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CME Objective
After completing this CME activity, participants should be able to select treatment for patients who fail to respond to an initial adequate trial of an antidepressant.

Statement of Need and Purpose
As many as 30% of patients with depression fail to achieve an adequate response to initial pharmacologic treatment. This CME activity was designed to meet the needs of physicians responding to CME questionnaires who have requested updated information on strategies for patients with treatment-resistant depression. There are no prerequisites for participation in this CME activity.

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Faculty Disclosure
In the spirit of full disclosure and in compliance with all ACCME Essential Areas and Policies, the faculty for this CME activity were asked to complete a full disclosure statement. The information received is as follows:

Drs. Posternak and Zimmerman have no significant commercial relationships to disclose relative to the presentation.

Disclosure of Off-Label Usage
To the best of their knowledge, the authors have determined that buspirone, methylphenidate, and moclobemide are not approved by the Food and Drug Administration for the treatment of depression.

Switching Versus Augmentation: A Prospective, Naturalistic Comparison in Depressed, Treatment-Resistant Patients

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Objective: (1) To directly compare the effectiveness of switching antidepressants with augmenting them in depressed patients who do not respond to an initial adequate trial and (2) to determine whether there is a decreased likelihood of response to a second switch or augmentation trial in those patients who did not respond to the first intervention for treatment-resistant depression.

Method: In a naturalistic, open-label design, all depressed outpatients (DSM-IV criteria) who were treatment resistant were prospectively assessed. Short- and long-term outcomes of switching versus augmentation were compared using the Clinical Global Impressions scale.

Results: In the acute phase, 37 (50.0%) of 74 subjects responded to 1 of the 2 interventions for treatment-resistant depression. Forty-five percent (N = 17) and 56% (N = 20) of the patients who had their antidepressant switched or augmented, respectively, responded to that intervention. Nearly three fourths (71.4%) of the acute responders maintained their response through 6 months of follow-up. In 18 patients who did not respond to the first switch or augmentation, 9 (50.0%) responded to a second trial.

Conclusion: Switching antidepressants was somewhat less effective than augmentation, although this difference was not statistically significant. For patients who do not respond to an augmentation or switch, our results suggest that a second trial for treatment-resistant depression may be as effective as the first.

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As many as 30% of depressed patients fail to respond to an adequate antidepressant trial.[1,2] Of those who do respond, an estimated 20% can be expected to relapse during the first 12 months of maintenance therapy.[3] Thus, treatment resistance occurs in roughly half the patients initiated on antidepressant treatment. Despite its ubiquity, no consensus exists concerning the most appropriate treatment intervention for refractory depression.[4,5]

Empirical studies support the use of lithium,[6–13] triiodothyronine (T_3),[13,14] buspirone,[15] pindolol,[16–18] stimulants,[19,20] or the combination of 2 antidepressants[21–23] as augmentation agents. The main pharmacologic alternative to augmentation is switching antidepressants. Open-label studies[24–29] indicate that patients resistant to one antidepressant often have favorable outcomes when switched to another antidepressant. Although most authorities recommend switching to an antidepressant with a different mechanism of action, 2 open-label studies[30,31] suggest that switching from one serotonin reuptake inhibitor to another may also be a viable strategy. In double-blind switch studies, usually performed in a "crossover" format, response rates have varied widely between 13% and 86%.[32–38]

Because augmentation and switching have never been directly compared, few scientific data exist to guide clinicians in choosing between these 2 strategies. In a recent review of the literature, Nelson[39] concluded that the collection of evidence suggests that the 2 interventions are probably equally effective, and that at this time, the choice between the 2 should probably rest on such factors as side effects,

cost, and ease of administration. To test this assertion, we sought to ascertain and compare the response rates of treatment-resistant patients whose antidepressant was switched with those who had their antidepressant augmented following a failed trial. We were also interested in determining whether the likelihood of response decreased in a second trial of switching or augmentation.

