Prospective, Long-Term, Multicenter Study of the Naturalistic Outcomes of Patients With Treatment-Resistant Depression

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Background: Treatment-resistant depression (TRD) is a long-term, disabling illness. We report on the characteristics and outcomes of a large cohort of patients with a level of treatment resistance that is very substantial and who were treated for 2 years with standard care.

Method: This 2-year prospective, multicenter, observational study (patients enrolled from January 2001 through July 2004) tracked the outcomes of 124 patients with treatment-resistant, nonpsychotic major depressive disorder (N = 109) or bipolar depressed phase disorder (N = 15) who received treatment as usual (TAU) (i.e., any therapeutic regimen agreed to by patients and psychiatrists, including medications, electroconvulsive therapy [ECT], and psychotherapy). Treatments could be adjusted, started, and stopped as necessary. The primary outcome, treatment response, was defined a priori as ≥ 50% improvement from baseline as measured by the 30-item Inventory of Depressive Symptomatology–Self-Report (IDS-SR-30). Remission was defined as an IDS-SR-30 score of ≤ 14. The Medical Outcomes Study (MOS) 36-item Short Form Health Survey (SF-36) was used to monitor quality-of-life changes.

Results: The 12- and 24-month IDS-SR-30 response rates were 11.6% (13/112) and 18.4% (19/103), respectively. Of the 13 responders at 12 months, only 5 were responders at 24 months. The 12- and 24-month IDS-SR-30 remission rates were 3.6% (4/112) and 7.8% (8/103), respectively. Only 1 of the 4 12-month remitters was also a remitter at 24 months. The SF-36 indicated globally poor quality of life in this sample.

Conclusions: Despite the wide range of treatment options available for depression, the response rates, remission rates, and quality-of-life results in this study show that most patients with a substantial degree of treatment resistance continue to have significant symptomatology and functional disability when receiving TAU.

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Treatment-resistant depression (TRD) is a disabling, chronic illness that poses a serious problem in depression management. TRD affects as many as 30% of patients with major depression[1–3] and is associated with high suicide risk, low treatment response, and high relapse and health care utilization rates—all of which are characteristics analogous to other severe psychiatric or chronic, disabling, life-threatening, general medical diseases.[4–9] Recently, several studies focusing on patients with TRD have highlighted some common characteristics: patients with TRD are often chronically depressed, have a higher frequency of suicide attempts, and have substantial functional impairment when compared with a group of depressed patients without TRD.[10–13] These findings highlight the limited effectiveness of treatment as usual (TAU) for patients with true TRD.

Major depressive disorders are commonly misdiagnosed, undertreated, or not treated.[14] And, unfortunately, some patients, particularly those with TRD who are not receiving benefit from treatment, give up and do not seek further treatment.[15] Patients with TRD are typically excluded from clinical trials conducted for drug registration purposes.[16,17] In addition, other treatment obstacles include the lack of a standardized definition of TRD, a poor understanding of the clinical characteristics of patients with TRD, and limited evidence for how to best treat this population.[17–19]

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Although there is no standardized definition for TRD, Thase and Rush[20] proposed a staging of treatment resistance by different treatments experienced. This staging places TRD on a continuum defined by the number of previous failed treatments, including monotherapy, polytherapy, psychotherapy, and electroconvulsive therapy (ECT). The 5-stage continuum ranges from lesser (Stage I) to greater (Stage V) degrees of treatment resistance, with selective serotonin reuptake inhibitors (SSRIs) a typical first-line therapy and nonselective monoamine oxidase inhibitors (MAOIs) and ECT typically associated with higher (Stages III–V) degrees of treatment resistance. Thus, even among patients with TRD, the degree of treatment resistance can vary dramatically from patient to patient and thereby further complicate treatment decisions.

The present 2-year study was designed to prospectively track the outcomes of patients with a high level of TRD who received TAU for their depression. The study was designed to assess (1) the clinical characteristics of a population with TRD; (2) the percentage of patients who met response and remission criteria at each measurement occasion; and (3) the changes in functional health and well-being that occur over time. Treatments and medication changes also were collected throughout the study.

Preliminary 1-year findings from this study were previously published as a comparison of those with TRD who received TAU versus those who received TAU combined with vagus nerve stimulation (VNS) therapy.[21] This article extends those findings by reporting the demographic features and clinical and functional outcomes of these patients with TRD who received TAU for 2 years. As the only 2-year observational study of patients with this level of TRD, these data add substantially to the current knowledge base of patients with TRD.

