811 O'Hara Street, Pittsburgh, PA 15213-2593, USA. Tel: +1 412-624-2634; fax: +1 412-624-0493; e-mail: chengappakn@msx.upmc.edu

Bipolar I illness represents a chronic, episodic, oscillating and complex disorder (1, 2). Much of the data regarding its treatment is derived from results obtained from clinical trials and from treatment guidelines gathered from surveys of 'experts' in the field. However, data regarding prescription patterns in more generalized situations are scant. Recently, our group (3) reported the prescription patterns in a voluntary registry of bipolar I subjects noting a tendency for extensive polypharmacy, especially in the prescription of antidepressant and antipsychotic medications. In brief, we reported that among the thymoleptic agents, lithium was prescribed in over 50% of bipolar subjects, valproate in approximately 40% of subjects, and carbamazepine in 11% of subjects. Eighteen percent of subjects had no prescriptions 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 one half of all subjects were receiving concomitant antidepressants of

whom nearly 50% received the selective serotonin reuptake inhibitor (SSRI) antidepressants and nearly 25% received bupropion. Nearly 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. We concluded that consistent with the anecdotal reports, these data confirm that combination treatment is far more common than monotherapy.

The prescription of drugs is a complex process influenced by a variety of interrelated factors (3). When faced with a decision to choose drug treatment strategies for bipolar I disorder, the psychiatrist may take into consideration a variety of factors including illness-related factors such as the phase of episode (mania or mixed or depressed), age at illness onset, duration of illness, number and nature of episodes and their severity (for instance, the need for hospitalization). The psychiatrist may also consider the existence of a history of suicidality as well as the impact of the disorder on the patient's functioning and employment.

The objective of the current paper was to gather data regarding certain characteristics associated with bipolar I disorder, such as age at illness onset, duration of illness, number of hospitalizations, suicidality and levels of functioning and to explore the effect of these characteristics on patterns of prescriptions for psychotropic drugs among bipolar subjects.

## Methods

Four hundred and fifty-seven bipolar I patients were selected from a voluntary registry for bipolar subjects at the Stanley Center for the Innovative Treatment of Bipolar Disorder located in Pittsburgh, PA, USA. Selection criteria for the current sample were detailed in Levine et al. (3) and will be repeated briefly here to inform the reader not familiar with the previous publication.

In 1995, a voluntary bipolar disorder case registry (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 trials. This effort has been described in detail by Cluss and colleagues (4).

After publicizing the registry efforts among consumer advocacy groups, psychiatrists, mental health providers and other agencies, persons who were self-identified as having bipolar disorder called the Stanley Center using a local number 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 are 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) (5). 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 mislabeled themselves as having bipolar disorder (4).

The data for the present study were extracted in October 1996 when the registry sample was 1486. As the registry was validated using SCID interviews based on subjects residing within a 150-mile radius of Pittsburgh (4), 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.

Demographic characteristics that were recorded included: age, gender, and marital status. Illness-dependent variables included: age at onset of illness (defined as time of appearance of first illness-related symptoms as reported by the subject or a close relative), years of illness, number of hospitalizations for mania and/or depression and/or mixed episodes. Data pertaining to functioning included the ability to live independently, employment status, and the ability to drive an automobile. Each of these factors was also evaluated for current or past disability. Suicidality was assessed by the history of one or more suicide attempts. Suicidal attempts constituted an act of self injury (i.e. taking an overdose of drugs, cutting wrists, hanging, shooting of oneself) with the clear intent to die. Hospitalization was not specifically required for defining a suicidal attempt.