METHOD

All subjects were outpatients seeking treatment at the Rhode Island Hospital Department of Psychiatry (Providence, R.I.) from 1996 to 1999. Our private practice group predominantly treats individuals with medical insurance (including Medicare, but not Medicaid) on a fee-for-service basis and is distinct from the hospital's outpatient residency training clinic. During their first visit, patients were either interviewed with the Structured Clinical Interview for DSM-IV (SCID)[40] (N = 58) or underwent a thorough diagnostic interview by one of the authors (M.Z.) with recognized expertise in nosology (N = 16). The severity of the depressive episode was assessed upon presentation (and not necessarily at the time of the switch or augmentation) using the Clinical Global Impressions-Severity of Illness scale (CGI-S). Further details of the baseline evaluations are presented elsewhere.[41] Those patients who met criteria for nonpsychotic major depression, bipolar I disorder, or bipolar II disorder were considered for analysis. Patients with a primary diagnosis of depressive disorder not otherwise specified were also included if they subsequently met full criteria for major depression at the time of the switch or augmentation. No patients were excluded because of medical or psychiatric comorbidity.

Physical examinations and laboratory evaluations were obtained at baseline when clinically indicated. All patients were treated naturalistically according to standard clinical practice. The initial selection of antidepressant was based on each individual patient's clinical presentation and preference.

Patients were considered to be treatment resistant if a positive response was not obtained following at least 4 weeks of antidepressant therapy at a minimum effective dosage (see criteria below for positive response). Patients who relapsed after initially responding were also included. A historical determination of nonresponse or relapse was accepted in those patients who entered treatment refractory to an antidepressant as long as the criteria for dosage and duration were met. Historical determinations were used for 5 patients (13.9%) in the augmentation cohort and 8 patients (21.1%) in the switch cohort. Only patients who did not respond to their antidepressant were considered; patients switched owing to side effects or intolerance were not included (although some patients may not have been able to tolerate the maximum recommended dosage). The first switch or augmentation trial of adequate duration (see below for definition of adequate duration) that met criteria for our study was utilized, whether this occurred upon entry into the practice or some time later. The decision to switch or augment an antidepressant was made purely on clinical grounds, as decided upon between the patient and his or her clinician.

The main outcome measure used was the Clinical Global Impressions-Improvement scale (CGI-I). The CGI-I scale has 7 anchor points from 1 (very much improved) to 7 (very much worse) with a score of 4 indicating no change in clinical status. All patients were rated prospectively at each visit by the treating clinician. The authors were the treating clinicians for all patients. The CGI-I score from the first visit between 35 and 70 days following the switch or augmentation was used (this time frame was selected because most patients returned for their second follow-up appointment during this period). For patients who dropped out or whose medication was changed prior to day 35, we used the last-observation-carried-forward (LOCF) method of analysis. A CGI-I score of 1 (very much improved) or 2 (much improved) at the follow-up visit was considered a positive response, a score of 3 (somewhat improved) was considered a partial response, and any score from 4 to 7 was considered a nonresponse.

To assess long-term outcomes, we used the CGI-I score from the first visit between 6 and 12 months following the switch or augmentation. Patients who initially responded but dropped out were excluded from the analysis, whereas those who dropped out after an initial nonresponse or partial response were considered to have negative outcomes in the maintenance phase. Change in the Global Assessment of Functioning (GAF) score, which was also rated at each visit, was used as a secondary outcome measure.

The study was approved by the Rhode Island Hospital institutional review board, and all patients provided written informed consent.

RESULTS

Thirty-eight patients whose antidepressant was switched and 36 patients whose antidepressant was augmented met criteria for analysis. No significant differences were found between these 2 groups on any demographic or clinical variables (Table 1). Patients whose antidepres-

sant was augmented tended to be somewhat more depressed, as indicated by the CGI-S ratings, mean GAF scores, and percentage with recurrent depression, although none of these factors were statistically significant.

Tables 2 and 3 summarize the medication trials and outcomes for the patients who were switched or augmented. Of the patients whose antidepressant was switched, the majority (N = 25) initially received a serotonin reuptake inhibitor (SRI) and were subsequently switched to a tricyclic antidepressant (TCA) (N = 8), a second SRI (N = 8), venlafaxine (N = 5), or another agent (N = 4). The most commonly employed augmentation strategies were the combination of an SRI + TCA (N = 17) or the addition of bupropion to an SRI (N = 6).

In the acute phase, 17 (44.7%) of 38 patients who were switched to a second antidepressant met criteria for positive response, and 22 (57.9%) of 38 met criteria for at least a partial response. Of the 17 switched patients who had a positive acute response, 3 dropped out prior to the 6-month follow-up (1 became pregnant, 1 moved, and 1 changed insurance). Three of the remaining 14 relapsed during the maintenance phase, while 1 acute responder was in partial remission at follow-up. Thus, 10 (71.4%) of 14 acute responders maintained their response for at least 6 months. One of the partial responders required surgery during the maintenance period, while the other 4 partial responders deteriorated over the maintenance period. Thus, of the original cohort whose antidepressant was switched (excluding the 3 dropouts), 10 (28.6%) of 35 had a positive response that was maintained for a minimum of 6 months.

