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Research report

Is bipolar disorder still underdiagnosed? Are antidepressants overutilized?

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Abstract

Background: Previous studies have suggested that bipolar disorder may be underdiagnosed, and that antidepressants may be over-utilized in its treatment. Methods: Consecutively admitted patients (n 5 48) diagnosed with DSM-IV bipolar disorder, type I, (n 5 44) or schizoaffective disorder, bipolar type, (n 5 4) were interviewed systematically and their charts were reviewed to confirm diagnosis before admission. They were then treated according to systematic structured interview diagnoses. These data reflect the changes in diagnoses and treatment. Results: 40% (19/48) were identified with previously undiagnosed bipolar disorder, all previously diagnosed with unipolar major depressive disorder. A period of 7.56 9.8 years elapsed in this group before bipolar diagnosis was made. Antidepressant use was high on admission (38%) and was reduced with acceptable treatment response rates. The adjunctive use of risperidone appeared to be a good treatment alternative. Limitations: While diagnoses were made prospectively, treatment response was assessed retrospectively, and was based on non-randomized, naturalistic therapy. Conclusions: Systematic application of DSM-IV criteria identified previously undiagnosed bipolar disorder in 40% of a referred population of patients with mood disorders, all previously misdiagnosed as unipolar major depressive disorder. Antidepressants appeared overutilized and risperidone was an effective alternative adjunctive therapy agent.

Keywords: Bipolar disorder; Drug therapy; Diagnosis; Nosology; Antidepressants; Treatment; Depression; Manic-depressive illness

1. Introduction

The diagnosis and treatment of bipolar disorder is often difficult. In the recent past, it was recognized

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that patients with bipolar disorder were often confused diagnostically with schizophrenia (Pope and Lipinski, 1978). With DSM-III and the adoption of neo-Kraepelinian nosology, this differential diagnosis was more carefully defined, and by DSM-IV, a broad consensus appeared to be reached in differentiating bipolar disorder from schizophrenia clinically (Goodwin and Jamison, 1990). However, since the introduction of newer safer antidepressant agents in the past decade, there may have been an increase in the diagnosis and treatment of major depression, perhaps in part related to the introduction of treatments for the diagnosis (''treatment-oriented observation bias'' or Klerman's ''pharmacocentric view of the world'') (Stoll et al., 1993). While this factor is only one of a variety of possible explanations for this cohort effect, the move towards more aggressive diagnosis and treatment of depression may explain reports of possible overutilization of antidepressants in the treatment of bipolar disorder (Wehr and Goodwin, 1987; Sachs, 1996). This overutilization of antidepressants has been associated with increased risk of drug-induced mania (30–70% of patients with bipolar disorder treated with antidepressants alone) (Goodwin and Jamison, 1990) and possible worsening of the long-term course of bipolar disorder by the induction of treatment-resistant rapid-cycling episodes (26–51% of patients with bipolar disorder treated with antidepressants chronically) (Kukopulos et al., 1983; Wehr and Goodwin, 1987; Altshuler et al., 1995; Kukopulos et al., 1980; Quitkin et al., 1981). There is some evidence that patients with milder variations of bipolar disorder, such as type II, may be at more risk of misdiagnosis as unipolar major depressive disorder and overtreatment with antidepressants resulting in a worsened rapid-cycling course (Altshuler et al., 1995).

Experts in the treatment of bipolar disorder have thus recommended careful diagnosis and avoidance of antidepressant treatment except in the brief short-term treatment of severe acute bipolar depression in conjunction with mood-stabilizing agents (Goodwin and Jamison, 1990; Stoll et al., 1993; Sachs, 1996). We wished to assess the standard of care in one community for the diagnosis and treatment of bipolar disorder, with special attention to the above recommendations. We asked the following questions: Is bipolar disorder underdiagnosed, and if so, is it frequently mistaken for unipolar major depressive disorder? Are antidepressants utilized more frequently than necessary and prudent? To what extent are mood-stabilizing agents used? Can the acute major depressive episode in bipolar disorder be effectively treated with mood-stabilizing agents alone without using antidepressant agents? Can the use of antidepressants be minimized by the aggressive utilization of mood-stabilizing agents and other adjuncts for the treatment of bipolar disorder (particularly, typical and atypical neuroleptic agents, and clonazepam)?