Psychotropic medications were grouped into established (or putative) mood stabilizers including: lithium, valproate (including valproic acid), carbamazepine, lamotrigine, gabapentin and their combinations. Other categories of psychotropic agents included antidepressants such as tricyclic, SSRIs, monoamine oxidase inhibitors, buproprion, and the more recently available antidepressants, antipsychotic agents including the first 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

The one-way ANOVA test and Student's $t$-test for independent samples were used to test significance for continuous variables. The Pearson correlation test was used to correlate continuous variables. The Pearson chi-square test was used to evaluate categorical and nonparametric data. The Bonferroni correction was applied to correct for multiple comparisons in the following way: As we had 20 groups of medications (including few combinations of two drugs and small groups of drugs such as first and second generation antipsychotics), statistical significance for any analysis associated with these groups was set at 0.0025. As two large groups of medications were considered in this study, i.e. antidepressants and antipsychotics, statistical significance for any analysis associated with these groups was set at 0.025. No Bonferroni correction was applied to the variable assessing the number of psychotropic agents used. No Bonferroni correction was applied to variables associated with illness characteristics when these were analyzed irrespective of their associations to psychotropic medications.

### Results

As the data were gathered from a voluntary self-report registry, some of the subjects chose to skip or not to answer certain questions and thus only a portion of the sample was assessed for certain parameters. The actual numbers are described later.

### Characteristics of the sample

Demographic data and other illness-related data for the 457 bipolar I patients are presented in Table 1.

Table 1. Demography, illness variables, and suicidality among subjects with bipolar I disorder

| General characteristics | n = 457 |
| --- | --- |
| **Age** | |
| Mean age ± SD (range) | 40 ± 10 (18–71) |
| Age <40 years; age >40 years | 230 (50.3%); 227 (49.7%) |
| Age >65 years | 5 (1.1%) |
| **Gender** | |
| Female/Male | 307 (67%)/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%) |
| **Age at onset of illness** | |
| Mean ± SD (range) | 30.9 ± 10 (8–59) (n = 394) |
| **Years of illness** | |
| Mean ± SD (range) | 9.8 ± 7 (1–35) (n = 395) |
| **Hospitalizations** | |
| Mean for mania ± SD (range) | 4.3 ± 6 (1–40) (n = 240) |
| Mean for depression ± SD (range) | 3.9 ± 6 (1–60) (n = 246) |
| Mean for mixed episode ± SD (range) | 4.7 ± 9 (1–75) |
| Mean total ± SD (range) | 5.5 ± 7.2 |
| **Suicidal attempts** | |
| All attempts | 233 (54%) (n = 433) |
| Only when depressed | 217 (93% of patients attempting suicide) (n = 233) |

Table 2. Comparison of age at onset of illness in several psychotropic treatment groups*

| Medication groups compared | Mean age at onset of illness ± SD | Independent t-test | Significance | Significance after Bonferroni correction |
|---|---|---|---|---|
| Atypical-AP (n = 58) | 27.7 ± 9 | −2.64 | p = 0.009* | No |
| AP (n = 146) | 29.2 ± 9 | t = −2.40 | p = 0.017** | Yes |
| Non-AP (n = 311) | 31.8 ± 10 | | | |
| AD (n = 261) | 31.8 ± 10 | t = 1.95 | p = 0.05*** | A trend |
| Non-AD (n = 196) | 29.8 ± 10 | | | |

AP = antipsychotic drugs; AD = antidepressant drugs.
* No significant results in one-way ANOVA were noted for all other specific psychotropic drugs and their combinations or for number of psychotropic drugs prescribed.
** Significance level after Bonferroni correction for specific drug was 0.0025.
*** Significance level after Bonferroni correction for antipsychotics and antidepressants was 0.025 (a trend was considered to be 0.05 or less).

Thirty-eight percent of these patients had been hospitalized within the year preceding the interview.

Data regarding independent living were available from 158 patients. Sixty-two percent of the patients reported that they were unable to live independently – requiring constant surveillance and the help of another adult with daily activities such as preparing food, cleaning the house, washing clothes, paying bills, etc. – for extended periods of time (not defined) since the onset of their illness. These subjects were further requested to report whether such disability had occurred in the remote past or within the past month. Sixty-eight subjects responded, of whom, 65% reported the disability occurred within the past month.

Data regarding employment status were obtained from 239 subjects. Eighty-four percent reported that they were unemployed as a consequence of their illness either currently or in the past. Eighty-nine subjects responded to whether the unemployment was in the past or current, of these, 85% reported current unemployment.

One hundred and seventy patients reported on whether the illness affected their driving ability. Of these, 55% reported past or current inability to drive, of whom 52 subjects reported on past or current inability to drive a vehicle. Of these, 69% reported they were currently unable to drive.