Of the patients whose antidepressant was augmented, 20 (55.6%) of 36 met criteria for positive response, while 25 (69.4%) of 36 had at least a partial response. Five of the 20 acute responders were lost to follow-up. Of the remaining 16, 3 relapsed during the maintenance phase, 1 self-discontinued medication, and 1 patient developed intolerable side effects. Ten (71.4%) of the remaining 14 patients maintained their response through 6 months of follow-up. Of the 5 partial responders, 1 subsequently fully responded, 1 remained a partial responder, and 3 patients deteriorated. Thus, of the original cohort who had their antidepressant augmented (excluding 4 positive responders who dropped out and 2 who discontinued their regimen), 10 (33.3%) of 30 maintained their positive response for at least 6 months.

Tables 4 and 5 summarize and compare these outcomes. Augmentation yielded somewhat more favorable acute response rates (55.6% vs. 44.7%), although this difference was not statistically significant ($p = .27$). In both cohorts, the identical number of patients (10/14, 71.4%) maintained a positive response through the maintenance phase. Changes in GAF scores were comparable in both groups of responders. Of note, 4 patients who responded to augmentation had their regimen tapered during the maintenance phase, and all 4 sustained their positive response on monotherapy (see Table 3).

We next analyzed acute outcomes as a function of whether the initial treatment resistance was due to relapse, nonresponse, or partial response. We found little variation between these 3 cohorts, regardless of whether the antidepressant was switched or augmented (Table 6). Although the number of subjects was small, partial responders fared no better than nonresponders or relapsers.

Finally, patients who did not respond to having their antidepressant switched or augmented were followed up

Table 1. Demographic and Clinical Features of Depressed Treatment-Resistant Patients Whose Antidepressant Was Switched or Augmented[a]

Characteristic	Augmented (N = 36)	Switched (N = 38)
Sex (female:male)	23:13	22:16
Age, y, mean ± SD	41.1 ± 9.6	42.5 ± 13.9
Range	26–62	18–83
White, N (%)	30 (83.3)	36 (94.7)
Married, N (%)	19 (52.8)	23 (60.5)
Education (≥ high school diploma), N (%)	34 (94.4)	36 (94.7)
Diagnosis, N (%)		
Major depression	34 (94.4)	36 (94.7)
Bipolar I	1 (2.8)	0 (0.0)
Bipolar II	1 (2.8)	2 (5.3)
Duration of current episode		
Median, wk	45	104
Range, wk	4–386	2–2288
Previous history of depression, N (%)	28 (77.8)	20 (52.6)
CGI-S score, N (%)[b]		
Mild	3 (8.3)	5 (13.2)
Moderate	18 (50.0)	24 (63.2)
Severe	15 (41.7)	9 (23.7)
GAF score, mean ± SD	49.4 ± 9.6	51.3 ± 10.1
Reason for switch or augmentation, N (%)		
Nonresponse	16 (44.4)	25 (65.8)
Relapse	15 (41.7)	10 (26.3)
Partial response	4 (11.1)	2 (5.3)
Unspecified	1 (2.8)	1 (2.6)
Taking more than one other ancillary psychotropic medication, N (%)	6 (16.6)	3 (7.9)
Days to follow-up assessment, mean ± SD	46.3 ± 10.7	47.2 ± 11.1
Number of visits to follow-up assessment, mean ± SD	2.1 ± 0.7	1.9 ± 0.8

[a]Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, GAF = Global Assessment of Functioning.
[b]Score of 2 = mild, 3 = moderate, 4 and 5 = severe.