2. Methods

Charts of all consecutive patients with the hospital diagnosis of bipolar disorder, type I (n 5 50) or schizoaffective disorder, bipolar type (n 5 5) hospitalized on an affective disorders unit over 12 months in an urban academic hospital were reviewed. Seven patients were excluded from further analysis due to experiencing a first manic episode (n 5 2) or not previously seeking psychiatric treatment (n 5 5). The final sample thus consisted of 48 patients, 44 with bipolar disorder, type I and four with schizoaffective disorder, bipolar type.

This consecutive sample of patients admitted to the hospital was interviewed with a semi-structured checklist of DSM-IV criteria and a diagnosis was made. The treatment that the patients received was based on that diagnosis. This was then compared to the diagnosis that was made by the referring physician or that the patients themselves were told they possessed when they came to the hospital. Data included in this assessment came from three sources where available: repeated clinical interview with the patient, outside report from family, case managers, or other clinicians, and review of previous hospital records.

Treatment response was judged retrospectively using the Clinical Global Impression scale of Improvement (CGI-I). Other clinical and demographic data gathered at chart review were the following: age, sex, race, family history of psychiatric illness, presence of comorbid personality disorders, current substance abuse status, length of hospitalization, age of 1st episode of illness, number of years ill,

presence of psychosis, years to diagnosis of bipolar disorder, medications on admission, evidence of past noncompliance, discharge mood stabilizer levels, and whether the patient was discharged against medical advice. Medication treatments before admission, on admission, and at discharge were also assessed.

Statistical analyses consisted of unpaired and paired t-tests, and Fisher's exact tests.

3. Results

Clinical and demographic characteristics of the sample are provided in Table 1.

Table 2 describes the diagnostic and treatment characteristics of the sample. Most patients were not previously diagnosed with bipolar or schizoaffective disorder. The most common previous diagnosis was unipolar major depressive disorder. The majority of patients were not receiving treatment with mood-stabilizing agents, 1/3 were receiving treatment with antidepressant agents, often without mood-stabilizing agents. 71% had received mood-stabilizing agents, and slightly more had received antidepressant medications, at some time in their treatment history. Almost all patients were successfully put on mood-stabilizing medications and taken off antidepressant agents by discharge, with an increase in use of (mainly atypical) neuroleptic agents compared to admission. Discharge mood stabilizer levels were therapeutic (lithium 0.716 0.17, valproate 69.16 21.8, and carbamazepine 7.56 2.4).

Fig. 1 illustrates the time that passed from the patients' first mental health professional contact until diagnosis of bipolar disorder was made. In the 57% (25/44) of patients with bipolar disorder who were previously diagnosed before admission into the study, bipolar diagnosis was made within the first

Table 2
Diagnostic and treatment characteristics of the sample (n 5 48)

Diagnoses before admission	% (n)
Bipolar disorder	56 (27)
Unipolar disorder	40 (19)
Schizophrenia	2 (1)
Schizoaffective disorder	2 (1)
Discharge diagnoses: Bipolar subtype or schizoaffective	
Depressed	21 (10)
Manic	29 (14)
Mixed	21 (10)
Rapid-cycling	21 (10)
Schizoaffective (manic)	8 (4)
Ever treated with mood stabilizers	71 (34)
Treated with mood stabilizers on admission	38 (18)
Treated with mood stabilizers on discharge	96 (46)
Ever treated with antidepressants	75 (36)
Treated with antidepressants on admission	33 (16)
Treated with antidepressants on discharge	8 (4)
Ever treated with neuroleptics	52 (25)
Treated with neuroleptics on admission	23 (11)
Treated with neuroleptics on discharge	50 (24)

Table 1
Clinical and demographic characteristics of the sample (n 5 48)

Race (%)	Sixty-nine Caucasian, twenty-seven African–American, four Hispanic or Asian
Gender (% female)	71
Age (mean 6 SD years)	36.26 9.6
Age at first episode (mean 6 SD years)	23.46 9.8
Years ill (mean 6 years)	12.76 8.1
Comorbid substance abuse (%)	48
Comorbid personality disorder (%)	38
History of medication noncompliance (%)	66
Psychosis present (%)	27
Definite family history of diagnosed bipolar disorder (%)	19
Family history of any psychiatric illness (%)	42
Ave. length of stay (mean 6 SD days)	9.16 7.5
Discharged against medical advice (%)	8