METHOD

Patients

This 2-year prospective, multicenter, observational study enrolled 127 patients (aged 18 to 80 years) from 13 clinical sites. The study was designed to assess the long-term outcomes of patients in a treatment-resistant major depressive episode (MDE) who received TAU. The current MDE was defined by DSM-IV-TR[22] criteria on the basis of the Structured Clinical Interview for DSM-IV-TR (SCID-I).[23] Individuals who were trained and certified in SCID administration performed the initial SCID-I evaluation at baseline at the investigative study sites under the supervision of the primary investigator. The current MDE had to be chronic (lasting at least 2 or more years), or there had to have been a history of recurrent MDEs (at least 4 in a lifetime, including the current MDE). Patients were allowed to enter the study if they had not responded to at least 2 but not more than 6 standard antidepressant treatments as defined by the modified Antidepressant Treatment History Form (ATHF)[9] for the current MDE. Patients with atypical or psychotic symptom features by DSM-IV criteria or who were unable to provide informed consent and/or participate in the study assessments were excluded. Patients who had attempted suicide within the 12 months before the study and who required medical attention or who were judged likely, in the opinion of the investigator, to attempt suicide within the next 6 months were also excluded. The study entry criteria were intended to be restrictive in nature so as to limit the study to a TRD population with a substantial degree of resistance who had entry criteria that were similar to those used for the VNS therapy pivotal study.[24,25] The complete list of TAU study inclusion and exclusion criteria was recently published (George et al.[21]).

Patients who presented to the study sites for clinical consultation or for potential research participation and who met the inclusion/exclusion criteria for this observational study were asked to participate. All patients who agreed to participate in this study provided written informed consent, and the appropriate human subjects review boards at the participating institutions approved the study procedures. Patients were either referred to the study from community psychiatrists or were under the care of the investigator at the study site. Those patients who were referred to the study continued to be treated by the referring psychiatrist and were asked to return to the study institution every 3 months for follow-up assessments. All study participants were paid $100 for in-clinic visits and $50 for telephone visits. The study sponsor, Cyberonics, Inc. (Houston, Tex.), monitored the study.

Study Analyses

Data were collected at 13 study sites, with evaluable study patients distributed as follows: 16, University of Washington; 15, University of Arizona Health Center; 14, University of Pittsburgh; 13, Medical University of South Carolina; 12, Baylor College of Medicine; 12, University of Maryland; 11, State University of New York Upstate Medical University; 8, Brown University/Butler Hospital; 8, Psychiatric Research Institute (Via Christi); 6, University of Minnesota; 4, Duke University Medical Center; 3, University of Miami School of Medicine; and 2, Emory University School of Medicine. There was no effort to enroll study patients in proportion to site TRD population size.

Data analyses were provided by Quintiles, Inc. (Research Triangle Park, N.C.). A repeated measures linear regression analysis using the generalized estimating equations (GEE) approach was used to analyze changes in response and remission rates over time, with baseline values as a covariate. The SAS (V9.1) GENMOD procedure was used to perform the analysis (SAS Institute, Inc., Cary, N.C.).

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Study Assessments

At baseline, patients underwent a diagnostic evaluation (SCID-I)[23] and a retrospective assessment of their treatment history for the current MDE using a modified version of the ATHF.[9,26–28] The 30-item Inventory of Depressive Symptomatology–Self-Report (IDS-SR-30)[29–31] was used to measure depressive symptoms over time. The Medical Outcomes Study (MOS) 36-item Short Form Health Survey (SF-36)[32,33] was used to measure quality-of-life outcomes over time. The SF-36, completed by patients, assessed quality-of-life outcomes for both functional health and well-being over time.[34,35] For each of the 8 SF-36 subscales and 2 component summary scales, scores range from 0 to 100, with 0 representing the poorest health on the scale and 100 representing optimal health. Subscale scores below 50 are considered below average in terms of health status. All assessments were performed at baseline and at 3, 6, 9, 12, 15, 18, and 24 months. This study did not systematically record safety information. However, a limited amount of data from self-report health information forms was available.

Definitions of response and remission were established a priori for each assessment. For the IDS-SR-30, response was defined as a ≥ 50% decrease in total baseline scores, and remission was defined as a score of ≤ 14. In addition, the duration of response and remission was reported for those who maintained responder or remitter status at consecutive visits. Changes in quality of life, as determined by the SF-36, were measured as a percent change in score from baseline.

