Complexity of Pharmacologic Treatment Required for Sustained Improvement in Outpatients With Bipolar Disorder

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Objective: To evaluate the clinical correlates of and types of naturalistic treatments associated with sustained improvement/remission for at least 6 months in outpatients with bipolar disorder.

Method: Five hundred twenty-five outpatients with bipolar disorder (77.7% bipolar I) gave informed consent, had their mood rated daily on the National Institute of Mental Health Life Chart Method for a minimum of at least 1 year, and recorded all medications. Demographics and clinical characteristics of patients with a "sustained response" (ratings of "improved" or "very much improved" on the Clinical Global Impressions-Bipolar Version for a period of at least 6 months) versus nonresponders were compared. The study was conducted from 1996 to 2002.

Results: Of the 429 patients who were ill at study entry, 195 (45.5%) showed a sustained response; 54.5% showed no or insufficient response. A mean of 2.98 medications was given at time of improvement, which occurred after a mean of 18 months of participation in the study. Lithium and valproate were the medications most frequently prescribed at the time of improvement and had among the highest overall success rates. Equally complex regimens were employed in the nonresponders who, however, had a more adverse clinical course prior to network entry. Nonresponders were ultimately exposed to more antidepressants and antipsychotics than the sustained responders.

Conclusions: A mean of 1.5 years and at times highly complex medication regimens were required to achieve a sustained response for 6 months during naturalistic outpatient treatment of bipolar disorder. Delineating the clinical and biologic correlates of individual response to combination treatment is a very high clinical research priority, as is developing new treatment strategies for the large proportion of patients who fail to respond in a sustained fashion.

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A number of recent studies have indicated that there is great variation in clinical responsiveness in bipolar outpatients during naturalistic treatment, with a substantial proportion of patients remaining ill. On average, patients are ill about 50% of the time and experience 3 times more weeks or days depressed than time manic, as in the longitudinal studies of Judd and colleagues[1] as well as those in our Bipolar Collaborative Network.[2–5]

Less well delineated, however, is what percentage of patients who are initially ill at study entry achieves substantial improvement or full remission and with which treatments and clinical and demographic characteristics this sustained response is associated. Also not well studied is whether there is an equal quality and quantity of medications to which the poor responders were exposed and hence whether the failure to improve may have been due to either treatment differences or inherent differences in responsivity.

In this study, the National Institute of Mental Health Life Chart Method (LCM) was used to describe in detail the long-term course and specific drugs used during naturalistic follow-up of patients receiving various pharmacologic treatments, which provided a unique opportunity to examine what treatments and which treatment combinations were associated with sustained improvement for at least 6 months. Such data are rarely available from the systematic randomized clinical trial (RCT) literature. The pharmacotherapeutic literature deals almost exclusively with RCTs addressing the efficacy of monotherapy, or, less frequently, specific medication combinations compared with other medications and/or placebo, and these studies use highly selected patients. The patients who satisfy the strict selection criteria for an RCT are often not representative of the patients treated in the community, since those with Axis I, II, and III comorbidities and more severely ill patients (eg, with suicidality) are typically excluded.

In contrast, the patients recruited into the former Stanley Foundation Treatment Outcome Network,[6] now called the Bipolar Collaborative Network, had almost no exclusions for comorbidity or suicidality and thus are more representative of patients as treated in academic and other outpatient settings. Recent data from different sources indicate the need for complex pharmacologic regimens in a high proportion of inpatients[7] and outpatients with bipolar illness,[8–17] but the details of what drugs and combinations are successful (or not) in achieving relative long-term stability in a prospectively followed cohort have rarely been delineated.

Previous work on this cohort[3,18] showed that some two-thirds of the patients in the first year of treatment in the network remained moderately to markedly ill for a substantial proportion of the year, and only one-third were minimally impacted by their illness. We now focus on the

For Clinical Use

- Finding a treatment regimen for bipolar disorder that achieves a sustained long-term response may require using many drugs in combination so that systematic longitudinal monitoring is desirable, as is careful titration of each drug to keep it below the side effects threshold for the entire regimen.
- Lithium, carbamazepine, and valproate are among the drugs most frequently associated with long-term response.
- Since nonresponders, compared with responders, have a variety of characteristics of a more adverse course of illness, such as a greater number of prior episodes, every attempt should be made to intervene earlier and more consistently to attempt to prevent or avoid the further evolution of these variables associated with a poor prognosis.

group who entered the network ill and then did or did not obtain substantial and sustained relief of their manic and depressive symptoms during further naturalistic treatment.

The current study specifically focuses on the differences between patients who obtained a sustained response and those who did not. We hypothesized that the nonresponders would be exposed to equally intensive and complex treatments but would have a variety of other demographic and clinical characteristics associated with a poor prognosis.

METHOD

Patients

The details of the methodology of the patients enrolled in this study are presented elsewhere.[2–4,6] Briefly, patients gave written informed consent for the procedures involved and were treated naturalistically or with protocols that were appropriate to a patient's emerging symptomatology.[2,6] The majority of these treatments involved open add-on treatment, and, less often, double-blind or open randomized comparative medication trials. Treatment in the naturalistic arm was driven by clinician assessment of a patient's mood state. Thus, during almost the entire time of participation in the study, investigator and patient-related choice of drugs or drug classes were made without a placebo arm. The 1 protocol during this period of time of observation included in this study (1996 to 2002) that involved placebo was a comparison of blind adjunctive omega-3 fatty acids for a period of 4 months versus placebo, after which an open continuation of up to 1 year was allowed in order to assess ultimate long-term clinical effectiveness.[19]

LCM Rating

Patients were rated on a daily basis on the LCM prospective clinician-rated form. This methodology[20] has been previously validated against more typical cross-sectional measures.[21,22] Patients were seen once to twice monthly, and clinicians rated the degree of daily mood-related dysfunction on the LCM.[20]

Five hundred twenty-five patients had daily LCM ratings in this fashion for the duration of at least 1 year[4] (mean, 2.72 years). These daily LCM ratings were computerized and printed graphically for the duration of a patient's participation in the network.

