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Research report

A closer look at treatment resistant depression: is it due to a bipolar diathesis?

Verinder Sharma*, Mustaq Khan, Angela Smith

Mood Disorders Program, Regional Mental Health Care London, 850 Highbury Avenue North, P.O. Box 5532, Station B, London, ON, Canada N6A 4H1

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Abstract

Background: Treatment resistant depression is a common clinical problem. Studies have shown that a large number of patients with depression do not have a satisfactory clinical outcome in spite of adequate trials of antidepressant drugs. In this study, we investigated demographic and clinical characteristics, diagnostic subtypes, and illness outcome of patients with resistant depression and a history of escape of response to adequate trials of at least two antidepressants for a previous episode. *Method*: Sixty-one patients who were seen consecutively at a mood disorders clinic with the diagnosis of "unipolar" treatment resistant depression, and followed up for at least one year, were interviewed using the Structured Clinical Interview for DSM-IV. Prospectively collected data including the occurrence of episodes of hypomania, and supplemental information from family members on illness course were also used for purposes of diagnostic re-evaluation. *Results*: At intake, 35% of the patients were diagnosed as having a bipolar disorder. At follow-up, there was a 59% prevalence of bipolar disorder. Of the patients with major depressive disorder, 52% were subsequently classified as having bipolar spectrum disorder. The most important finding was that 80% of patients were found to show evidence of bipolarity. Moreover, the most common change in medication was a switch to mood stabilizers. CGI ratings showed significant improvement in functioning from the time of initial consultation. *Limitations*: This was a naturalistic study, and the data were collected in a non-blind fashion. *Conclusions*: The findings suggest that the majority of cases of unipolar treatment resistant depression, occurring in the context of loss of antidepressant response, have a bipolar diathesis.

Keywords: Resistant depression; Antidepressants; Loss of response; Mood stabilizers; Bipolar disorder

1. Introduction

The pharmacological treatment of depression has been revolutionized since the introduction of antidepressant drugs five decades ago. The availability of safe and well-tolerated drugs, combined with a heightened awareness of the disabling and recurrent nature of depression, has led to a significant increase in the utilization of these drugs. Despite such a widespread use of antidepressants (Hemels et al., 2002), treatment resistance is a common clinical problem. A meta-analysis of clinical trials reported rates of partial response in 12–15%, and nonresponse in 19–34% among antidepressant-treated patients (Fava and

* Corresponding author. Tel.: +1-519-455-5110x47392; fax: +1-519-455-3011.

E-mail address: vsharma@uwo.ca (V. Sharma).

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Davidson, 1996). Authors of a recent study from England concluded that the long-term outcome of depression does not appear to have changed in the last 20 years (Kennedy et al., 2003).

Treatment resistance has a major impact on health care utilization and costs, due to the extensive use of depression and non-depression related medical services. Patients with treatment resistant depression require more hospitalizations and are likely to receive more psychotropic medications (Crown et al., 2002). Due to its ubiquitous nature and the associated functional impairment, major depression is a major cause of disease burden around the world (Murray and Lopez, 1996).

Variables associated with poor response to antidepressants include the presence of psychiatric or medical comorbidity, older age, chronicity, and greater illness severity (Kornstein and Schneider, 2001). The diagnosis of bipolar disorder is not an uncommon cause of treatment resistance (Fagiolini and Kupfer, 2003). Antidepressants are commonly prescribed to patients with bipolar depression, in spite of limited evidence for efficacy (Ghaemi et al., 1999, 2001, 2002a,b). In addition to risks such as induction of mania or rapid cycling associated with their use (Goodwin and Jamison, 1990; Wehr and Goodwin, 1979), antidepressants are less effective for treating bipolar depression than major depressive disorder (Frankle et al., 2002). A study on the relationship between episode duration and antidepressant therapy concluded that over the past couple of decades little progress has been made in reducing the length of depressive episodes in bipolar disorder (Frankle et al., 2002).