Treatment as Usual

TAU included any therapeutic strategy that patients and treating psychiatrists chose to follow. Experimental treatments were proscribed. Concomitant psychotropic medications of any type could be adjusted, started, and stopped as necessary. In addition to medications, nonpharmacologic treatments such as psychotherapy, bright light therapy, or ECT also could be used. TAU included a multitude of augmentation strategies, including use of multiple antidepressants, stimulants, thyroid supplementation, lithium, atypical antipsychotics, and anticonvulsants.

Changes in the doses and types of concomitant mood medications were collected at each study visit. To ensure an adequate treatment trial for each medication, an Antidepressant Resistance Rating (ARR) score was assigned a priori to each drug trial using a modified version of the ATHF.[6,9,24,26,28] Detailed study methods for determining medication trial adequacy were previously published.[24] In brief, medications included on the ATHF form used in this study are heterocyclic/tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, bupropion, mirtazapine, nefazodone, trazodone, venlafaxine, and ECT. Selected anticonvulsants and lithium also were considered as an adequate treatment for patients with bipolar disorder. A change in ARR score by at least one point counted as a medication dose change. We also conducted a medication analysis that counted changes in other medications that were not included on the original ATHF form (e.g., stimulants, trazodone, and thyroid medications).

Table 1. Baseline Demographics and Treatment History (N = 124)

Characteristic	Value
Mean age, y	45.5
Female, %	68.5
Caucasian, %	89.5
Unipolar, %	87.9
Bipolar I or II, %	12.1
Recurrent depression, %	75.0
Chronic current MDE (2 years in duration), %	68.5
Mean duration of current MDE [median; range], mo	68.6 [36.0; 1–471]
Mean total duration of illness [median; range], y	25.8 [26.0; 4–58]
Mean age at onset of illness [median; range], y	20.8 [17.5; 5–52]
Depression episodes, lifetime, No. (%)	
0–2	31 (25.0)
3–5	36 (29.0)
6–10	18 (14.5)
> 10	32 (25.8)
Unknown	7 (5.6)
Suicide attempts, lifetime, No. (%)	
0	80 (64.5)
1	16 (12.9)
2	11 (8.9)
3	10 (8.1)
4	3 (2.4)
5	2 (1.6)
≥ 10	2 (1.6)
Treatment History	
Number of failed adequate (ATHF) drug trials, current MDE, mean ± SD	3.5 ± 1.3
Patients with failed adequate (ATHF) drug trials, current MDE, N (%)[a]	
2 trials	32 (26.2)
3 trials	35 (28.7)
4 trials	31 (25.4)
5 trials	16 (13.1)
6 trials	8 (6.6)
Number of total failed treatment trials (including ATHF adequate trials), current MDE, mean ± SD	4.3 ± 1.6
Number of total failed treatment trials, lifetime, mean ± SD	5.5 ± 1.9
ECT treatment, lifetime, %	25.8
ECT treatment, current episode, %	12.1
Mean number of prior hospital admissions for mood disorders, lifetime [median; range]	2.1 [1.0; 0–15]

[a]One patient had 1 adequate trial in the current MDE, and 1 patient had 7.
Abbreviations: ATHF = Antidepressant Treatment History Form, ECT = electroconvulsive therapy, MDE = major depressive episode.

RESULTS

Patient Demographics and Treatment History

Of the 138 patients who signed consent forms to enter this study from January 2001 through July 2004, 11

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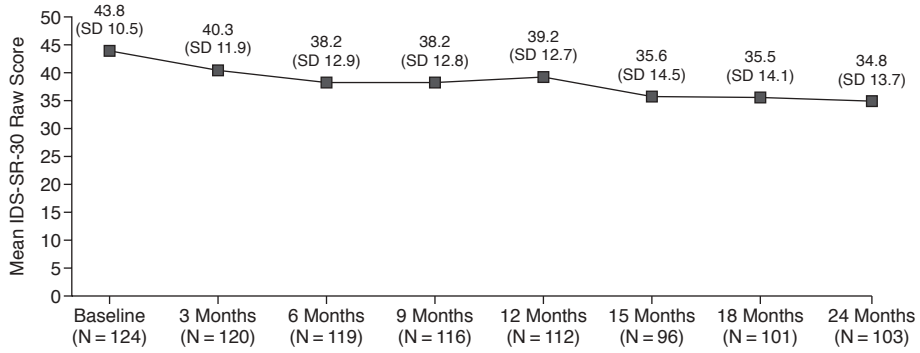
Figure 1. Mean IDS-SR-30 Raw Score Changes Over 24 Months