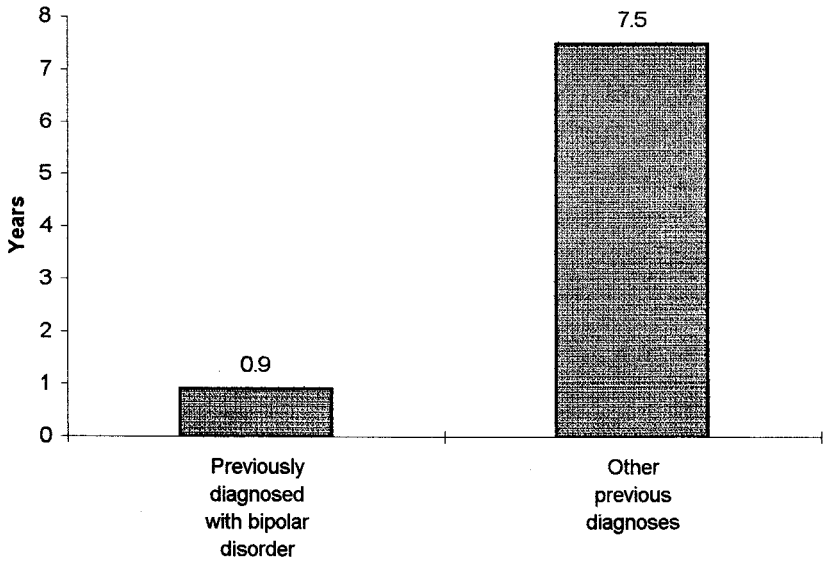

Fig. 1. Years to bipolar diagnosis from first contact with a mental health professional (psychiatrist or psychotherapist) in those previously diagnosed with bipolar disorder (n 5 25) vs. those with other diagnoses (all unipolar major depressive disorder) before study (n 5 19).

year of mental health treatment (0.96 2.2 years). In the 43% (19/44) of patients with bipolar disorder who did not get diagnosed until entry into this study (all of whom were previously diagnosed with unipolar major depressive disorder), 7.56 9.8 years elapsed before the diagnosis of bipolar disorder was made (t 5 2.96, df 5 41, P 5 0.005, paired t-test).

By discharge, 63% (n 5 30) of the sample was treated with valproate, 27% (n 5 13) with lithium, and 19% (n 5 9) with carbamazepine, with some treated in combination. Two patients refused any medication treatment on discharge against medical advice. The three most common treatment choices were valproate plus adjunct (30%), valproate alone (20%), and lithium and anticonvulsant6 adjunct (13%). The most common adjuncts were ''typical neuroleptic'' (30%), risperidone (22%), and clonazepam (17%). Only two patients (4%) were discharged with antidepressant treatment. Response rates (defined as moderate to marked improvement on the CGI scale (score . 2)) were the same (50%) across bipolar subtypes: acute bipolar depression (n 5 10), acute pure mania (n 5 16), acute mixed episodes (n 5 14), and rapid-cycling episodes (n 5 10). All four patients with acute mania as part of schizoaffective disorder responded.

Fig. 2 summarizes treatment response in the entire sample of patients treated with any mood stabilizing agent alone or in combination with another mood stabilizer (valproate plus lithium was the main combination used), clonazepam, typical neuroleptic agents, and risperidone. As shown in the figure, the combination of mood-stabilizing agent with risperidone compared favorably to the other treatment groups, particularly the neuroleptic-treated and clonazepam-treated groups.

Among ten bipolar patients with acute major depressive episodes, five showed moderate improvement. Eight were admitted on antidepressants, but only two were discharged on them. All received mood stabilizers on discharge. Lithium monotherapy was effective in 2/2 patients, and valproate monotherapy in 1/3 patients. When those treated with adjuncts are included, lithium-treated bipolar depressed patients seemed to respond somewhat better (4/5) than valproate-treated patients (1/5), although this difference was not statistically significant (P 5 0.21, Fisher's exact test).