There is also a concern that the use of antidepressants in some patients with major depression may lead to chronicity and treatment refractoriness. The majority of these patients, who experience a relapse in spite of the continued use of—or "overuse" of—antidepressants may have a bipolar diathesis or belong to a "soft" bipolar spectrum (Akiskal and Mallya, 1987) as suggested by irritable, cyclothymic or hyperthymic temperamental antecedents, depressive mixed states, antidepressant-induced alterations in the cyclic pattern of the illness, brief hypomanic features, and bipolar family history. These are the very patients those authors found to respond to lithium and/or low-dose neuroleptic augmentation. In another study, patients who relapsed on (an) apparently previous successful antidepressant(s) were more likely to have atypical symptoms of depression, postpartum episodes, and a family history of bipolarity (Sharma, 2001). Loss of antidepressant response or antidepressant "wear-off" usually refers to the phenomenon of acute but not prophylactic response (Ghaemi et al., 2002a,b). Results of a recent study showed that late loss of antidepressant response (defined as occurrence of major depression > 6 months post resolution of symptoms) was significantly more common in bipolar as opposed to unipolar depression (Ghaemi et al., 2002a,b). The loss of antidepressant effect has been described with various drugs from different classes. A variety of strategies including dose optimization, substitution or combination with another antidepressant, or addition of an augmenting agent have been recommended (Sharma, 2001). Some patients nevertheless require discontinuation of antidepressant therapy and introduction of mood stabilizers for alleviation of depression (Sharma, 2001).

In this paper we describe the demographic and clinical characteristics of patients who were referred to a mood disorders program for refractory depression. The patients had a history of escape of antidepressant response to at least two adequate trials of antidepressants for a prior episode. We were particularly interested in determining the prevalence of bipolarity, as a previous study reported that treatment resistance in certain patients might represent a bipolar diathesis (Sharma, 2001).

2. Method

A chart review was conducted during June 2000–May 2001 on consecutive outpatients who attended a mood disorders clinic at a psychiatric hospital over the past 1–10 years. The hospital, with a catchment area of over one million people, serves as a tertiary care facility for the Southwestern region of the province. Family physicians and psychiatrists referred the patients for assessment and treatment of refractory unipolar depression. To be eligible for assessment, the patient must have received continuous follow-up care for at least 1 year. Eligible patients were approached to participate in the study. Their participation was required because the study involved collecting some

new data from a diagnostic interview. The study received ethics approval from the institutional review board.

2.1. Definitions

For the index episode, treatment refractoriness was defined as failure to respond to two adequate trials of antidepressants. Adequacy of pharmacotherapy was determined using the criteria described by Amsterdam and Hornig-Rohan (1996). For example, treatment with imipramine ≥ 250 mg or phenelzine ≥ 60 mg for ≥ 6 weeks and fluoxetine ≥ 20 mg for 8 weeks amounted to "adequate" therapy. For at least one previous episode of depression, our patients had shown an antidepressant response but were unable to achieve full remission on two separate adequate trials of medications from different classes. Response was defined as absence of significant symptoms with no functional impairment over a period of less than 2 months. Full remission required a 2-month period of absence of significant symptoms while the antidepressant dose remained constant. In keeping with the MacArthur guidelines for operationalizing relapse (Hart et al., 2001), a relapse was defined as fulfillment of DSM-IV criteria for a major depressive episode less than six months following resolution of depression. Patients who showed an inadequate response that was sustained for six or more months were therefore excluded. Patients initially referred with bipolar I disorder, schizoaffective disorder, concurrently comorbid substance abuse disorder, mental retardation, or major physical illness were also excluded.

2.2. Clinical data

Detailed clinical information including demographic data, age of illness onset, duration and frequency of mood episodes, nature of symptoms, and DSM-IV diagnoses was obtained from 61 patients. Information regarding pharmacotherapy, including names, doses, and duration of use of antidepressants and other medications was gathered. At least one first-degree family relative was interviewed to obtain collateral information. Whenever possible, converging evidence from other sources—including previous treating physicians and hospital records—was obtained. Patients were diagnosed using DSM-IV criteria at the time of initial assessment. Diagnoses were modified according to our prospectively collected data on illness course as well as collateral information from family members.

Patients were re-evaluated in 2001–2002 using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1994). Patients were also diagnosed using the recently proposed criteria for bipolar spectrum disorder (Ghaemi et al., 2002a,b). We were interested in determining the prevalence of this disorder because some of the diagnostic criteria, including antidepressant "wear-off" and lack of response to antidepressant therapy, were the defining characteristics of our patient population.