Based on visual inspection of all of the daily printed LCMs ratings, the degree of sustained clinical improvement persisting for at least 6 months was assessed independently by 2 raters (R.M.P. and S.P.) on the Clinical Global Impressions-Bipolar Version (CGI-BP).[23] Interrater reliability was extremely high (over 90% agreement), and the few instances in which there were differences were resolved by consensus of the 2 raters. The outcome criterion was whether these initially ill patients achieved much or very much improvement for at least 6 months.

In order to receive a rating of A, or a CGI improvement rating of 1 (ie, "very much improved"), the patients had to achieve a clinically distinct and robust change from their previous mood state to the extent that they were essentially well during a minimum of 6 months of follow-up. This was based on the longitudinal view of all daily LCM ratings. A rating of B (2 or "much improved") on the CGI-BP improvement of overall illness involved a clinically distinct and robust change from the patients' previous mood state for at least 6 months, but with some residual mild to low-moderate symptomatology periodically occurring. A C (3 or "minimally improved") rating included those in whom there was a detectable improvement compared to previous ratings, but this improvement was not of a magnitude that indicated a clinically meaningful degree of change. Ratings of D (no change) and E, F, or F– (minimally, much, or very much worse, respectively) were included together with the C ratings in the nonresponder category.

Only individuals rated A or B were considered sustained responders for this analysis. In those meeting these criteria, the duration of response beyond 6 months was examined to see if it was sustained until network exit or if it was gradually lost with the reappearance of episodes of increasing severity or duration (in the absence of a change in medication status). If this were the case, it was considered a pattern of illness reflective of the development of tolerance.

A subgroup (18.3%) of patients, who were minimally impacted by their illness at network entry were characterized as "well on admission" if they continued to show this degree of clinical remission for a period of at least 6 months of prospective follow-up, and their treatment regimens were also examined. They are included for comparative purposes only, as this article focuses specifically on prospective medication patterns in those who were ill at network entry and then did or did not respond subsequently.

In order to compare the initial severity of illness in the sustained responders and the nonresponders, a separate

CGI rating (encompassing a 2-month time frame) was made. The severity of illness was rated on the CGI-BP-Severity of Illness scale[23] from 1 (normal or not ill) to 7 (very severely ill) separately for mania, depression, and overall illness at 3 time points: (1) at network entry, (2) after 1 year of participation in the study, and (3) at the end of their participation.

Assessment of Medications Involved in Treatment Response/Nonresponse

In the sustained responders group, medications were categorized and recorded as follows: (1) baseline medications that had been present for more than 2 months prior to the inflection point of the beginning of the period of sustained response, (2) medications that were newly started, or (3) those increased in dose in close proximity to the inflection point (ie, within 2 months prior to or after the beginning of the clinical improvement). Medications present prior to the inflection point but discontinued before the improvement started were also listed and considered ineffective drugs (although the data were not sufficient to ascertain whether this was due to side effects or lack of efficacy).

Medications for the nonresponders were considered in 3 groups: (1) those utilized briefly (for less than 2 weeks), (2) those utilized more than 2 weeks, or (3) those with sustained use that extended at least 3 quarters of the time of observation. Their number and quality were compared to those used in the responders. The medications used at network entry in those who were well at entry were also recorded.

Characteristics of the Differentially Responsive Groups

Demographic and retrospective clinical course of illness characteristics were compared. Specific comparisons of characteristics that might have been linked to differential responsivity of sustained responders and nonresponders were examined.

Statistics

An independent samples *t* test was used to compare severity of mania, depression, and overall severity of A/B versus C/D patients at network entry. The number of drugs taken while in network was compared with a 1-way between-subjects analysis of variance (ANOVA). Post hoc tests among the 3 groups used a Bonferroni-corrected significance level of .016. Comparisons among the demographics were done using a χ^2, independent samples *t* test (age at entry, age at onset, drugs at entry) or Mann-Whitney *U* (treatment delay) as appropriate. Significant results from the demographics were used to select variables to be entered into a generalized linear regression with logit link; thus, corrections for multiple comparisons are not presented with the demographics.

RESULTS

The Range of Prospective Outcomes

Ninety-six of the 525 patients (18.3%) met the criteria for being minimally impaired or essentially well at network entry and remained so for at least 6 months (Table 1). One hundred twenty-one patients (23%) eventually met the A criterion for very much improved, ie, essentially clinical remission. Seventy-four patients (14.1%) met B criteria, or much improved, and thus, 195 of the patients (37.1%) had clinically meaningful sustained response during prospective follow-up with essentially naturalistic treatment. Seventy-five patients (14.3%) met criteria for C, or minimally improved, while 159 patients (30.3%) showed either no change or worsening of their symptomatology during naturalistic treatment, thus resulting in a total of 234 patients (44.6%) with lack of sustained response.

Table 1. Long-Term Outcome in Bipolar Outpatients in Naturalistic Multimodal Treatment (N = 525)[a]

Group	n	%
Well at network entry	96	18.3
Responders for > 6 months	195	37.1
A (very much improved)	121	23.0
B (much improved)	74	14.1
Nonresponders[b]	234	44.6
C (minimally improved)	75	14.3
D or F (no change or worse)	159	30.3

[a]Distribution of outcomes in patients rated daily on the National Institute of Mental Health Life Chart Method for a minimum of 1 year and then rated on the Clinical Global Impressions Scale for Bipolar Illness overall degree of change rating.
[b]Nonresponders could have had brief periods of excellent improvement; but if the improvement did not persist for at least 6 months, they were not considered responders.