4. Discussion

These results support the suggestion that bipolar

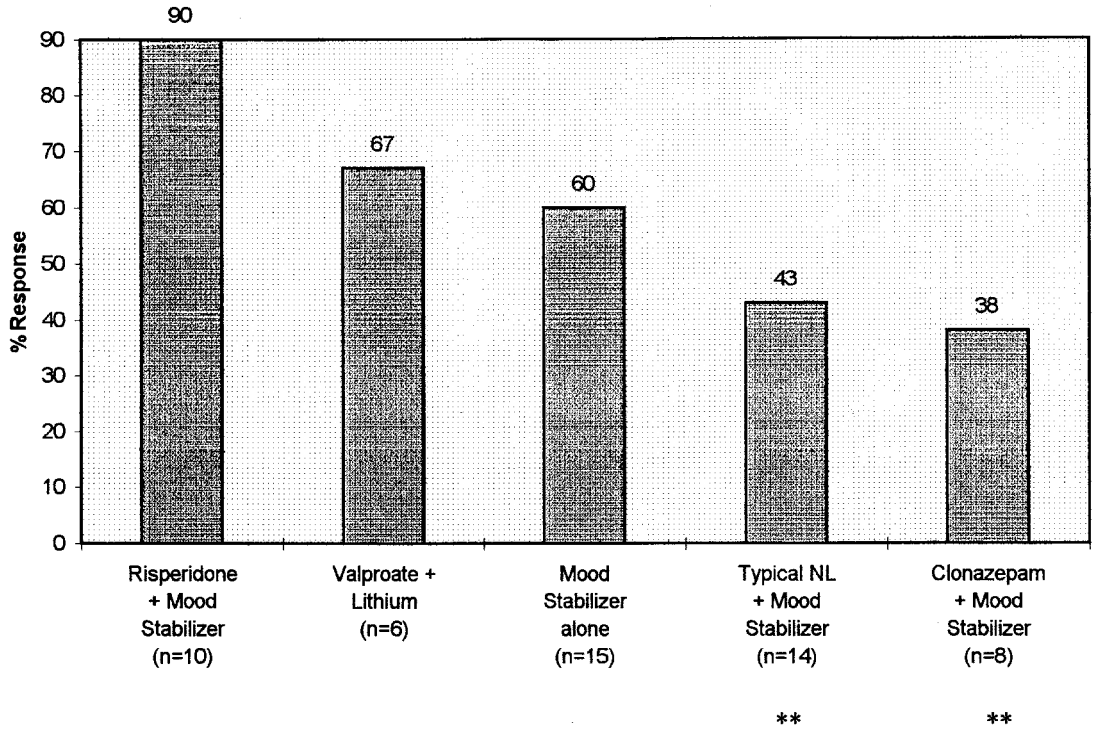

Fig. 2. Treatment response to mood-stabilizing agents and adjunctive treatments (n 5 46). Two patients refused treatment. Treatment response was based on the use of the specific agent (e.g., clonazepam) with any other combination of treatment i.e., (along with a mood stabilizer). Thus, there is some overlap in treatment groups in patients treated with two or more adjuncts simultaneously, and the sample sizes above add up to more than the 46 patients treated. **Differences between risperidone 1 mood stabilizer and typical NL 1 mood stabilizer, and between risperidone 1 mood stabilizer and clonazepam 1 mood stabilizer were statistically significant (P , 0.05, Fisher's exact test).

disorder is underdiagnosed. 40% of those patients who were diagnosed with bipolar disorder in this study had not been previously diagnosed with it (excluding first episode patients and those who did not seek previous treatment), and all of them were previously diagnosed with unipolar major depressive disorder. In those who were diagnosed with conditions other than bipolar disorder, about 7.5 years elapsed from their first mental health professional contact until the diagnosis of bipolar disorder was made. Further, mood stabilizing agents appeared underused in these patients, with only around one-third of patients taking them prior to hospitalization. Part of this underuse may involve patient non-compliance, but part of it probably also was related to lack of appropriate diagnosis of bipolar disorder. One-third of these patients were also taking antidepressants on admission. By discharge, all but 8% were off antidepressants and all but 4% were on mood-stabilizing agents, with a 50% response rate across the board in all bipolar subtypes, including acute bipolar depression. These results suggest that antidepressant use can be reduced with clinical improvement even in acutely depressed bipolar patients, at least in short-term treatment. In addition, among adjunctive treatments used, the two most promising approaches appeared to be adjunctive treatment with atypical antipsychotic agents like risperidone and the combination of mood stabilizers such as valproate plus lithium.

To our knowledge, this is the first clinical study of the relationship between the diagnosis of bipolar disorder in the community and subsequent rediagnosis in an academic center specializing in the disorder. The only other data that bears on this issue is from a survey of members of the National Depressive and Manic Depressive Association, who reported that they saw 3.3 psychiatrists on average

over about 8 years before being diagnosed with bipolar disorder (Anonymous, 1993). The present clinical study, in which the diagnosis of bipolar disorder was made with DSM-IV criteria applied prospectively to each patient, is consistent with the NDMDA survey results; that is, we found that about 8 years elapsed between initial clinical evaluation and the eventual bipolar diagnosis.