2.3. Statistical analyses

Continuous variables were analyzed using an unequal groups one-way analysis of variance (ANOVA) or a non-directional dependent groups *t*-test. Categorical variables were analyzed with a chi-square goodness of fit test. All tests of significance were carried out at the 0.05 level.

3. Results

At intake, 35% of the patients were diagnosed as having a bipolar disorder. Patients with major depressive disorder ($n = 12$) or bipolar spectrum disorder ($n = 13$) were compared on clinical characteristics with patients who were diagnosed with a bipolar disorder ($n = 2$ for bipolar I, $n = 26$ for bipolar II, and $n = 8$ for bipolar NOS). The demographic data for these two groups are presented in Table 1.

At follow-up, there was a 59% prevalence of bipolar disorder in our sample. The DSM-IV diagnostic breakdown was as follows: major depressive disorder = 25 (41%), bipolar I = 2 (3%), bipolar II = 26 (43%), and bipolar NOS = 8 (13.1%). Of the patients with major depressive disorder, 13 (52%) were subsequently classified as having bipolar spectrum disorder. The most striking finding is that 80% of our sample of patients, all of whom were referred initially for treatment resistant unipolar depression, was found on follow-up and our subsequent diagnostic interviews to show evidence of a bipolar diathesis.

Table 1
Clinical and familial characteristics of 61 patients with treatment-refractory depression, grouped according to a diagnosis of bipolar spectrum/major depressive vs. bipolar disorder

	MDD + BSD Combined (%)	Bipolar I, II, and NOS Combined (%)
Percentage of patients	41	59
Sex		
male	20	11
female	80	89
age (years)	42.6 (SD = 9.67)	42.6 (SD = 10.33)
Marital status		
married	64	64
widowed	0	0
divorced	16	17
separated	4	3
never married	16	17
no. of children	1.64 (SD = 1.55)	1.83 (SD = 1.56)
Education		
grades 7–12	16	14
high school grad	28	31
some college/univ	8	14
college grad	24	19
university grad	24	19
profess. school grad	0	3
age of illness onset (years)	19.44 (SD = 7.37)	18.08 (SD = 8.91)
Comorbidity		
current	24	19
lifetime	20	17
current and lifetime	20	42
none	36	22
Symptoms		
typical	52	50
atypical	48	50
Treatment		
inpatient	4	8
outpatient	96	92
ECT	8	8
Percent of patients previously		
hospitalized	56	64
family history of mood disorder	88	86
family history of suicide	20 (unsure: 8)	3 (unsure: 11)

For the continuous variables, the ANOVAs showed no group differences in any of the variables (all $F(1,59) < 1$). In other words, the two patient groups were statistically equivalent on age, age of illness onset, and number of children. Table 1 shows the group means for these variables.

For the categorical variables, within each group there were more females than males (bipolar: $\chi^2(1) = 60.48$, $p < 0.01$; major depressive + bipolar spectrum disorders combined: $\chi^2(1) = 36.0$, $p < 0.01$). Consistent with our hypothesis, there were no group differences in any of the categorical variables. The only exception was the following: significantly more patients with current and lifetime comorbidity were found in the bipolar disorder group ($\chi^2(1) = 5.0$, $p < 0.05$) than in the bipolar spectrum + major depression group.

Table 2 shows, for each diagnostic group, the mean CGI rating at first visit and at the most recent visit with the psychiatrist. Non-directional dependent groups *t*-tests revealed that CGI ratings were significantly lower at the most recent visit compared to ratings at the first visit for the following groups: major depressive disorder, bipolar NOS, bipolar II, and bipolar spectrum ($t(11) = 3.0$, $p < 0.01$; $t(7) = 4.3$, $p < 0.003$; $t(23) = 9.0$, $p < 0.001$; respectively). The comparison for bipolar I involved only two patients, hence was not powerful enough to detect any difference that might exist ($t(1) = 1.0$).

Table 2 also summarizes the type of medication received by patients in each group. This data is subdivided into medication taken at the first consultation visit with the psychiatrist, and at the last visit. In each group, the percentage of patients receiving a change in medication from what they were taking at the time of initial consultation is as follows: 67% for the bipolar spectrum group, 67% for major depressive disorder, 100% for bipolar I, 83% for bipolar II, and 75% for the bipolar NOS group.