Mean ± SD duration of prospective follow-up time in the network for the 195 sustained responders was 38.9 ± 18.0 months, with a range of 10 to 80 months, while the nonresponders remained in the network for a mean ± SD of 32.6 ± 18.0 months. For the well-at-entry patients, the mean ± SD duration of prospective follow-up was 36.0 ± 19.8 months.

The mean duration of clinical responsiveness of those with sustained response was 17.8 months, with a median of 14 months. These responses began after a mean ± SD period of time of 18.7 ± 1.6 months of participation and treatment in the network. Thirty-two of the original 195 patients (16.4%) showing a sustained response for at least 6 months appeared to gradually lose that response in the context of continued medication treatment in what appeared to be a pattern of loss of efficacy by the development of tolerance. When this tolerance pattern was seen, it occurred after a mean ± SD of 14.8 ± 7.51 months of initial good response.

Figure 1 illustrates the CGI-BP severity ratings for overall illness in the 3 differentially responsive groups. Particularly noteworthy is the observation of equal severity of overall illness at network entry of the eventual sustained responders and the eventual nonresponders. Those who were well on admission maintained this status throughout their participation in the network.

Complexity of Drug Treatment Associated With Responders Versus Nonresponders

The number of drugs that patients were exposed to is summarized in Table 2. Approximately 96.5% of the sustained

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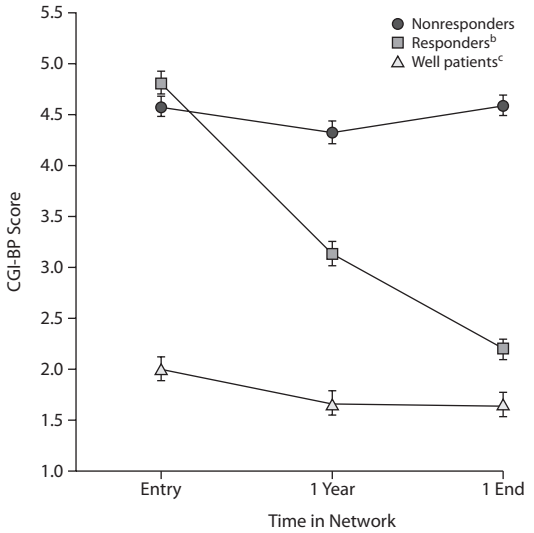
Figure 1. Overall CGI-BP Severity Ratings in Patients Who Improved or Remitted[a]



[a]The CGI-BP severity of overall illness rating was based on visual inspection of 2-month epochs at 3 time points: at network entry, 1 year of prospective treatment, and upon leaving the network.
[b]Patients who responded to treatment for a minimum of 6 months.
[c]Patients who were well at network entry and then maintained that improvement for at least 6 months.
Abbreviation: CGI-BP = Clinical Global Impressions-Bipolar Version.

Table 2. Number of Drugs Used to Maintain Wellness, Produce Improvement in Responders, and Attempt to Improve Nonresponders[a]

Drug Category	Mean	± SD	± SE	Range
No. of drugs used to maintain well state in those well at entry	1.65	0.89	0.17	0–5
No. of drugs involved at time of improvement in A/B responders[b]				
No. of drugs at improvement	2.98	2.18	0.16	0–13
New drug	1.18	1.13	0.08	0–5
Drug dose increased	0.45	0.65	0.05	0–3
Baseline drug	1.35	1.22	0.09	0–7
No. of drugs used and discontinued prior to improvement	2.04	2.18	0.16	0–13
No. of drugs used in C/D nonresponders[c]				
At network entry	2.83	1.51	0.10	0–7
At 1 y	3.08	1.66	0.11	0–8
At exit	3.04	1.71	0.11	0–9
No. of drugs used in network	2.96	1.37	0.09	0–21
Clinical trials/d	1.25	0.82	0.05	0–4
Baseline medications	1.72	1.32	0.09	0–7
Short-term medications/y	0.31	0.56	0.04	0–4

[a]Well patients were on fewer drugs (1.65) than both responders (2.98) and nonresponders (2.96), who were virtually identical. The average of about 3 drugs for nonresponders was maintained throughout their time in the network despite many different drugs (7.39) being tried.
[b]Individuals considered sustained responders received a rating of A (CGI-BP improvement rating 1 [very much improved]) or B (CGI-BP improvement rating 2 [much improved]).
[c]Individuals considered nonresponders received a rating of C (CGI-BP improvement rating 3 [minimally improved]) or D (no change, minimally worse, much worse, or very much worse).
Abbreviation: CGI-BP = Clinical Global Impressions Scale for Bipolar Illness.

responders were on 1–5 medications, with over 55% being on 2 or 3 medications. Baseline drugs in particular stayed at close to 50% of the total number of medications taken, regardless of whether the responsive patient was on 2 or up to 5 medications. A similar distribution of mean numbers of medication used was seen in the nonresponders.

A difficulty in interpreting the numbers of medications in Table 2 is the differing time frame. The drugs of interest for sustained responders are those present around the time of improvement. As the nonresponders did not have a time of improvement, there is no directly analogous point at which to compare them. To deal with this issue, 2 techniques were used. First, the mean number of drugs simultaneously taken during the nonresponders' entire course of treatment was calculated, and, second, the number of drugs at selected time points (network entry, at 1 year, at Network exit) was listed. We chose to examine medications at 1 year for the C/D nonresponders as this was a time point at which we had maximal data and could include everyone. Patients who were well at entry presented a slightly different problem in that we were interested in what drugs kept them well and, hence, included only drugs they were on for the majority (> 75%) of their time in the network.

The mean number of drugs involved at the inflection point, ie, at the beginning of sustained response, as summarized in Table 2, was 2.98, with 1.8 already present at baseline (or dose increased at improvement) and 1.18 new drugs added. The maximum number of medications taken at the inflection point was 8. A mean of 2.04 drugs had also been used and had discontinued prior to the inflection point of improvement.