Four hundred and thirty-three subjects responded to questions about suicide attempts. Significantly and disturbingly, more than half the subjects had attempted suicide. The majority of suicide attempts (93%) occurred during the course of a depressive episode. These statistics are a matter of major individual and public health concern.

Duration of illness

Not unexpectedly, duration of illness showed a significantly higher mean value for subjects above the age of 40 years, as compared to subjects below the age of 40 years, $11.7 \pm 8$ vs. $8.0 \pm 5$ years (one-way ANOVA: F = 28.4, df = 1, p < 0.0001). No significant effect of gender was noted on duration of illness (mean ± SD, $10.1 \pm 7$ for males, $9.6 \pm 7$ years for females). The prescription of the main psychotropic drug classes was compared to the duration of illness. Using a one-way ANOVA with Bonferroni correction for multiple comparisons, the mean duration of illness in years for patients taking antidepressants was 2 years shorter compared to patients not taking antidepressant therapy ($8.9 \pm 7$ vs. $10.9 \pm 8$ years, F = 7.8, df = 1, p = 0.006). No other statistically significant difference for duration of illness between patients taking specific or combinations of psychotropic drugs and patients not taking them was noted. Surprisingly, no difference was noted for duration of illness between patients taking either one or two or three or four or more psychotropic drugs.

Age at onset of illness

Age at onset was positively correlated with age (r = 0.736, p < 0.01), and the mean age of illness onset for younger patients born after 1955 was nearly 12 years lower as compared to older patients born before 1955 (mean ± SD: $25.2 \pm 7$ vs. $37.1 \pm 9$, respectively, t = −14.7, p < 0.0001). No difference in the age of illness onset was noted between men and women (mean ± SD: $31.6 \pm 11$ vs. $30.6 \pm 10$, respectively). A trend for an earlier age of illness onset was noted for patients treated with atypical antipsychotic agents versus patients not treated with these drugs, however, this trend disappeared after applying the Bonferroni correction. An earlier age of illness onset was also noted in patients receiving neuroleptics versus patients not receiving them (see Table 2).

Patients receiving antidepressants tended to have a later age at onset of illness versus patients not receiving them (see Table 2). No other statistically significant differences were noted for age of illness onset between patients taking any other specific drug or combination of these drugs compared to patients not taking them. Using a one-way ANOVA, no difference for age at onset of illness was found between the groups of patients taking one or two or three or four or more psychotropic drugs.

Number of hospitalizations for manic, depressive or mixed episodes

Patients taking either antidepressants or lithium and carbamazepine in combination had a lower mean number of hospitalizations for mania as compared to patients not taking them.

Patients taking antipsychotic drugs had a higher mean number of hospitalizations for mania as compared to patients not taking them. The number of drugs used was found to correlate with number of hospitalizations for depression. Thus, in subjects receiving one psychotropic drug, the mean number of hospitalizations for depression was 3.5 ($\pm 4$), in those receiving two drugs it was 3 ($\pm 5$), three drugs it was 3.7 ($\pm 5$), four drugs it was 4.9 ($\pm 6$), five drugs it was 5.2 ($\pm 11$), six drugs it was 6.8 ($\pm 4$), and in one subject receiving seven drugs it was 7 (r = 0.132, p < 0.04) (see Table 3). No other differences were found for either the number of total hospitalizations, number of hospitalizations for mania, depression or for mixed states among subjects receiving certain types or combinations of psychotropic agents versus those not receiving them.

Independent living and employment status

There were no significant differences between men versus women or younger versus older patients regarding independent living or employment status. No significant difference in the ability to live independently or employment status (unemployed versus employed) was noted between subjects taking any specific drug or combination of drugs versus subjects not taking them. Similarly, no statistically significant difference for the number of psychotropic drugs used was found between subjects whose independent living was affected by the illness (i.e. unable to live independently) versus those subjects who were unaffected. Similarly, there were no effects noted for the numbers of prescribed psychotropic agents and employment status.