The most frequent change in medication appears to have been a switch to mood stabilizers alone, accounting for 36% of all the medication changes from the time of initial consultation. At time of initial consultation, 93% of patients were receiving an antidepressant (either alone or in combination with other types of medications). At last visit, over half (52%) of those who were initially receiving antidepressants was no longer receiving any antidepressant. This decrease in use of antidepressants is statistically significant ($t(53) = 7.6$, $p < 0.001$). Following the initial consultation, mood stabilizers and/or atypical neuroleptics were introduced at follow-up for two-thirds (66%) of patients who had been taking antidepressants at the time of initial consultation. This represents a signifi-

Table 2
Comparison of CGI ratings and class of medication at intake and at most recent visit, according to diagnostic category

	Bipolar spectrum disorder	MDD	Bipolar I	Bipolar II	Bipolar NOS
Percentage of patients	21	20	3	43	13
CGI at intake	4.3 (SD = 0.87)	4.8 (SD = 0.75)	5.0 (SD = 0)	4.8 (SD = 0.74)	4.0 (SD = 0.53)
CGI at most recent visit	2.1[a] (SD = 1.08)	3.3[a] (SD = 1.36)	3.5 (SD = 2.12)	2.3[a] (SD = 1.43)	2.4[a] (SD = 1.19)
Percentage of patients according to medication[b] at intake	1–50% 5–25% 7–25%	1–50% 4–8% 5–8% 7–25% 8–8%	6–50% 7–50%	1–54% 4–4% 5–8% 6–13% 7–4% 9–13% 11–4%	1–50% 5–13% 9–37%
Percentage of patients according to medication[b] at most recent visit	1–25% 2–25% 5–8% 7–8% 8–17% 9–8% 11–8%	1–33% 2–8% 3–8% 5–8% 6–17% 7–17% 9–8%	2–50% 11–50%	1–17% 2–29% 4–4% 5–17% 8–21% 9–8% 10–4%	1–25% 2–50% 3–13% 9–13%

[a] Statistically significant decrease between intake and most recent CGI rating.
[b] Legend: 1 = antidepressant monotherapy; 2 = mood stabilizer monotherapy; 3 = neuroleptic monotherapy; 4 = benzodiazepine monotherapy; 5 = antidepressants and mood stabilizers; 6 = antidepressants and neuroleptics; 7 = antidepressants and benzodiazepines; 8 = mood stabilizers and neuroleptics; 9 = antidepressants, mood stabilizers, benzodiazepiness; 10 = neuroleptics and benzodiazepines; 11 = mood stabilizer and benzodiazepine.

cant increase in the use of mood stabilizers and/or atypical neuroleptics ($t(37) = 8.4$, $p < 0.001$).

4. Discussion

This study examined demographic and clinical characteristics, types of pharmacotherapy, and illness outcome of refractory depression in a cohort of 61 patients. The patients were seen consecutively at a specialty clinic, after having failed to respond to adequate trials of two antidepressants. These patients additionally had a history of inability to attain full remission on two adequate trials of antidepressant for at least one prior episode. We also studied in this sample the prevalence of bipolar II and other types of bipolarity, as well as the presence of comorbid psychiatric disorders.

The main finding was that the majority of patients with a clear history of treatment resistant "unipolar" depression actually suffered from bipolar disorders, with bipolar II as the most common diagnosis, followed by bipolar spectrum disorder. Our findings extend the preliminary report by Akiskal and Mallya (1987) suggesting that the "soft bipolar spectrum" may underlie treatment resistance. Assessment of demographic and clinical features differentiating bipolar spectrum disorders is beyond the purpose of this study.