The mean number of drugs nonresponding patients took at any 1 time similarly was 2.95. For the selected time points, the nonresponding patients were on 2.83 drugs at network entry, 3.08 drugs at 1 year, and 3.04 drugs at network exit. The total mean number of drugs used during the nonresponding patient's entire time in network was 7.29. This value consisted of a mean of 1.82 baseline drugs, 4.7 drugs whose trial lasted more than 2 weeks but less than 75% of the network time, and 0.67 drugs whose trial lasted less than 2 weeks. These data suggest that although the mean number of drugs in nonresponding patients remained relatively stable over the course of follow-up, frequent switches in the specific drugs used were made in an attempt to find a drug combination that would alleviate their symptoms.

Patients well at entry maintained their improvement on a mean number of only 1.6 drugs. A 1-way between-subjects ANOVA found a significant difference in the number of drugs used in the 3 groups ($F_{2,521} = 40.08$; $P < .001$). Bonferonni-corrected post hoc tests using a significance level of .016 showed that the well-at-entry patients were on significantly fewer drugs then the other groups ($P < .001$), but the sustained responders and nonresponders were not significantly different ($P > .99$).

Types of Drugs Used in the Responders

Table 3 lists the individual medications utilized in the sustained responders versus the nonresponders and well-at-entry groups. The number of sustained responders who

Table 3. Drugs Used by the Sustained Responders, Nonresponders, and Well-at-Entry Patients [a]

	Sustained Responders (n = 195)[b]				Nonresponders (n = 234)			Well-at-Entry Patients (n = 96)			Overall Exposure		
Drug	No. of Successful Trials	No. of Successful and Unsuccessful Trials[c]	Exposure to Drug, %[d]	Trials per Patient, %[e]	No. of Unsuccessful Trials	Exposure to Drug, %	Trials per Patient, %[e]	Well	Exposure to Drug, %	Trials per Patient, %[e]	n[f]	Success, n[g]	Success, %
Overall drugs used	580	977			1,690			155			2,822	735	26.0
Lithium	100	123	12.6	63.08	148	8.8	63.08	66	6.8	68.80	337	166	49.3
Anticonvulsants													
Carbamazepine	34	48	4.9	24.62	62	3.7	26.61	16	1.6	16.67	126	50	39.7
Gabapentin	22	47	4.8	24.10	87	5.1	37.34	1	0.1	1.04	135	23	17.0
Lamotrigine	23	38	3.9	19.49	70	4.1	30.04	5	0.5	5.21	113	28	24.8
Topiramate	18	35	3.6	17.95	65	3.8	27.90	0	0.0	0.00	100	18	18.0
Valproate	83	115	11.8	58.97	163	9.6	69.96	21	2.1	21.88	299	104	34.8
Other anticonvulsant	2	5	0.5	0.03[h]	16	0.9	0.07[h]	2	0.2	0.02[h]	23	4	17.4
Combined anticonvulsant	182	288	29.5	1.48[h]	463	27.4	1.99[h]	45	4.6	0.47[h]	796	227	28.5
Combined thyroid	50	60	6.1	0.31[h]	99	5.9	0.42[h]	11	1.1	0.11[h]	170	61	35.9
Combined typical antipsychotic	5	19	1.9	0.10[h]	50	3.0	0.21[h]	3	0.3	0.03[h]	72	8	11.1
Combined atypical antipsychotic	53	88	9.0	0.45[h]	187	11.1	0.80[h]	5	0.5	0.05[h]	280	58	20.7
Antidepressant													
Bupropion	11	27	2.8	13.85	39	2.3	16.74	2	0.2	2.08	68	13	19.1
SSRI	46	100	10.2	0.24[h]	185	10.9	0.79[h]	6	3.9	0.06[h]	237	52	21.9
Trazodone	11	26	2.7	13.33	31	1.8	13.30	1	0.1	1.04	58	12	20.7
Other antidepressant	48	98	10.0	0.50[h]	202	12.0	0.86[h]	3	30.0	0.03[h]	303	51	16.8
Combined antidepressant	116	251	25.7	1.29	457	27.0	1.96	12	1.2	0.13	720	128	17.8
Combined benzodiazepines	63	119	12.2	0.61	228	13.5	0.97	11	7.1	0.12	358	74	20.7
Combined stimulants	5	15	1.5	0.08	29	1.7	0.12	1	0.1	0.01	45	6	13.3

[a]This table shows the specific drugs used by the sustained responders, nonresponders, and well-at-entry patients. In addition, it calculates the overall success rate of each drug (in the far right column).
[b]Drugs are divided into 2 categories for sustained responders: drugs used during the inflection period of improvement (the No. of Successful Trials column) and drugs that were tried prior to the inflection period, were discontinued, and considered ineffective.
[c]The sum of successful and unsuccessful drug trials in the sustained responders.
[d]The percentage of the sustained responders exposed to a given drug as a function of all drugs taken by that group. For example, lithium made up 12.6% of all the drugs given to sustained responders.
[e]The percentage of patients who were given one of the listed drugs at some point during their time in the network or the average number of trials of drugs in one of the listed drug categories that each patient experienced. The determination to present these data as a percent or as a mean was dependent upon whether the category was a single drug (ie, lithium) or a category of drugs (eg, SSRIs, as patients may have had several different SSRIs). For example, 63.1% of all sustained responders had tried lithium at some point, while sustained responders used on average 1.29 antidepressants.
[f]Includes successful drug exposures plus the drug utilization in the failed trials (of the responders prior to the improvement inflection period) as well as anytime in the nonresponders. In the lithium example, this would yield 166 successes in 337 total exposures for a 49.3% overall success rate for that drug.
[g]The number of times a drug was used at the time of improvement in the sustained responses plus the number of times the drug was used in the well-at-entry group.
[h]Mean value.
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

had an unsuccessful trial of a drug (such that the drug was withdrawn prior to the inflection point of improvement) was counted so that the number of successful trials versus the total number of overall exposures to that drug was used to yield a success rate for each drug specifically in these responding patients.