Attempted suicide

There was a trend for more females (71%) than males (29%) to attempt suicide (165 females/68 males attempted suicide versus 127 females/75 males not attempting suicide respectively; $\chi^2 = 3.09$, df = 1, p < 0.08).

More subjects below the age of 40 attempted suicide compared to subjects 40 years or older [129/220 (59%) vs. 104/215 (48%), $\chi^2 = 4.6$, df = 1, p < 0.04]. When the years of education were considered as a continuous variable, subjects attempting suicide tended to have fewer years of education (t = 5.018, df = 433, p < 0.001). Subjects attempting suicide were also more likely to be unable to live independently at some time point in their illness as compared to patients not attempting suicide [66/92 (72%) vs. 31/65 (48%); $\chi^2 = 9.33$, df = 1, p = 0.002]. Subjects attempting suicide were also

Table 3. Comparison of number of hospitalizations in several psychotropic treatment groups*

| Medication groups | Mean $\pm$ SD hospitalizations for mania | Independent t-test | Significance | Significance after Bonferroni correction** |
|---|---|---|---|---|
| AD (n = 116) | 3.1 $\pm$ 4 | t = 2.92 | p = 0.004 | Yes |
| Non-AD (n = 124) | 5.3 $\pm$ 7 | | | |
| AP (n = 95) | 5.4 $\pm$ 7 | t = 2.57 | p = 0.01 | Yes |
| Non-AP (n = 145) | 3.5 $\pm$ 5 | | | |
| Li & Car (n = 12) | 2.3 $\pm$ 2 | t = −3.56 | p = 0.01 | Yes |
| Non-Li & Car (n = 228) | 4.4 $\pm$ 6 | | | |

AD = antidepressant drugs; Non-AD = non-antidepressant drugs; AP = antipsychotic drugs; Non-AP = non-antipsychotic drugs; Li & Car = lithium and carbamazepine combination; Non-Li & Car = other psychotropic drugs excluding lithium and carbamazepine combination.

* No significant results in one-way ANOVA were found for all other specific psychotropics and its combinations for number of hospitalizations of mania. No such significant results were found for all specific psychotropics and its combinations for number of hospitalizations for depression or mixed episodes.

** Significance level after Bonferroni correction for specific drugs and its combinations was 0.0025, and for the larger groups of antipsychotics and antidepressants it was 0.025.

Table 4. Percentage of subjects attempting or not attempting suicide distributed among the different psychotropic drug classes #

| | Lithium (n = 226) | SSRIs (n = 123) | AD (n = 250) | Traditional AP (n = 93) | AP (n = 141) |
|---|---|---|---|---|---|
| Attempting suicide (n = 233) | 45% | 33% | 63%* | 25% | 37%* |
| Not attempting suicide (n = 202) | 55% | 23% | 51% | 17% | 27% |

AD = antidepressants; AP = antipsychotic agents; SSRIs = selective serotonin reuptake inhibitors.
# No significant results in one-way ANOVA were found for all other specific psychotropics and its combinations, or with number of psychotropic drugs used. All psychotropic drugs mentioned above had statistical significance for Pearson chi-square test before Bonferroni correction for multiple correlations.
# Significance level after Bonferroni correction for specific drugs and its combinations was 0.0025, and for the larger groups of antipsychotics and antidepressants was 0.025.
* Pearson chi-square test corrected with Bonferroni correction for multiple correlations showed statistical significance.

more unlikely to live independently presently compared to subjects not attempting suicide [31/41 (72%) vs. 13/27 (48%); $\chi^2 = 5.38$, df = 1, p = 0.02]. Also, subjects attempting suicide tended to be more unemployed at the time of the interview than at some other time point of their illness compared with subjects not attempting suicide [45/49 (92%) vs. 31/40 (78%); $\chi^2 = 3.63$; df = 1, p = 0.057]. Subjects attempting suicide had an earlier age of illness onset as compared to subjects not attempting suicide (29.4 ± 10 vs. 32.71 years, t = 3.24, df = 392, p = 0.01). Table 4 presents data regarding the use of specific drugs and their combinations in patients with a history of attempted suicide versus subjects without such a history. Using the *t*-test for independent samples, no difference for the numbers of psychotropic drugs prescribed was found between subjects with and without a history of suicide attempts.