Akiskal's group has provided both the clinical description (Akiskal and Pinto, 1999) and the validation status of the bipolar spectrum (Akiskal, 1996; 2002). Previous studies have reported that many patients with a bipolar disorder are initially treated for major depression. Ghaemi et al. (2002a,b) reported a 40% rate of misdiagnosis of major depression among patients with bipolar disorder. Similar findings were described in a French study of 250 patients with major depression (Hantouche et al., 1998). In that study, 28% of the patients initially met the DSM-IV diagnosis of bipolar disorder; but the rate jumped to 55% when more in-depth assessments were conducted. The much higher figure of 80% in the present study was likely due to our sample being biased towards having an overrepresentation of patients with a bipolar diathesis. Specifically, our patients experi-

enced an escape of antidepressant response and failed to show a favorable response to trials of several antidepressants. Both of these clinical features are among the proposed criteria for the diagnosis of bipolar spectrum disorder (Ghaemi et al., 2002a,b). Other factors might help account for our 80% rate; that is, the uncovering of occult bipolarity. These factors arise from the regular gathering of supplemental information. They include systematic follow-up over a long period, expert questioning to elicit symptoms of hypomania, and routine interviews with family members to obtain supplemental information (including family history of psychiatric disorders).

Another important finding was that the two groups—the "nonbipolar" (major depressive disorder + bipolar spectrum disorder) and the bipolar (I, II, and NOS)—were remarkably similar on most of the variables examined. There are some possible reasons for this similarity. A large number of patients in this study met the criteria for bipolar spectrum disorder. Such a change in diagnosis occurred because the DSM-IV does not recognize that antidepressant-induced hypomanic episodes should be subsumed under the rubric of bipolar disorder. In addition, some patients received the diagnosis of bipolar NOS, as their episodes of hypomania were not long enough to reach the DSM-IV duration threshold. While the nosological status of recurrent major depression with non-spontaneous episodes of hypomania remains a contentious issue, it has recently been argued that some of these cases (e.g., those with antidepressant-induced episodes of hypomania) may have a genetically less penetrant version of bipolar II illness.

The findings from this study have important clinical and research implications. Patients who have treatment resistant depression occurring in the context of loss of antidepressant response should have a thorough assessment to rule out bipolarity. Close monitoring of clinical condition over a period of time may be required in some patients to clarify the diagnosis. During episodes of depression, patients may have difficulty recalling any hypomanic spells, or may tend to report these as periods of well-being. Because the use of antidepressants in individuals with a bipolar diathesis may convert their "atypical" presentation into an agitated, anxious state with accompanying insomnia and racing of thoughts, it is important to make a distinction between their symptoms before and after the introduction of antidepressants.

There should be caution regarding the use of antidepressants in patients with histories of repeated loss of antidepressant response, due to the risk of inducing treatment refractoriness. The use of mood stabilizers at the time of initial referral was quite low in our sample. However, there was no evidence that illness outcome in patients on mood stabilizers combined with antidepressants was any different from those patients receiving antidepressant monotherapy. Some patients do benefit from discontinuation of antidepressants, to be treated instead with mood stabilizers alone. By contrast, other patients require the use of an antidepressant with their mood stabilizer. A trial of a monoamine oxidase inhibitor should be considered for some patients who have persistent depression in spite of adequate trials of mood stabilizers.

There are some limitations of this descriptive study that should be acknowledged. The present results might not necessarily generalize to the entire population of patients who show a loss of antidepressant response. Our sample represents a select group referred from primary care settings. There are conceivably many more patients showing a loss of response, who do not receive specialized consultation. Because this was not a randomized study, confounding factors were not ruled out. For example, those who are referred for consultation might possess illness characteristics that differentiate them from the larger population of patients with treatment resistant depression. Treatment was not controlled, which makes the data vulnerable to experimenter and participant expectancy effects. For instance, the experimenter's bias to discover bipolarity could have affected the judgment about whether a particular symptom is indicative of mood elevation. Such bias was reduced by use of structured interviews; nevertheless, clinical judgment was eventually used in arriving at a diagnosis. From the patient's perspective, there could have been a strong expectancy to improve due to a placebo effect; that is, the change in diagnosis as a result of the consultation reduced the patient's uncertainty over why their depression did not remit. The new diagnosis and/or change in medication likely elicited increased hope. Another limitation concerns the measure of treatment outcome. More indicators than the CGI alone are required in order to strengthen the conclu-

sion that treating for bipolarity produces improved outcomes.

Due to poor response of bipolar depression to antidepressants, controlled studies with other drugs including mood stabilizers are urgently needed. Studies are also needed to determine whether there is also a loss of response to other treatment modalities such as electroconvulsive therapy.

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