How these data relate to community diagnoses cannot be judged, but they clearly indicate an underdiagnosis of bipolar disorder in this population. The explanation for this difference could be varied. Clinical studies suggest that 35–60% of bipolar patients may experience at least one major depressive episode before their first manic episode. In this study, patients with first manic episodes were excluded and most patients were ill for over a decade (mean duration of illness 12 years), making the first factor an unlikely one. Also, in females, depressive episodes tend to predominate over manic episodes, whereas in males the reverse is often the case. (Goodwin and Jamison, 1990) There was a predominance of female patients in the sample, suggesting that this may, in part, explain the underdiagnoses. Another important clinical factor leading to misdiagnosis is lack of insight on the part of patients with bipolar disorder, especially during manic episodes, which keeps them from seeking assistance when manic or from reporting past manic symptoms when they do visit a clinician. It has been shown that about one-half of patients in an acute manic episode have moderate to severe impairment of insight (Ghaemi et al., 1995). In addition, perhaps clinicians do not ask about current or past manic symptoms in a systematic manner. The seven criteria described in DSM-IV may not be applied as frequently as the 8 major depressive criteria (Sprock, 1988), simply due to a lack of education regarding them. In this study, we simply applied those criteria to each patient, and we noted a marked increase in diagnosis of bipolar disorder. Also, we relied on outside information (chart, family report, with patient consent) in addition to the patient interview; such information may not be obtained frequently, perhaps due to excessive confidentiality concerns. In the Iowa 500 study (Tsuang et al., 1980), it was found that including information outside of the clinical interview increased diagnostic rates of bipolar disorder threefold. Further, one study (Keitner et al., 1996) found that families reported prodromal behavioral symptoms of mania twice as frequently as patients, while the two sources did not differ for depressive symptoms. Lastly, since patients frequently seek assistance while acutely depressed, it is possible that previous histories of manic symptoms were not elicited by clinicians who focused mainly on current symptomatology (Goodwin and Jamison, 1990). This would lead to underdiagnosis particularly in bipolar depressed and mixed bipolar patients, where confirming major depressive symptoms may not have been followed by careful examination of manic symptoms. Again, Kraepelin's appraoch of emphasizing longitudinal data, along with cross-sectional data, possesses diagnostic value.

Clinicians need to know that there are clinical considerations which assist in the diagnosis of bipolar disorder. Akiskal and Puzantian (1979) have identified a number of possible clinical features that may confuse the diagnosis: incomplete interepisode recovery can be confused with the declining course of schizophrenia; a rapid-cycling course impedes recognition of the classic recurrent course with episodic recovery; the predominance of irritability rather than euphoria may lead to underdiagnosis if euphoria is one's diagnostic standard; mixed states can be difficult to distinguish from agitated depression; superimposed substance abuse (which occurs in 60% of patients at some point in life; Brady and Sonne, 1995) can confuse the presence of manic symptoms; flight of ideas may be mistaken for formal thought disorder; and excessive reliance on Schneiderian criteria will lead to overdiagnosis of schizophrenia. We would also add that rapid-cycling bipolar disorder may be confused with chronic unipolar depression or borderline personality disorder (Bolton and Gunderson, 1996). If clinicians are aware of these phenomenological varieties of bipolar disorder, a certain amount of misdiagnosis might be avoided.

A simple consideration that needs to be mentioned is applying the manic criteria in themselves with each patient that is being screened for mood disorders. The DIGFAST mnemonic (Table 3) has been helpful to generations of residents at McLean Hospital. Even if applied assiduously, the criteria for bipolar disorder as stated in DSM-IV have been criticized for being too narrow. Akiskal (1996), for instance, has suggested that a spectrum of conditions

Table 3
The DIGFAST mnemonic for mania

Distractibility – the inability to maintain one's concentration, as opposed to the decreased concentration of depression, where one is unable to initiate concentration. In mania, this leads to multiple tasks, none of which are finished; and in depression, no task can be started easily.
Insomnia – decreased need for sleep, as opposed to the decreased sleep of depressive insomnia. the patients sleeps less, but has intact or increased energy the next day.
Grandiosity – can be inflated self-esteem as well, need not be delusional
Flight of ideas – the subjective experience of racing thoughts
Activities – increased goal directed activities (social, sexual, school, work, home activities); these are goal-directed and thus not dysfunctional. Increased libido is either not expressed in activity or associated with increased activity with one's usual sexual partner.
Speech – pressured; this is an objective sign observed on the mental status examination. A subjective alternative is increased talkativeness, which is determined by asking the patient or others whether the patient has been more talkative than usual (when euthymic).
Thoughtlessness – this refers to increased pleasurable activities with potential for painful consequences. Four stereotypic behaviors that may be asked about are sexual indiscretions, spending sprees, impulsive traveling, and reckless driving.