Abbreviation: IDS-SR-30 = 30-item Inventory of Depressive Symptomatology–Self-Report.

patients did not meet study inclusion criteria at baseline, 2 withdrew at baseline, and 1 had no postbaseline assessments and was excluded from the analyses. Data were available for the evaluable observed sample at baseline (N = 124), at 12 months (N = 112), and at 24 months (N = 103). Of the 21 patients who discontinued at some point during the study, 13 withdrew consent, 3 were excluded because of significant noncompliance, and 5 were withdrawn by investigator decision or lost to follow-up.

Demographic data and treatment history for all study patients (N = 124) are presented in Table 1. Patients had not adequately responded to an average of 3.5 medication trials that were adequate in both dose and duration as defined by the ATHF for the current MDE. During their lifetime, all patients had been treated with at least 1 SSRI, and 86 patients (69.4%) had failed to respond to at least 5 different treatments in their lifetime. Most patients had a history of chronic or recurrent major depressive disorder (MDD), with approximately one-fourth of the patients having more than 10 lifetime depressive episodes.

Response and Remission

As determined by the IDS-SR-30 for the observed sample, the 3-, 12-, and 24-month response rates were 5.8% (7/120), 11.6% (13/112), and 18.4% (19/103), respectively. The difference in response rates from 3 months to 12 months was not statistically significant (p = .125), and the change from 3 months to 24 months was significant (p = .003). The difference in response rates from 12 to 24 months was not significant (p = .109). For remission, the 3-, 12-, and 24-month rates were 1.7% (2/120), 3.6% (4/112), and 7.8% (8/103), respectively. The difference in remission rates from 3 to 12 months was not significant (p = .376), and the difference from 3 to 24 months was significant (p = .049). The difference in remission rates from 12 to 24 months was not significant (p = .172). The mean IDS-SR-30 scores at baseline and 3, 6, 9, 12, 15, and 24 months are shown in Figure 1.

For this study, response and remission were determined at each visit and were defined by the symptom severity for the prior 7 days. Therefore, these rates do not represent longer time periods. Table 2 shows how many responders at each time point had an additional response visit during the remainder of the study. For example, of the 7 patients with a response at the 3-month visit, 2 patients also showed a response at 6 months, none showed a response at 9 and 12 months, 3 showed a response at 15 months, and 2 showed a response at 18 and 24 months, respectively. Of the 44 patients showing a response at some point during the study, 4 had no follow-up data or withdrew from the study as responders (1 after the 6-month, 1 after the 9-month, 1 after the 12-month, and 1 after the 18-month visit). Three additional patients had no follow-up data or withdrew from the study as nonresponders (1 after the 6-month, 1 after the 9-month, and 1 after the 18-month visit). Of the 19 patients showing a response at the 24-month visit, 5 were first-time responders. Table 3 shows how many remitters at each time point had an additional visit showing remission during the remainder of the study. Of the 24 patients showing remission at some point during the study, 1 remitter at the 18-month visit was missing data at the 24-month visit. Of the 8 patients with a remission visit at 24 months, 2 were first-time remitters.

The majority of patients with a response at any one point during the study had only intermittent and transient response patterns. There were no persistent remitters during the first year of the study (i.e., no patients had more than 1 "remission visit" during the first 4 study visits). Five of the patients who remitted after the first year (after the 12-month visit) also showed remission at 24 months. One patient with a remission visit at 12 months also showed remission at 24 months. Nineteen patients had intermittent, transient remission. Sixty-five percent of

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Table 2. Number of Responders at Each Visit Month and Subsequent Repeat Responders Over Time (observed cases)[a]

Month of Follow-up Visit						
3 (N = 120)	6 (N = 119)	9 (N = 116)	12 (N = 112)	15 (N = 96)	18 (N = 101)	24 (N = 103)
7	2	0	0	3	2	2
	10	3	2	2	3	5
		9	5	3	4	3
			13	5	5	5
				16	8	8
					16	10
						19[b]

[a]The bold numbers in each visit month column indicate the total number of responders at that visit. The numbers in each row to the right of the bold number are repeat responders at subsequent visits. Patients with multiple response visits are counted in each row in which they are responders and, therefore, patient numbers are not meant to be totaled from top to bottom within each column. Seven of the 44 patients showing a response at some point during the study withdrew or had no follow-up data, 4 as responders and 3 as nonresponders.
[b]Five of the patients responding at the 24-month visit were first-time responders.