## Discussion

### Characteristics of the 'average' bipolar I patient

The emerging data (see Table 1) indicate the characteristics of the average bipolar I patient presenting himself to a voluntary registry. Such a patient is typically in his 40s, more prone to be single, divorced or separated with a high school education or higher. He has been ill for about 10 years with an illness onset in his early 30s. Such a patient would have experienced about five to six hospitalizations and have a one in two chance of having attempted suicide, nearly always during a depressed episode.

Although the information regarding employment status and independent living was gathered only from a sub-sample, it does appear that a significant number of patients are impacted by the illness in both these important functional areas. If these data are generalizable, this may suggest that the average bipolar patient has more than a 50% chance to be unemployed and/or to be unable to live independently. Such a high rate of suicidality, unemployment and inability to live independently seems to be in agreement with the reports of other groups. Thus, Roy-Byrne et al. (6), Kessler et al. (7) and Goodwin and Jamison (8) reported that 25–50% of bipolar patients attempted suicide at least once. Kessler et al. (7) conducting a US National Comorbidity Survey (NCS) reported that their 29 bipolar subjects were significantly more likely to have an income of less than $20000 (OR = 15.2, 95% CI = 4.7–49), possibly indicating illness-related impairment of functioning. Also, Dion et al. (9) reported that 6 months after discharge from hospital, almost 80% bipolar patients were symptom free or only mildly symptomatic, however, only 43% were employed, and only 21% worked at their expected level of employment. In the Dion et al. study (9), additional analysis showed that while 64% of first admission patients worked, this was true only for 33% of multiple admissions subjects.

Finally, Lish et al. (10) in a large self report survey of members of the National Depressive and Manic-Depressive Association which included bipolar I and II patients (based on the subjects' self report) reported that 37% of these subjects were unemployed, another 17% were employed only part time, another 10% were retired, 4% were students, and only 33% worked full time.

### Age of onset

Goodwin and Jamison (8) surveying the literature suggest that the mean age of onset for bipolar illness is about 30 years. A more recent report of Lish et al. (10) reported a much earlier age of onset. Eighty-four percent of their subjects reported an age of onset before the age of 30 years and 59% before the age of 20 years. Our overall results seem to agree with Goodwin and Jamison (8). However, the mean age of illness onset in the current study for younger patients born after 1955 was found to be significantly lower (nearly 25 years) compared to that for patients born before

1955 (nearly 37 years). Such an association between young current age and younger age of onset was also reported by Grgoroiu-Serbanescu et al. (11). Although other explanations are possible, this finding may be in agreement with evidence regarding the phenomenon of 'anticipation' in bipolar illness. Anticipation is mainly defined by the appearance of an earlier age of illness onset and/or increased severity of the illness in subsequent generations. However, it may be argued that the data presented here are much too crude to address a complex concept like anticipation, and so the above suggestion should be taken as tentative.

### Level of functioning

Except for suicidality, the current study found no correlation between the inability to live independently or to work or drive with other demographic and illness-related variables measured or with any of the prescribed psychotropic medication and its combinations. However, Meeks (12) studying global functioning in bipolar disorder in later life, using the GAS reported that early age of illness onset in these subjects was associated with poor functioning, and that this was apparently associated with increased number and severity of depressive episodes. Solomon et al. (13) suggested that adequate lithium treatment (therapeutic serum lithium levels) was associated with improved social functioning as compared to patients with low serum lithium levels. As our data were cross sectional rather than longitudinal, this last suggestion could not be evaluated in our sample.