Table 2. Medication Regimens and Outcomes for Depressed Treatment-Resistant Patients Whose Antidepressant Was Switched[a]

Patient	Antidepressant Switched From	Dose,[b] mg/d	Duration, wk	Reason for Switch	Antidepressant Switched to	Dose,[c] mg/d	Acute Response	Maintenance Response
1	Fluoxetine	40	28	Relapse	Venlafaxine	150	–	+
2	Clomipramine	100	8	Nonresponse	Venlafaxine	300	–	0
3	Venlafaxine	300	24	Nonresponse	Nefazodone	300	+/–	–
4	Fluoxetine	40	100	Partial response	Sertraline	200	–	0
5	Sertraline	200	8	Nonresponse	Venlafaxine	225	+	Change insurance
6	Fluoxetine	40	6	Nonresponse	Nortriptyline	75	–	0
7	Sertraline	100	5	Nonresponse	Nortriptyline	75	+	0
8	Sertraline	100	4	Nonresponse	Nortriptyline	75	+	Pregnancy
9	Paroxetine	40	12	Partial response	Fluoxetine	40	–	0
10	Desipramine	150	16	Relapse	Sertraline	50	–	0
11	Paroxetine	45	16	Nonresponse	Venlafaxine	300	+/–	–
12	Paroxetine	40	28	Relapse	Fluoxetine	10	+	+/0
13	Paroxetine	20	80	Relapse	Nortriptyline	75	+	+
14	Fluoxetine	80	8	Nonresponse	Clomipramine	250	+	+
15	Amitriptyline	75	104	Unspecified	Sertraline	100	–	–
16	Paroxetine	20	8	Nonresponse	Bupropion	150	+	+
17	Sertraline	100	6	Nonresponse	Nortriptyline	75	–	0
18	Bupropion	200	40	Nonresponse	Sertraline	200	–	0
19	Fluoxetine	40	52	Relapse	Venlafaxine	300	–	+
20	Bupropion	300	32	Relapse	Nefazodone	300	–	Moved
21	Sertraline	100	8	Relapse	Nortriptyline	100	+	+
22	Fluoxetine	60	16	Relapse	Citalopram	40	+	+
23	Phenelzine	60	40	Relapse	Citalopram	20	+	+
24	Citalopram	20	20	Relapse	Fluoxetine	40	–	+
25	Bupropion	300	6	Nonresponse	Clomipramine	200	+/–	Surgery
26	Mirtazapine	15	4	Nonresponse	Sertraline	50	+	+
27	Fluoxetine	20	11	Nonresponse	Nortriptyline	100	+	0
28	Nefazodone	300	52	Partial response	Desipramine	150	+	+/–
29	Fluoxetine	40	14	Nonresponse	Venlafaxine	225	+	–
30	Nortriptyline	50	10	Nonresponse	Bupropion	150	+	+
31	Paroxetine	30	18	Nonresponse	Sertraline	200	+/–	0
32	Venlafaxine	300	9	Nonresponse	Nortriptyline	75	–	0
33	Fluoxetine	60	35	Nonresponse	Sertraline	150	+	+
34	Sertraline	150	29	Nonresponse	Bupropion	300	–	0
35	Paroxetine	20	26	Nonresponse	Nefazodone	600	–	0
36	Fluoxetine	40	8	Nonresponse	Paroxetine	20	–	0
37	Citalopram	40	5	Nonresponse	Nortriptyline	100	+/–	0
38	Moclobemide	300	24	Nonresponse	Fluoxetine	20	+	Moved

[a]Symbols: + = positive response; – = negative response; +/– = partial response; 0 = antidepressant ineffective, discontinued; +/0 = positive response, medication tapered.
[b]Dosage at time of switch. Maximum dosage during trial may have been higher.
[c]Dosage at the time the acute response was assessed. Maximum dosage during trial may have been higher.

in subsequent trials using the same criteria for treatment resistance and response. Of the patients who had not responded to an initial switch or augmentation, 18 underwent a second trial for treatment-resistant depression (10 augmentations and 8 switches). Nine of these patients responded (50.0%), yielding a response rate identical to that of the first trial.

DISCUSSION

From a sample of 74 treatment-resistant depressed patients, we found that the 2 most frequently employed interventions—switching antidepressants and augmentation—were relatively comparable, although augmentation may be somewhat more effective. It should be pointed out that a sample size of 74 subjects provides sufficient statistical power to detect only moderate differences, i.e., an effect size of 0.5 or greater. If the effect size is small (0.2), as might be expected in comparing these 2 approaches, a sample size of 200 subjects would be required to have an 80% power of detecting a statistically significant difference. Clearly, then, larger controlled studies are needed to clarify this issue.