Lithium was most often involved in the improvement (in 100 of the 196 responders or 51%) of these patients, and it also had the highest success rate of 81.3% in these responders. That is, lithium failed to work (prospectively observed prior to improvement) in 23 of the 123 patients who tried lithium and then eventually responded to any medication. Valproate was the next most commonly used drug (83 times, or in 42%) of these patients; it failed to work in 32 of these eventual responders to other agents, such that its success rate was 72.2%, specifically in this group of responders. The third most likely drug involved was carbamazepine, which also had a high success to failure ratio. Next was lamotrigine followed by the anticonvulsants topiramate and gabapentin, with a more equal success to failure ratio.

Antidepressants were often present at the time of improvement, but these drugs had as many or more failures than successes. There was moderate use of benzodiazepines and related sedative/anxiolytics, with clonazepam leading the list. Triiodothyronine (T_3) or thyroxine (T_4) were involved in 31.4% of these good responders, and they had a very high success rate (50 of 60 trials), as they were rarely discontinued prior to the time of improvement.

We also examined the pattern or time frame of drug use in these responsive patients (data not included in the Table). It is noteworthy that lithium was already involved in the baseline

Table 4. Clinical and Demographic Comparisons of Responder Versus Nonresponder Patients[a]

	Well-at-Entry Patients[b]		Responders[b]		Nonresponders[b]		Statistic, Responders vs Nonresponders			
Variable	n	%	n	%	n	%	χ^2	*P*	Relative Risk	95% CI
Men	56	58.30	79	40.50	96	41.00	0.012	.914	0.988	0.785 to 1.242
Married	38	41.30	91	48.90	100	47.20	0.122	.767	1.037	0.845 to 1.273
Regular work status	78	86.60	111	62.00	104	50.50	5.160	.023*	1.228	1.029 to 1.467
Highest education level										
High school/GED	9	9.78	28	15.05	25	11.74	1.991	.369	1.198[c]	0.742 to 1.934
2 years of college	55	59.78	74	39.78	97	45.54			0.908[c]	0.731 to 1.127
Graduate/professional degree	28	30.43	84	45.16	91	42.72				
Bipolar I disorder	76	79.20	138	70.80	194	83.30	9.345	.002**	0.859	0.776 to 0.951
No. of mood episodes > 20	25	27.80	97	54.20	147	71.40	12.164	.000**	0.759	0.647 to 0.891
Total hospitalizations										
None	13	14.29	45	24.86	58	27.88	6.527	.038*		
1–5	54	59.34	97	53.59	86	41.35			1.114[d]	0.960 to 1.362
> 5	24	26.37	39	21.55	64	30.77			0.885[d]	0.665 to 1.177
Rapid cycling	15	16.30	93	50.00	148	64.60	9.021	.003**	0.774	0.651 to 0.920
Dysphoric mania	28	30.40	107	57.50	149	67.10	3.982	.046*	0.857	0.735 to 1.000
Lifetime anxiety disorder	17	17.70	81	42.20	98	42.60	0.008	.931	1.007	0.855 to 1.187
Lifetime alcohol abuse	23	24.20	61	31.40	90	38.60	2.390	.122	0.814	0.626 to 1.059
Lifetime drug abuse excluding alcohol	12	12.80	32	17.70	59	26.20	4.209	.040*	0.647	0.460 to 0.989
Physical abuse as child[e]	13	14.30	39	21.30	52	24.60	0.613	.434	0.865	0.600 to 1.246
Physical abuse as child or adolescent[e]	15	16.50	44	23.90	61	28.90	1.258	.262	0.827	0.593 to 1.155
Any sexual abuse as child	6	6.50	32	17.50	47	22.20	1.346	.246	0.789	0.527 to 1.181
Any sexual abuse as child or adolescent	12	13.00	44	24.00	65	30.70	2.152	.142	0.784	0.565 to 1.088
Parental depression	18	23.40	64	40.30	73	38.80	0.073	.787	1.037	0.799 to 1.346
Parental bipolar disorder	19	23.20	48	30.20	61	33.70	0.480	.489	0.896	0.655 to 1.224
Parental history of alcohol abuse	11	12.80	39	21.40	67	32.70	6.140	.013*	0.656	0.466 to 0.922
Parental history of drug abuse	1	1.20	10	5.90	24	12.20	3.742	.053	0.504	0.247 to 1.028
	Mean		Mean		Mean		*t* (*z*)	*P*	Mean Difference	95% CI
Age at entry, y	43.50		40.90		43.50		−2.28	.023*	−2.56	−4.77 to −0.35
Age at onset, y	28.30		24.40		22.70		1.32	.190	1.64	−0.80 to 4.07
Treatment delay, y	6.31		8.34		9.44		−1.13	.260	NA	NA
No. of drugs at entry	1.85		2.07		2.32		−1.98	.049*	−0.25	−0.49 to 0.00

[a]This table contains the clinical and demographic variables examined as a function of the responder versus nonresponder category. The top portion used χ^2s, while the bottom 4 rows used independent sample *t* tests except for treatment delay, which required a Mann-Whitney *U* test. Relative risk and confidence intervals for each variable are presented in the column at the right. Fifteen bipolar not-otherwise-specified patients were excluded from the bipolar subtype analysis due to low n. As can be seen, work status, bipolar subtype, number of mood episodes greater than 20, rapid cycling, dysphoric mania, lifetime drug abuse excluding alcohol, parental history of alcohol abuse, total hospitalizations, and age at entry all were potential significant differentiators between the responder patients and nonresponder patients. As these were entered in a logistic regression (see Table 5), no corrections for multiple comparisons are presented.
[b]Not all patients provided the full set of data; the percentages listed reflect this reduced n.
[c]Risk is relative to graduate/professional degree.
[d]Risk is relative to none.
[e]Occasionally or greater.
*$P < .05$; **$P < .01$.
Abbreviation: GED = General Educational Development.

treatment regimen 82% of the time, as opposed to 18% of instances in which it was newly added at the time of improvement. Carbamazepine was in the baseline regimen of 76% of patients, and valproate, 70%. This contrasts with the second-generation atypical antipsychotics (as a class), which were part of the baseline regimen (47%) and were newly added just as often or more often (53%). Similarly, antidepressants (as a class) were being used 44% of the time at baseline and were newly added 56% of the time. In contrast, benzodiazepines (as a class) were present in the baseline regimen only 33% of the time and newly added in two-thirds of the instances.