### Suicide attempts

More than half of the subjects attempted suicide, nearly always while experiencing a depressive episode. Such suicide attempts tend to occur in younger subjects and in subjects with an earlier age of illness onset. Our findings suggest that these subjects are more likely to be female, to demonstrate an earlier age of illness onset, tend to have fewer years of education, and tend to be currently unemployed and/or are unable to live independently. Goodwin and Jamison [(8), p. 228] reported that 25–50% of bipolar patients attempted suicide at least once, and that similar to the general population, there were more women who attempted suicide. For instance, Roy-Byrne et al. (6) found that in a sample of 67 bipolar subjects and 20 unipolar subjects, 65% of the females attempted suicide as compared to 42% of the male subjects. However, Kessler et al. (7) in a small sample (n = 29) of bipolar patients found no clear differences in

suicide attempts between males and females. Interestingly, Goodwin and Jamison [(8), p. 239] analyzing the literature, suggested that increased risk for attempted suicide tended to occur at the first episode of affective illness or early in the course of illness, but the severity of such attempts was correlated with the duration of illness. Johanson and Hunt (14) studying the timing of suicide attempts, reported that 30% of such attempts occurred at the onset of illness or during the first episode of depression. The median lag time was 5.5 years, suggesting that such attempts tended to occur during the early years of the illness. While our data could not be analyzed as to the timing of the attempt, it does indicate that most attempts occurred during depressive episodes.

Other studies also suggest that there is an increased risk for such behavior in subjects showing depressive symptoms either as a part of mixed state or mania. Thus, Dilsaver et al. (15) and Goldberg et al. (16) reported that patients with mixed states had higher rates of suicidality compared to manic patients (55% vs. 2% and 58% vs. 1%, respectively), while Strakowski et al. (17) – studying suicidality among patients with mixed and manic bipolar disorder – reported that it is the severity of concurrent depressive symptoms in mania rather than the presence of depressive syndrome *per se* (i.e. mixed state), that is associated with suicidality in bipolar patients.

### Associations among prescribed psychotropic drugs, illness-related variables, levels of functioning and suicidality

Since our data regarding psychotropic drug therapy are cross sectional, the associations found between specific psychotropic drugs and their combinations with illness-related variables, levels of functioning and suicidality may indicate whether these variables influence the 'real life' decision making of the psychiatrist regarding the use of different psychotropic drugs in these patients. Being cross-sectional, our data cannot examine findings from other reports of decreased suicidality with lithium (18) and possibly by other mood stabilizers (19) or the effect of mood stabilizer therapy on levels of functioning and course of illness.

*Antidepressants*. The duration of illness was found to be shorter for subjects treated with antidepressants, and subjects treated with these drugs also showed a later age of onset. Also, patients treated with antidepressants had fewer hospitalizations for manic episodes, and a higher number of subjects

taking them attempted suicide compared with those not taking them. This may suggest that clinicians may be more likely to prescribe these drugs to patients having fewer manic episodes, more depressive episodes, and having a positive history of one or more suicide attempts. Also, perhaps there is a tendency to prescribe antidepressants less in the management of younger groups of bipolar illness probably due to their mania-inducing or cycle-accelerating effects. Alternatively, it might be that patients that are prescribed antidepressant agents came to treating physicians later because the dominant feature of the illness was depression and thus were first diagnosed at a later stage of their illness.

*Antipsychotic agents.* Patients who were treated with antipsychotic drugs tended to have a younger age at onset. This confirms earlier data that earlier age of onset is more likely to be associated with psychotic manic symptoms (20) or that psychiatrists are more likely to use antipsychotic agents in younger subjects due to a more severe manic episode with agitation. Patients taking antipsychotic medications had more hospitalizations for manic episodes compared to those not taking them, and were also more prone to suicide attempts. This suggests that psychiatrists tend to use more antipsychotic treatment in younger patients having several manic episodes and history of suicidality.

*Mood stabilizers.* Patients taking a combination of lithium and carbamazepine (n = 12) tended to demonstrate fewer hospitalizations for manic episodes compared to those not taking them. This cannot be easily interpreted as a tendency of psychiatrists to prescribe this combination to patients having fewer hospitalizations for mania and may reflect advantages of this combination in preventing manic episodes and consequent hospitalizations. Previous reports suggested that lithium and carbamazepine combination may have an advantage in the treatment of bipolar disorder over each drug given separately (21, 22). However, at the present, there are no large scale studies comparing the efficacy of this combination therapy to monotherapy employing random assignment to parallel groups. As stated above, maintenance studies reported that lithium may be associated with a lower suicide risk, and it is an open question whether anticonvulsants share such effects (18, 19, 23, 24). As stated above for other variables, these cross-sectional data do not enable the evaluation of anti-suicidal effects of lithium, as have been noted by others (25).