Table 3. Number of Remitters at Each Visit Month and Subsequent Repeat Remitters Over Time (observed cases)[a]

Month of Follow-up Visit						
3 (N = 120)	6 (N = 119)	9 (N = 116)	12 (N = 112)	15 (N = 96)	18 (N = 101)	24 (N = 103)
2	0	0	0	1	1	0
	3	0	0	1	0	1
		2	0	0	1	0
			4	1	1	1
				12	6	4
					10	3
						8[b]

[a]The bold numbers in each visit month column indicate the total number of remitters at that visit. The numbers in each row to the right of the bold number are repeat remitters at subsequent visits. Patients with multiple remission visits are counted in each row in which they are remitters and, therefore, patient numbers are not meant to be totaled from top to bottom within each column. Of the 24 patients showing remission at some point during the study, 1 remitter at the 18-month visit was missing data at the 24-month visit.
[b]Two of the patients remitting at the 24-month visit were first-time remitters.

patients (80/124) showed no response at any point during the study, and 81% (100/124) showed no remission at any point during the study.

Quality of Life

For the SF-36, after 12 months of TAU, 48.2% (54/112) were about the same, 29.5% (33/112) were somewhat to much better, and 22.3% (25/112) were somewhat to much worse in terms of change in health compared with baseline. At 24 months, 42.2% (43/102) of patients reported relatively no change in quality of life as measured from baseline, 36.3% (37/102) were somewhat to much better, and 21.6% (22/102) were somewhat to much worse. Changes over time for the average physical and mental component scores are shown in Figure 2. The mean ± SD change from baseline at 24 months was –1.5 ± 11.1 for the physical component and +8.8 ± 11.4 for the mental component. Subscale scores are shown in Table 4.

Study Treatments and Medication Changes

The distribution of mood-disorder treatments received during the 24-month study period is shown in Table 5. Medication changes for 12 and 24 months are shown in Table 6 for the ATHF treatments listed in the Methods section. For the IDS-SR-30 responders (N = 19) at 24 months, 1 patient was reported to be on no medication therapy; the remaining responders were receiving at least 1 medication and had experienced a change in medication dose or type at least once as collected during the study. Sixteen of these responders had medications added or doses increased; 1 responder stopped or decreased a medication without adding or increasing any medications.

Study Retention Rates and Suicide Attempts

This 24-month study had a retention rate of approximately 81% (103/127). Although safety data were not systematically collected during this study, 3 emergency room visits for suicide attempts were self-reported by the patients during the 24-month study period. No completed suicides were reported by the study investigators.

DISCUSSION

Despite a wide range of treatment options, TRD continues to be a serious and debilitating illness for many. This study shows that patients with substantial levels of TRD had a very low likelihood of sustained treatment response, even after 2 years, despite receiving a variety of treatments consisting of various classes of antidepressants with augmentation and combination strategies, psychotherapy, and ECT. Furthermore, as defined by the SF-36, patients experienced a poor quality of life throughout the duration of the study despite receiving active treatment. These less-than-optimal outcomes demonstrate the difficulty in successfully treating such patients.

Consensus-based algorithms (e.g., Crismon et al.[36]) have been suggested for managing TRD patients. Such algorithms are more effective than TAU,[37] yet outcomes after 1 year suggest symptom remission in only a very modest minority of patients.[16] The current study also showed modest improvements over time, but neither response nor remission was consistently maintained. Only 35% of patients showed a response at some point during the study, and most of these patients had only transient or intermittent responses. Furthermore, more than 90% of patients continued to experience substantial levels of depressive symptoms (i.e., did not remit) after 2 years of active treatment.