The overall response rate of 50.0% we found after a switch or augmentation is consistent with the mean from other studies that have independently assessed switching

Table 3. Medication Regimens and Outcomes for Depressed Treatment-Resistant Patients Whose Antidepressant Was Augmented[a]

Patient	Antidepressant Augmented	Dose,[b] mg/d	Duration, wk	Reason for Augmentation	Augmentation Agent	Dose,[c] mg/d	Acute Response	Maintenance Response
1	Paroxetine	40	20	Nonresponse	Nortriptyline	50	–	0
2	Imipramine	100	8	Nonresponse	Fluoxetine	20	+	+/0
3	Sertraline	200	60	Relapse	Nortriptyline	50	–	0
4	Nortriptyline	100	16	Nonresponse	Paroxetine	20	–	0
5	Fluoxetine	60	8	Nonresponse	Nortriptyline	50	+	Dropout
6	Bupropion	450	12	Partial response	Dextroamphetamine	30	–	+/–
7	Fluoxetine	40	8	Partial response	Nortriptyline	75	–	+/0
8	Sertraline	100	150	Relapse	Nortriptyline	30	+	+
9	Nortriptyline	150	62	Partial response	Sertraline	50	+	+
10	Nefazodone	200	16	Relapse	Citalopram	40	+	+/0
11	Fluoxetine	40	6	Nonresponse	Bupropion	300	+	Dropout
12	Fluoxetine	60	24	Relapse	Bupropion	150	–	0
13	Venlafaxine	300	52	Relapse	Bupropion	400	–	+
14	Fluoxetine	80	24	Nonresponse	Phentermine	30	–	0
15	Sertraline	200	8	Nonresponse	Bupropion	150	+	+/0
16	Sertraline	200	150	Relapse	Buspirone	30	+	0
17	Fluoxetine	30	150	Relapse	Bupropion	200	+/–	+
18	Paroxetine	30	50	Unspecified	Buspirone	15	–	0
19	Fluoxetine	60	120	Relapse	Bupropion	300	+/–	0
20	Nortriptyline	75	8	Nonresponse	Sertraline	50	–	0
21	Sertraline	200	5	Nonresponse	Bupropion	300	+	+
22	Fluoxetine	20	30	Relapse	Nortriptyline	50	+	Dropout
23	Nortriptyline	100	16	Nonresponse	Fluoxetine	40	–	0
24	Nortriptyline	75	10	Nonresponse	Fluoxetine	20	+	SE
25	Venlafaxine	300	13	Nonresponse	Methylphenidate	20	+/–	0
26	Bupropion	300	17	Nonresponse	Fluoxetine	10	+/–	+/–
27	Fluoxetine	80	17	Nonresponse	Buspirone	45	+	SD
28	Nortriptyline	50	175	Relapse	Citalopram	20	+	+
29	Sertraline	300	6	Nonresponse	Nortriptyline	75	+	+
30	Venlafaxine	450	76	Relapse	Bupropion	300	+	0
31	Nefazodone	300	11	Relapse	Nortriptyline	50	+	Dropout
32	Nefazodone	200	104	Relapse	Bupropion	300	+	+
33	Desipramine	150	17	Relapse	Sertraline	100	+/–	0
34	Paroxetine	40	10	Nonresponse	Buspirone	35	+	+
35	Sertraline	150	74	Relapse	Nortriptyline	50	+	Dropout
36	Paroxetine	40	75	Partial response	Nortriptyline	50	+	0

[a]Abbreviations: SD = self-discontinued, SE = discontinued because of side effects. Symbols: + = positive response; – = negative response; +/– = partial response; 0 = regimen ineffective, discontinued; +/0 = positive response, regimen tapered.
[b]Dosage at time of switch. Maximum dosage during trial may have been higher.
[c]Dosage at the time the acute response was assessed. Maximum dosage during trial may have been higher.

and augmentation.[39] That the majority of these patients (71.4%) maintained a sustained improvement over 6 months indicates that these responses were not merely transient.