*Limitations of the current study*

The current study has several limitations. First, the current study was a cross-sectional, and not a longitudinal study. It thus did not enable the longitudinal assessment of psychotropic treatment effect on variables as suicidality and level of functioning. Secondly, no data about the patients symptomatology at the time of the study were available. Such data would enable to examine the association between the psychotropic medication prescription and current symptomatology. It would also have enabled us to make some judgmental evaluations as to the nature and quality of information supplied by the subjects. For example, manic patients tend to minimize impairment associated with the illness, while depressed patients may exaggerate it. Thirdly, comorbidity of physical illnesses, drug and alcohol abuse and other psychiatric disorders may affect the level of functioning, and these were not reported here. In addition, self report has its own limitations, and it may be influenced by various motivations unknown to the researchers.

Our results should be considered as suggestive only when other geographical and cultural regions are considered. Cultural habits and ways of communicating such as the patient role, shared belief systems, and/or symbolic concepts whether mediated (or not) by language vary across geographic regions [(8), pp. 177–185]. Also, different patterns of inbreeding and migration may affect gene pools, and factors such as level and quality of nutrition as well as daily hours of light are different from one geographical location to the other.

The present data were gathered from a voluntary self-report registry. Some of the subjects chose to skip or not to answer certain questions and thus only a portion of the sample was assessed for certain parameters. Although such refusal may suggest that there may be a tendency to deny distressing issues, including impaired level of functioning, history of suicidality, yet other explanations are possible. We preferred to avoid speculating about such phenomena. Other self-report surveys demonstrate the same phenomena (10), and this is a clear limitation of the current study.

### Conclusions

The results of the current and previous reports (3) suggest that the psychiatrist deciding upon a treatment strategy for his bipolar patient is less likely to be influenced by the patient's ability to live independently or by his employment status or by the age of onset and duration of illness, indirectly suggesting that it is the nature, course and severity

of the illness episode and its symptomology that influence treatment strategies.

Based upon the data presented in the current paper as well as in a previous one (3), both analyzing the same cohort of patients, our data suggests that polypharmacy is the rule rather than the exception with bipolar I patients. More than two-thirds of subjects were prescribed antidepressant medications and more than one-third were prescribed antipsychotic agents. On the other hand, about 18% of these patients were not prescribed any mood stabilizers at all. Only a few illness-associated trends seemed to emerge demonstrating a specific influence on prescribing patterns of the psychiatrist treating these patients. However, it appears that the majority of these subjects are either currently unemployed or unable to live independently or unable to carry on with daily activities such as driving. These data also suggest that so called 'rational polypharmacy' while impacting symptoms may be inadequate at returning subjects to improved productivity or functioning. This is especially troublesome as many subjects had achieved significant levels of education prior to the onset of the illness. Therefore, although combination therapy is used widely, and its use supported by the literature, its therapeutic impact on functioning capacity appears to be far from satisfactory.

Finally, as the data are cross sectional and not longitudinal in nature, and we do not have data on the patient symptomatology, our conclusions should be considered tentative and preliminary.