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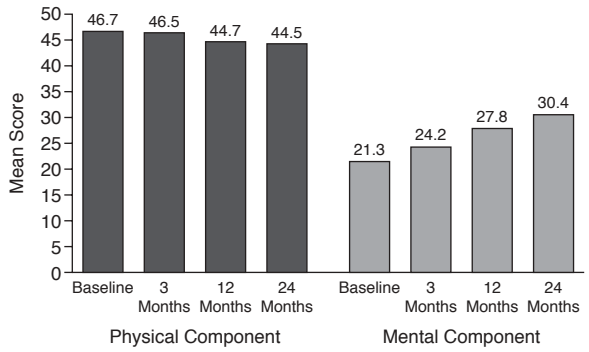
Figure 2. Mean SF-36 Component Score Changes Over 24 Months



Abbreviation: SF-36 = 36-item Short Form Health Survey of the Medical Outcomes Study.

Table 4. Mean (SD) SF-36 Subscale Scores at Baseline and 3, 12, and 24 Months

SF-36 Subscale	Baseline (N = 124)	3 Months (N = 120)	12 Months (N = 112)	24 Months (N = 103)
Physical functioning	63.6 (25.3)	65.5 (24.3)	63.0 (26.8)	63.1 (26.9)
Role functioning–physical	32.5 (39.9)	38.1 (40.6)	31.0 (39.3)	38.7 (40.2)
Bodily pain	53.3 (24.1)	53.7 (24.7)	54.0 (22.7)	53.1 (24.7)
General health perception	47.2 (23.5)	45.1 (24.2)	47.4 (24.4)	47.8 (24.4)
Vitality	16.0 (14.9)	22.5 (17.8)	24.5 (19.8)	26.7 (21.9)
Social functioning	31.1 (22.6)	34.2 (23.6)	40.2 (27.2)	43.8 (27.6)
Role functioning–emotional	11.6 (22.1)	16.9 (29.0)	23.8 (33.3)	26.5 (34.3)
Mental health	29.9 (14.3)	36.1 (17.4)	39.6 (19.3)	45.7 (21.5)

Abbreviation: SF-36 = 36-item Short Form Health Survey of the Medical Outcomes Study.

Changes in quality-of-life measures were minimal, with SF-36 subscale scores remaining predominately below average for the duration of the study. The subscale scores reported in this study were well below those reported for other patient samples with depression as well as with chronic medical conditions other than depression, such as congestive heart failure.[8]

Although the level of treatment resistance to enter this study required failure on at least 2 antidepressant treatments in the current MDE, in fact study patients had failed an average of 3.5 adequate treatment trials defined by the ATHF before study entry. Overall, patients had failed on an average of 4.3 total trials of different psychotropic agents in the current episode and failed on an average of 5.5 total trials during their lifetime, with approximately 70% of patients failing 5 or more treatment trials. Most patients added/increased, as well as stopped/decreased, their medications at least once during the study. A modified ARR rating scale that included a broader range of medications, such as stimulants, trazodone, and thyroid

Table 5. Mood Medication/Treatment Distribution (%)[a]

Medication/Treatment	Prestudy Lifetime (N = 124)	Baseline (N = 124)	12 Months[b] (N = 112)	24 Months[b] (N = 103)
Heterocyclics/TCAs	70.2	8.9	8.9	13.6
SSRIs	100.0	35.5	45.5	53.4
MAOIs	28.2	3.2	2.7	3.9
Other antidepressants[c]	98.4	51.6	58.0	66.0
Lithium	46.8	7.3	10.7	10.7
Anticonvulsants	51.6	32.3	36.6	35.0
Atypical antipsychotics	39.5	16.1	23.2	28.2
Typical antipsychotics	14.5	3.2	2.7	2.9
Stimulants	32.3	11.3	17.9	15.5
Anxiolytics	68.5	42.7	42.0	45.6
Hormones[d]	…	8.9	13.4	11.7
Hypnotics[d]	…	8.9	8.9	10.7
ECT	25.8	0.0	1.8	1.9

[a]Patients are only counted once for each medication category.
[b]Medications starting after the baseline visit and stopping before month 12 are not included in this analysis, nor are medications that started after month 12 but stopped before month 24.
[c]Includes bupropion, venlafaxine, mirtazapine, nefazodone, trazodone, amoxapine, and reboxetine.
[d]Data for hormones and hypnotics were not collected for lifetime use, but the use of these agents was tracked during the study.
Abbreviations: ECT = electroconvulsive therapy, MAOIs = monoamine oxidase inhibitors, SSRIs = selective serotonin reuptake inhibitors, TCAs = tricyclic antidepressants.
Symbol: … = no data.