Drugs Used in the Nonresponders

We tested 3 hypotheses as to why nonresponse might have occurred during prospective treatment in the network. Compared to the responders, the nonresponders might have had (1) a greater severity of illness at network entry, (2) less intense or lesser quality of treatment, or (3) characteristics of a more adverse prior course of illness conveying a poor prognosis and a greater degree of treatment resistance.

To test hypothesis number 1, we examined baseline CGI-BP severity ratings at network entry and found that the sustained responders and nonresponders were equally ill (as shown in Figure 1). An independent samples *t* test found no differences in the baseline severity of mania ($t_{427} = -0.79$, $P = .42$, 2-tailed), of depression ($t_{427} = 0.056$, $P = .95$, 2-tailed), or of overall illness ($t_{427} = 0.14$, $P = .889$, 2-tailed) in the sustained responders versus the nonresponders, suggesting that the lack of responsiveness in the nonresponders was not related to initial measures of severity of illness at entry.

To examine hypothesis number 2, we compared number and quality of medications in the nonresponders in comparison to the sustained responders (as summarized

Table 5. Generalized Linear Model Using All Variables Found to Have a Significant or Trend Relationship With Responder Versus Nonresponder Outcome in the Univariate Analysis[a]

Variable	Likelihood Ratio χ^2	*P* Value	Coefficient	95% CI
>20 mood episodes	5.007	.025	0.647	0.079 to 1.216
Bipolar I subtype	3.832	.050	−0.639	−1.284 to 0.006
Work status	3.674	.055	0.503	−0.014 to 1.020
Drug abuse	3.656	.056	0.600	−0.024 to 1.223
Rapid cycling	1.973	.160	0.395	−0.155 to 0.944
No. of drugs at entry	0.833	.361	0.429	−0.506 to 1.365
Parental alcohol	0.762	.383	0.255	−0.318 to 0.828
Age at entry	0.284	.594	−0.025	−0.119 to 0.068
Parental drug use	0.171	.679	−0.005	−0.026 to 0.017
Hospitalizations	0.143	.706	−0.036	−0.224 to 0.152
Dysphoric mania	0.124	.725	0.095	−0.434 to 0.624

[a]Number of mood episodes greater than 20 and bipolar subtype were significant independent predictors of responder/nonresponder outcome. Work status and drug abuse were strong trends, while the relationship between the other variables and outcome was not independently significant. The percentage of patients who were bipolar I subtype was 77.7%.

in Tables 2 and 3). The percentage of the nonresponding patients exposed to a given mood stabilizer was highly similar to those in the sustained responding group, with lithium and valproate being present in about two-thirds of the nonresponsive patients (63.3% for lithium, 69.7% for valproate). This contrasts with a much lower percentage of exposure to gabapentin, lamotrigine, topiramate, and carbamazepine, ranging from 37.2% with gabapentin to 26.5% with carbamazepine. It is noteworthy that 41% of the nonresponsive patients were exposed to T_4 or T_3 augmentation.

If all the patient groups who were exposed to a given treatment are taken into consideration, an overall success rate for each drug can be derived (see Table 3, far right column). This would include how often a drug was included in the well-at-entry regimen and in the responders at the time of improvement. The nonresponse rate included when the drug was present in the nonresponders, as well as how often a drug was used and discontinued prior to the time of improvement in the responders. Again it is noteworthy that in this fashion lithium had the highest overall response rate (49.3%), followed by carbamazepine (39.7%), valproate (34.8%), and lamotrigine (24.8%), although thyroid augmentation showed a high response rate of 35.9%. The success rate of the typical antipsychotics (11.1%) was half that of the atypicals (20.7%), and the antidepressants as a group showed an overall success rate of 17.8%.

Demographic and Illness Characteristics of the 3 Groups

In an attempt to ascertain whether (as in hypothesis number 3 above) differential clinical and demographic variables might be associated with the poor response in prospective naturalistic treatment and follow-up, we examined a number of variables previously associated with treatment outcome in patients with bipolar illness, as shown in Table 4. Differences were examined with χ^2, independent samples *t*, or Mann-Whitney *U* tests as appropriate.

As illustrated, compared to responders, the nonresponders had more medications on entering the network; a history of more manic and depressive episodes, hospitalizations, rapid cycling, dysphoric mania, and substance abuse; and a greater incidence of positive parental history of alcohol and substance abuse. Nonresponders were a mean of 2.5 years older, were ill for a mean of 4.3 years longer, and were significantly more likely to have bipolar I disorder than the sustained responders. Pertinent variables that were not significantly different included childhood history of physical or sexual abuse, lifetime history of an anxiety disorder, gender, and educational attainment. The variables that were significantly different or showed strong trends were then entered into a generalized linear regression, and only prior work status, the bipolar I subtype, drug abuse, and prior number of mood episodes were independent predictors of response/nonresponse (Table 5).

Convergent with this general viewpoint of a more adverse prior course of illness contributing to the poor responsiveness of the nonresponding patients were the observations of the patients who were well at network entry. These patients had the most positive clinical and demographic prognostic factors compared with those who entered ill and subsequently responded or not. They also required treatment with fewer medications (mean = 1.64). Lithium was the major mood stabilizer employed in 70% of these individuals, and few medications from the other categories of drugs were needed. Only 12.4% of the well-at-entry patients required more than 2 medications; 38.5% used 2 medications; and 45.8% used 1 medication.