## References

1. Post RM, Frye MA, Leverich GH, Denicoff KD. The role of complex combination therapy in the treatment of refractory bipolar illness. CNS Spectrum 1998; 3: 66–86.
2. Sachs GS. Bipolar mood disorders: practical strategies for acute and maintenance phase treatment. J Clin Psychopharmacol 1996; 16 (Suppl 1): 32S–47S.
3. Levine J, Chengappa KNR, Brar JS, Gershon S, Yablonsky E, Stapf D, Kupfer DJ. Psychotropic drug prescription patterns among patients with bipolar I disorder. Bipolar Disord 2000; 2: 120–130.
4. Cluss PA, Marcus SC, Kelleher KJ, Thase M, Arvay LA, Kupfer DJ. Diagnostic certainty of a voluntary bipolar disorder case registry. J Affect Disord 1999; 52: 93–99.
5. First MB, Spitzer RL, Gibbon M, Williams JBW. Structured Clinical Interview for DSM-IV Axis I Disorders – Patient Edition. New York: New York State Psychiatric Institute, 1995.
6. Roy-Byrne PP, Post RM, Hambrick DD, Leverich CG, Rosoff AS. Suicide and course of illness in major affective disorder. J Affect Disord 1988; 15: 1–8.
7. Kessler RC, Rubinow DR, Holmes C, Abelson JM, Zhao S. The epidemiology of DSM-III-R bipolar I disorder in a general population survey. Psychol Med 1997; 27: 1079–1089.
8. Goodwin FK, Jamison KR. Manic-depressive Illness. New York: Oxford University Press, 1990.
9. Dion GL, Tohen M, Anthony WA, Waternaux CS. Symptoms and functioning of patients with bipolar disorder six months after hospitalization. Hosp Community Psychiatry 1988; 39: 652–657.
10. Lish JD, Dime-Meenan S, Whybrow OC, Price RA, Hirschfeld RMA. The national depressive and manic depressive association (DMDA) survey of bipolar disorder. J Affect Disord 1994; 31: 281–294.
11. Grgoroiu-Serbanescu M, Wickramarante PJ, Hodge SE, Milena S, Mihailescu R. Genetic anticipation and imprinting in bipolar I illness. Br J Psychiatry 1997; 170: 162–166.
12. Meeks S. Bipolar disorder in the latter half of life: symptoms presentation, global functioning and age of onset. J Affect Disord 1999; 52: 161–167.
13. Solomon DA, Ristow WR, Keller MB, Kane JM, Gelenberg AJ, Rosenbaum JF, Warshaw MG. Serum lithium levels and psychosocial function in patients with bipolar I disorder. Am J Psychiatry 1996; 153: 1310–1317.
14. Johanson SF, Hunt G. Suicidal behavior in bipolar manic-depressive patients and their families. Comprehensive Psychiatry 1979; 20: 159–164.
15. Dilsaver SC, Chen YW, Swann AC, Shoaib AM, Krajewski KJ. Suicidality in patients with pure and depressive mania. Am J Psychiatry 1994; 151: 1312–1315.
16. Goldberg JF, Carno JL, Leon AC, Kocsis JH, Portera L. Association of recurrent suicidal ideation with nonremission from acute mixed mania. Am J Psychiatry 1998; 155: 1753–1755.
17. Strakowski SM, McElroy SL, Keck PE, West SA. Suicidality among patients with mixed and manic bipolar disorder. Am J Psychiatry 1996; 153: 667–674.
18. Tondo L, Baldessarini RJ, Hennen J. Lithium and suicide risk in bipolar disorder. Primary Psychiatry 1999; 6: 51–56.
19. Goodwin FK, Ghaemi SN. The impact of mood stabilizers on suicide in bipolar disorder: a comparative analysis. Primary Psychiatry 1999; 6: 61–66.
20. Rosen LN, Rosenthal NE, Van Dusen PH, Dunner DL, Fieve RR. Age of onset and number of psychotic symptoms in bipolar I and schizoaffective disorder. Am J Psychiatry 1983; 140: 1523–1524.
21. Fawcett J, Kravitz HM. The long-term management of bipolar disorders with lithium, carbamazepine, and antidepressants. J Clin Psychiatry 1985; 46: 58–60.
22. Denicoff KD, Smith-Jackson EE, Disney ER, Ali SO, Leverich GS, Post RM. Comparative prophylactic efficacy of lithium, carbamazepine, and the combination in bipolar disorder. J Clin Psychiatry 1997; 58: 470–478.
23. Nilsson A. Lithium therapy and suicide risk. J Clin Psychiatry 1999; 60 (Suppl 2): 85–88.
24. Goodwin FK. Anticonvulsant therapy and suicide risk in affective disorder. J Clin Psychiatry 1999a; 60 (Suppl 2): 89–93.
25. Baldessarini RJ, Tondo L, Hennen J. Effects of lithium treatment and its discontinuation on suicidal behavior in bipolar manic-depressive disorders. J Clin Psychiatry 1999; 2: 77–84.