The diagnosis of mania is made when euphoric mood is present for one week with three of the DIGFAST symptoms, or irritable mood is present for one week with four of the DIGFAST symptoms, and there is significant social or occupational dysfunction. If there is no significant dysfunction, and the symptoms last four days at least, the diagnosis of hypomania is made. If the symptoms last less than four days, or if they are only present with antidepressant medications, a diagnosis of bipolar disorder, NOS, may be made. Credit this adaptation to S.N. Ghaemi, 1998.

constitute bipolar illness, and may involve similar pathophysiologies and treatment response characteristics (Table 4). Specifically, assessing patients' interepisodic personalities may be relevant. Hyperthymic temperament is characterized by a permanent hypomanic state at baseline personality, outside of specific mood episodes; these patients are ''cheerful and exuberant, extroverted, habitual short sleepers (less than 6 hours/night)'' and highly energetic, among other characteristics suggested by Akiskal. Patients with cyclothymic temperament have the same hypomanic baseline personality, alternating with mildly depressive symptoms that do not meet criteria for major depressive episodes. If baseline personalities are thus examined, perhaps a good number of patients currently diagnosed with unipolar

Table 4
The bipolar spectrum[a]

Subtype	Description
Bipolar I	At least one manic episode
Bipolar II	Recurrent major depression with hypomania and/or cyclothymic temperament
Bipolar III (NOS)	Recurrent major depression without spontaneous hypomania but often with hyperthymic temperament and/or bipolar family history
Unipolar major depression	No evidence for hypomania, cyclothymia, hyperthymic personality, or family history of bipolar disorder

[a]Based on Akiskal, 1996.

depression would be rediagnosed in the "soft" bipolar spectrum. While these considerations are relevant to any discussion of the nosology of bipolar disorder, it should be noted that the underdiagnosis documented in this paper involved classic type I bipolar patients, suggesting that broadening our nosology of the bipolar spectrum would reveal even more underdiagnosis than suggested in this paper. Table 4 most clearly delineates how unipolar major depression is essentially a diagnosis of exclusion, once mania, hypomania, cyclothymia, hyperthymia, and a bipolar family history are excluded. Our study would suggest that the clinical effort required to make these exclusions is sometimes not successfully achieved.

These findings regarding difficulties in the diagnosis of bipolar disorder are consistent with the observed treatment findings. As in a number of previous studies, antidepressant agents appeared overused in the treatment of bipolar disorder. In agreement with some other reports (Goodwin and Jamison, 1990; Davis et al., 1996), mood stabilizing treatment appeared to exert moderate antidepressant effects that were clinically helpful. Also, as in a number of previous studies, the use of atypical antipsychotic agents like risperidone (Tohen et al., 1994; Jacobsen, 1995; Ghaemi et al., 1997) and the combination of mood stabilizing agents (valproate plus lithium in particular) (Solomon et al., 1997) appeared clinically effective in this naturalistic setting. This would suggest that a good treatment paradigm for bipolar disorder would be to aggressively maximize mood stabilizing agents, combining them where necessary, and adding atypical antipsychotic agents like risperidone as adjunctive agents. Antidepressant agents might be reserved for those who do not show an antidepressant response to aggressive combination treatments after one to three months of pure chronic depression, and then tapered within one month of euthymia (Sachs, 1996). An algorithm derived from this study, the research literature, and our clinical experience, is included in the appendix as a guide for clinical practice.