DISCUSSION

These results reveal new perspectives on the long-term outcome of bipolar patients studied in detail with daily mood ratings during naturalistic treatment. A little more than one-third (37.9%) of patients were able to achieve a sustained clinically meaningful response (2 or B improvement on the CGI-BP) or even remission (1 or A on the CGI-BP) after a period of illness during their participation in the study for a mean of 1½ years. These patients, taken with the 18.3% who were well at network entry and remained so thereafter, yield a total of 56.2% of outpatients who ultimately did well in long-term prospective naturalistic treatment.

Conversely, some 43.4% of patients continued to have at least moderately severe manic or depressive symptomatology, ie, not improving to a clinically meaningful degree, staying the same, or, rarely, even worsening during naturalistic treatment. It appears that the quality and intensity of medication treatment were generally similar in the sustained responders compared to the nonresponders, as was their initial severity of illness at network entry. The nonresponders in the univariate analysis had multiple measures reflecting a more adverse prior course of illness. However, in the generalized linear regression, greater numbers of prior episodes, a history of drug use, lesser work status, and the

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bipolar I subtype remained independently associated with the lack of sustained response to naturalistic treatment.

A primary message of this study is that a substantial number of medications were often utilized to achieve a clinically meaningful sustained response in this representative, but relatively high functioning and highly educated, group of outpatients with bipolar disorder.[4,24] This need for polypharmacotherapy appears generally in concert with observations in other adult populations[7,8] as well as in pediatric bipolar disorder, in which numerous medications in combination are often utilized.[9,10] Findling et al[25] observed that the majority of children with mania required the combination of lithium and valproate in addition to a psychomotor stimulant, and most of the two-thirds who relapsed upon randomization to monotherapy rapidly reresponded to the readdition of the discontinued drug. Those data indicate that 3 or more drugs are often needed in even carefully screened children with bipolar disorder in an RCT.[10]

While a mean of 3 drugs were used at the time of response in our sustained responders, 31.8% of this group required 4 or more drugs and 13.8% required 5 or more drugs. It is noteworthy that the largest percentage of sustained responders had lithium or valproate in their baseline regimen or had one of them added at the inflection point of their improvement/remission. These data are, in part, consistent with the observations of Calabrese and colleagues[26] that these 2 drugs are often needed in combination in patients with a rapid cycling course of their illness. While only 25% of the evaluable sample in that study was transiently stabilized on the combination of lithium and valproate, about 50% of these patients who were randomly assigned to either monotherapy relapsed on the single drug.[26] This suggests that only about 12.5% of their original cohort of rapid cyclers had a good response to either lithium or valproate monotherapy, and three-quarters required further adjunctive measures or other medications if they were to eventually respond at all. In our outpatient sample, about 38% were rapid cyclers in their first year of treatment and these had been treated with a mean of 4.6 classes of medications in year 1 in the network.[4]

When lithium and valproate failed or were inadequate in our study population, other drugs such as carbamazepine or lamotrigine were next most often used. Two anticonvulsants, gabapentin and topiramate, that are not in themselves antimanic and thus not considered mood stabilizers were also widely used, but about equal numbers of times these drugs were tried and discontinued (failed) prior to these patients' responding to other regimens. The medications used here reflect an interaction of the drugs most widely used in the 1996 to 2002 epoch and their likelihood of being involved in a positive response.

An interesting result was that the addition or dose increase of antidepressants was present in 59.5% of the sustained responders, but other antidepressants were even more often used and discontinued because they failed to be effective prior to the inflection point of obtaining a sustained response. These observations are perhaps related to those of Altshuler et al[27,28] and Joffe et al,[29] whose studies revealed that antidepressant continuation (in a small subgroup of only about 15% of the total number of patients exposed to antidepressants who initially showed a good antidepressant response for 8 weeks) appeared to be associated with fewer relapses into depression over the next year than in those who more immediately discontinued the antidepressant. However, Ghaemi et al,[30] in a randomized open study, reported that antidepressant continuation versus discontinuation in initial responders did not affect subsequent morbidity, but they did find that antidepressant continuation was associated with an increased duration of time until a depressive relapse compared with those who stopped their antidepressant.

In our study, antidepressants were even more widely used in the nonresponding patients, such that each of them had been exposed to a mean of 1.95 antidepressant drugs. Most interesting, antidepressants were involved in the treatment of only 12.5% of the well-at-network entry patients. If one takes these well-at-entry patients plus the sustained responders versus the failed antidepressant trials in the nonresponding patients, antidepressants only had a 17.8% overall sustained success rate in this entire outpatient population.

This low rate of long-term success is, perhaps in part, consistent with the observed failure of antidepressant augmentation of a mood stabilizer to exceed that of placebo on any outcome measure in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study.[31] Moreover, in previous reports from our network, Leverich et al[32] and Post et al[33] found a moderate incidence of switching upon antidepressant (bupropion, sertraline, or venlafaxine) addition to mood stabilizers, and only a relatively small percentage (16% of all the intent-to-treat antidepressant trials in that double-blind randomized study) showed a good antidepressant response during up to 1 year of continuation treatment without experiencing either a depressive recurrence or a switch into mania. Thus, the data in the literature appear relatively consistent in showing a low sustained response rate to the addition of an antidepressant to a mood stabilizer regimen for the emergence of a bipolar depression. However, delineating the characteristics of the very small subgroup of bipolar depressed patients who are likely to benefit in a sustained fashion from acute and continuation antidepressant augmentation would appear to be of substantial clinical importance.

Altshuler et al[34] and Leverich et al[32] also reported from our network that bipolar II disorder patients in general were less likely to switch into mania than bipolar I disorder patients. In addition, our data here also suggest that bipolar II disorder patients are more likely than bipolar I disorder patients in general to have a good sustained ($\geq$6 months) response to naturalistic treatment.