Table 6. Medication Changes[a] for the Observed Sample Between Baseline and 12 Months and Between 12 and 24 Months

Medication Change	12 Months (N = 110[b]), N (%)	24 Months (N = 103), N (%)
No medications or no change	13 (11.8)	7 (6.8)
Additions or increases	90 (81.8)	89 (86.4)
Discontinuations or decreases	87 (79.1)	83 (80.6)
Only discontinuations or decreases with no additions or increases	10 (9.1)	4 (3.9)
Only additions or increases with no discontinuations or decreases	7 (6.4)	6 (5.8)

[a]Defined as an addition or removal of a drug or a dose change of an ARR of ≥ 1 dose level. Changes in each category were counted for the first occurrence by patient.
[b]One patient did not have any medication data, and 1 patient was missing medication data at the 12-month time point.
Abbreviation: ARR = Antidepressant Resistance Rating.

medications, showed that even more medication changes were occurring in this sample. However, only small and intermittent improvements in depressive symptoms were achieved despite frequent treatment changes and utilization of a variety of treatment options. Such a transient response pattern may be reflective of the waxing and waning nature of the underlying disease process.

This study has several limitations. Although the primary outcome was not a clinician rating, the IDS-SR-30 relates well to the Hamilton Rating Scale for Depression.[38,39] However, because the assessments were self-rated, the frequency of measurement visits in this study could have resulted in a test/retest phenomenon that

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skewed the outcome results over time. The definition of response and remission was based on only the 7 days prior to the ratings. Ratings, therefore, did not fully sample the time period. Finally, the sample is not a random sample, either of participating practitioners or of all potentially eligible TRD patients. Thus, the generalizability of results is limited. On the other hand, a sample with this degree of resistance defined by research methods a priori has rarely been followed for 2 years. Additionally, the adequacy of each new treatment trial patients received during the study could not be verified.

Reports of results with TAU methods for depression such as augmentation, substitution, and novel treatments are seldom published. Furthermore, the available reports on TRD studies are often short-term, do not include subjects with high levels of treatment resistance or include patients with a range of treatment resistance, and often exclude patients with a long duration of illness (MDE > 2 years).[16,40–43] These factors make it difficult for clinicians to accurately assess optimal treatment options and outcomes among such a difficult-to-treat population. The recently published report on depressed public sector outpatients being treated as part of the Texas Medication Algorithm Project included patients with a range of depression severity.[16] Although some subjects in this study were considered treatment resistant, the sample was not representative of a severe TRD population and, moreover, treatment outcomes represented the best-case scenario for these patients. Therefore, this study provides a much-needed reference group of patients with recurrent and chronic TRD receiving TAU.

Several factors may account for the relatively poor outcomes among patients with TRD. One possibility is that a distinct biology or genetic makeup that is not corrected with currently available treatments may characterize TRD. A recent study by Nemeroff et al.[44] showed that differences in the etiology and pathogenesis of depression correlated with differences in response to various treatments. For example, the study showed that patients with a history of early trauma had a more favorable response with psychotherapy versus pharmacotherapy. And a combination of psychotherapy and pharmacotherapy versus psychotherapy alone showed only a modest advantage in the subgroup of patients with early life trauma and chronic MDD. Therefore, biological factors may need to play a larger role in the treatment selection process for patients with TRD. Another possibility that may be attributed to the poorer outcomes seen with patients with TRD is the greater medication burden often seen in this population. The pharmacologic burden resulting from polytherapy may prevent new medications from being used at the maximum possible potentially therapeutic doses. Finally, poor treatment adherence by patients cannot be ruled out as a contributor to the variable response patterns observed over this extended study period.

This study focuses on patients with a very substantial level of TRD (i.e., failed on medication therapy with an average of 4 or more different psychotropic agents in the current episode and failed on medication therapy with an average of more than 5 trials during their lifetime). This population has not previously been followed up for 1 or 2 years. As such, this study is a benchmark for substantial or at least stage II-III or greater treatment resistance. Findings do not generalize to all TRD patients (i.e., those with lesser degrees of TRD may have better outcomes). These results do suggest, however, that little is gained with standard care applied over 1 to 2 years in terms of meaningful improvement that is lasting or sustained to any reasonable degree for many patients with TRD.

Drug names: bupropion (Wellbutrin and others), lithium (Lithobid, Eskalith, and others), mirtazapine (Remeron and others), trazodone (Desyrel and others), venlafaxine (Effexor).

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