4.1. Limitations of the current study

There are a number of limitations to the current report. First, the diagnostic rates obtained are based on the diagnostic methods and clinical interviewing skills of the researchers, as discussed in the methods section. Second, the data on previous treatments and symptoms are limited since they are based on a retrospective chart review; one would expect that such data would be limited by only revealing symptoms or treatments that were relatively severe and thus remembered by patients or available via hospital charts. Thus, the finding about the length of time that elapsed from first known professional contact until diagnosis of bipolar disorder may be, if anything, an underestimation of the time period involved. Third, the data regarding treatment outcome during hospitalization is limited due to being retrospective, uncontrolled, and limited to acute treatment without follow-up data after discharge; thus, one would have to view these data as limited and representative only of the acute inpatient naturalistic setting, needing to be confirmed with prospective, controlled methods. They serve nonetheless to make the point that bipolar disorder can be treated in this setting in the manner suggested. Fourth, the absence of some statistically significant treatment differences among adjunctive treatments may be due to the limitations just noted of the uncontrolled naturalistic setting, but also it may be influenced by the small sample sizes and resulting increased probability of type II error.

5. Conclusions

These results support the conclusion that bipolar disorder is underdiagnosed and frequently misdiagnosed as unipolar major depressive disorder. If not diagnosed early, patients with bipolar disorder remain undiagnosed for 7.5 years. Patients with bipolar disorder are not adequately treated with mood stabilizers in the community, and appear over-treated with antidepressant medications. Aggressive use of mood stabilizing agents produced acute response rates that were as good for depression, mixed states, and rapid-cycling as for pure mania. The addition of atypical neuroleptic agents to mood-stabilizing agents appeared to be among the more effective adjunctive treatments.

Acknowledgements

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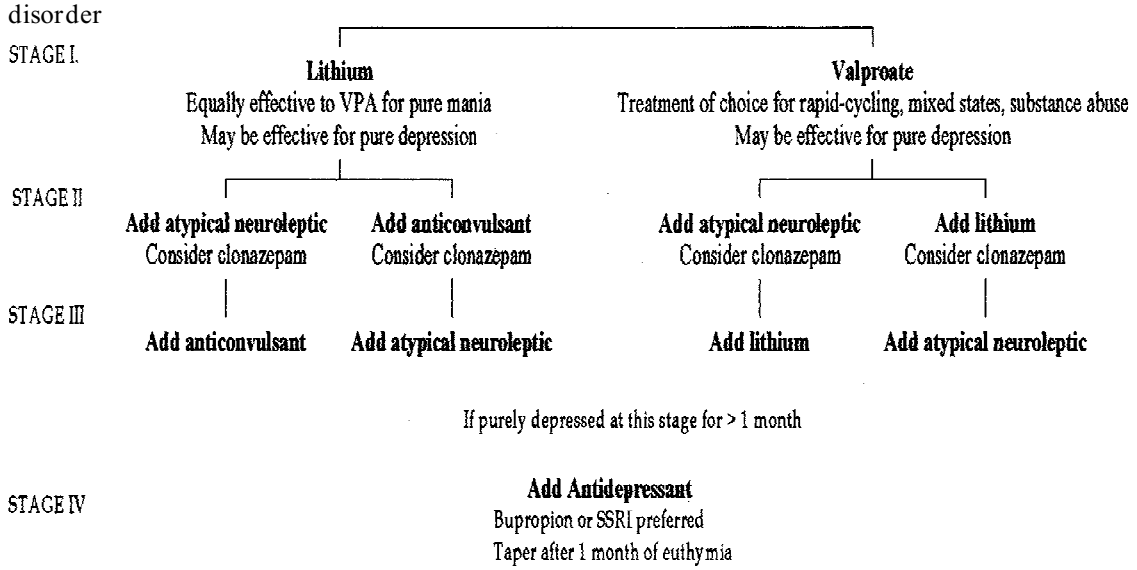
Appendix

An algorithm for the treatment of bipolar disorder



In stage I, it should be kept in mind that certain individuals may respond to lithium but not valproate, and vice versa. Sequence of agents in stages II and III is not yet definitively established based on the current data available. Stage IV may be moved up to earlier stages after stage I depending on the clinical setting (such as markedly suicidal hospitalized depression). Paroxetine may be preferred over other SSRIs at the present time because currently there is an absence of comparable controlled studies with other SSRI antidepressants while a double-blind, tricyclic-controlled study supports a decreased risk of mania with paroxetine (Young et al., 1997). Bupropion has been shown in double-blind (Sachs et al., 1994) and in clinical conditions to be a preferred agent as well with lower risk of mania than tricyclic agents. The availability of new anticonvulsants, like lamotrigine and gabapentin, may allow their use in this algorithm at stages II or III in the near future.

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