Use of any atypical antipsychotic showed the same general pattern as the antidepressants, ie, for greater use (79.9%) in the nonresponders than in the sustained responders (45.1%) or the well-at-entry patients (5.2%), and they also showed a low overall success rate (20.7%) in the entire cohort as a whole.

A number of limitations must be noted in the interpretation of this study. The high percentage of persistent nonresponse (49%) during long-term prospective follow-up and naturalistic treatment could reflect a selection bias of more severely ill people being attracted to join the network than in the general population of patients with bipolar illness. Yet we attempted to recruit a representative cohort of outpatients, especially since we had few exclusions for medical or psychiatric comorbidity or suicidality.

Our chosen criterion of having to show a sustained complete or robust response for at least 6 months is more rigorous or stringent than that employed in most other studies. However, we chose it to reflect a clinically meaningful time frame for illness improvement and prophylaxis that patients and clinicians would likely want to maintain to have some certainty that a given treatment regimen was really working for them. Other limitations include that treatment was uncontrolled and also biased by the availability and general use patterns of drug treatments in the epoch of 1996 to 2002. Some might argue that our results are consistent with the view that fewer drugs are better than larger numbers of drugs, but causal influences from these naturalistic data cannot be readily drawn.

Implications

The use of multiple agents in combination raises a number of difficult problems for treating physicians and patients in arriving at the most appropriate treatment regimen for a given individual. For those patients who were ill at network entry, it took a mean of another 18.7 months before their clinically relevant improvement or remission was achieved. There is a negligible systematic literature about optimal treatment sequences and paradigms for these types of individual outpatients who, after an average of more than 15 years of illness, appear to require complex pharmacotherapy in order to achieve mood stabilization for at least 6 months. Many patients with highly common types of more complicated presentations, such as those with rapid cycling, comorbidities, substance abuse, or suicidal ideation, were included in this study, but inferences from the literature about ultimate response of these types of patients are limited because they are typically excluded from many traditional RCTs, which may also overestimate rates of response to monotherapies. Moreover, the majority of the trials aimed at FDA registration are short term, lasting 6 to 8 weeks, and information about what it takes to achieve and sustain a good response is not usually available even in the literature on long-term prophylaxis.[18]

Elsewhere, Post and Kowatch[35] and others[36,37] have suggested the importance and utility of performing more practical clinical trials, including those involving open randomized comparisons of 2 different agents, such as those utilized in some Sequenced Treatment Alternatives to Relieve Depression (STAR-D)[38] and Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)[39] network studies. If those assessments of relative effectiveness and tolerability can ultimately be combined with a more detailed picture of the clinical and neurobiological correlates of individual responsivity, one might then begin to develop a more systematic literature for assessing the best treatment sequencing and algorithms for the large group of patients with bipolar illness (in academic settings and elsewhere) who apparently require very complex psychopharmacologic regimens in order to achieve and sustain a good to excellent response.

The subgroup of nonresponding patients during naturalistic treatment in the network constitutes a large proportion of patients who continue to do poorly despite aggressive attempts at medication management and revision. What remains to be determined is ultimately what might be the best approach to therapeutics in these patients with a high degree of treatment resistance. It is noteworthy that the bulk of these patients were studied at a time prior to the wide utilization of lamotrigine for long-term prophylaxis and prior to the evidence that several of the atypicals had major antidepressant as well as antimanic efficacy.

Whether greater use of these or other different medications and combinations would have made a substantial impact on the illness of these treatment-refractory individuals remains to be further investigated. Supportive of this possibility are the naturalistic data of Ketter and colleagues[40] who observed that two-thirds of their ill patients remitted when either lamotrigine or quetiapine was added into a regimen involving the other drug. These speculations are also in line with results from a placebo-controlled study showing efficacy of the addition of lamotrigine compared to placebo in patients with a depression occurring during treatment with lithium.[41]

The nonresponders in our study differed from those who eventually responded well to pharmacologic treatment, not so much in terms of exposure to differential treatments, but in many variables prior to network entry often associated with a more difficult course and poorer response to treatment, including in the generalized linear regression poor prior work status, drug abuse, a bipolar I diagnosis, and a greater prior number of mood episodes.

New initiatives are urgently needed to ascertain to what treatments and strategies these individuals might respond. Traditional RCTs directed at new drug registration often exclude these more treatment-resistant patients, and specific investigative approaches to the very large group with a high degree of treatment resistance despite use of complex combinations of drugs are now required. At the same time, major public health efforts should be directed at the earlier identification and appropriate treatment of bipolar illness in hopes of successfully reducing episode burden, and, potentially, modifying and preventing the high degree of treatment resistance revealed here and in so many other treatment cohorts. Our patients often have long lags from the onset of their illness to first treatment; this delay is longest in those with the earliest onsets[42]; and the delay to first treatment is an independent correlate of a poor outcome in adulthood.[43] In addition, in one recent, large database, half the patients with new onset of a bipolar diagnosis were

treated with antidepressants without a mood stabilizer,[44] an approach widely accepted as inadequate and inappropriate. Earlier use of more effective treatment might have lessened the extremely adverse impact of the illness in our large group of nonresponders, a possibility that deserves further clinical exploration.

Drug names: bupropion (Aplenzin, Wellbutrin, and others), carbamazepine (Carbatrol, Equetro, and others), clonazepam (Klonopin and others), gabapentin (Neurontin and others), lamotrigine (Lamictal and others), lithium (Lithobid and others), sertraline (Zoloft and others), topiramate (Topamax and others), trazodone (Oleptro and others), venlafaxine (Effexor and others).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, bupropion, carbamazepine, sertraline, and venlafaxine are not approved by the US Food and Drug Administration for the treatment of bipolar depression; clonazepam, gabapentin, topiramate, and trazodone are not approved for the treatment of bipolar disorder; and lamotrigine is not approved for the treatment of mania or acute bipolar depression.

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