This overall response rate, although perhaps encouraging, is lower than what we found in a cohort of unselected depressed patients who entered our practice and were started on treatment with an antidepressant. Of these patients (N = 92), 56 (60.9%) obtained a positive response ($p = .16$), and 73 (79.3%) had at least a partial response ($p < .05$) (M.Z., unpublished data). Thus, while a significant number of treatment-resistant patients do respond to a second intervention, the likelihood of responding appears to decrease once a history of treatment resistance has been established. Paradoxically, we found no decrement in response rates in those patients who underwent a second trial for treatment-resistant depression. We are aware of 2 other studies[42,43] that have also found good results in patients refractory to 2 prospective trials for treatment-resistant depression.[43,44]

Although our long-term outcomes focused only on those patients who responded in the acute phase, follow-up assessments were made for all patients. Inspection of these data reveals that 3 (18.8%) of 16 initial responders to a switch experienced a "delayed response" during maintenance treatment (see Table 2, patients 1, 19, and 24). Similarly, 2 (18.2%) of 11 of the augmented nonresponders had a delayed response (see Table 3, patients 7 and 13). In all cases, the improvement was a slow, gradual process that began only after 2 months of a pharmacologic

Table 4. Acute Outcomes of Depressed Treatment-Resistant Patients Whose Antidepressant Was Switched or Augmented

	Augmented (N = 36)		Switched (N = 38)		
Response	N	%	N	%	p Value
Positive response	20	55.6	17	44.7	.27
Partial response	5	13.9	5	13.2	
Nonresponse	11	30.6	16	42.1	

Table 5. Maintenance Outcomes of Depressed Patients Who Had a Positive Response to a Switch or Augmentation in the Acute Phase[a]

Response	Switched (N = 14[b])	Augmented (N = 14[c])
Positive response, N (%)	10 (71.4)	10 (71.4)
Relapsed, N (%)	4 (28.6)	4 (28.6)
Increase in GAF scores in responders, mean ± SD	9.2 ± 10.6	12.7 ± 8.0

[a]Abbreviation: GAF = Global Assessment of Functioning.
[b]Three patients who initially responded to a switch dropped out (see Table 2).
[c]Four patients who initially responded to augmentation dropped out, 1 self-discontinued medication for unclear reasons, and 1 discontinued owing to side effects.

Table 6. Acute Outcomes of Switching and Augmentation Based on Reason for Antidepressant Failure[a]

Response	Augment (N = 35)	Switch (N = 37)	Total
Nonresponse	9/16 (56.3%)	11/25 (44.0%)	20/41 (48.8%)
Relapse	9/15 (60.0%)	5/10 (50.0%)	14/25 (56.0%)
Partial response	2/4 (50.0%)	1/2 (50.0%)	3/6 (50.0%)

[a]Two patients for whom the nature of the antidepressant failure was unclear are not included in this table.

intervention. We are aware of several other reports[44–46] of delayed responses in certain individuals, which raises the question of how long an antidepressant trial (and in this case, a treatment-resistant trial) should be.

Our small sample size precludes any conclusive statements regarding the outcomes reported in Table 6. However, the consistency of responses in each cohort suggests that while the biological mechanisms for nonresponse and relapse may differ, these differences may not affect response to treatment. That partial responders fared no better than either nonresponders or relapsers is particularly surprising considering that our definition of response required only slight improvement in these patients, i.e., a CGI-I of 1 point. Although counterintuitive, Price et al.[47] similarly found that partial responders fared no better than nonresponders in a lithium augmentation study.

One final point is worth noting. Among the augmentation agents selected, neither of the 2 best-documented agents, lithium or triiodothyronine, was chosen. The combination of 2 antidepressants was by far the most favored strategy. Despite a lack of well-documented controlled trials, this was also the most popular augmentation strategy in a recent survey of 20 psychopharmacologic experts.[48] Most likely, this reflects a belief that antidepressants with different mechanisms of actions can work synergistically and that once a positive response is obtained, a patient can often successfully be tapered back to monotherapy. This may be an important and underappreciated factor influencing the popularity of combining antidepressants. If so, controlled studies demonstrating its efficacy as compared with lithium and/or triiodothyronine augmentation in treatment-resistant depression are desperately needed.

These results should be viewed in the context of several limitations. This was a naturalistic, open-label study that lacked a control group. It is therefore possible that patient and/or clinician bias may have inflated the overall response rates. However, the fact that over three fourths (82.4%) of the patients were prospectively found to be nonresponders or relapsers under the care of the same clinician makes this unlikely to be a major factor. A second limitation is that patients were not randomly assigned to antidepressant switch or augmentation. Although no baseline demographic or clinical features were found to be significantly different between the 2 groups, it is possible that some inherent differences existed that we were unable to detect. Several points regarding this possible bias should be kept in mind, however. All treatment decisions were made to achieve the best possible outcome in each case, and at the time these decisions (and ratings) were made, the plan to analyze outcomes had not yet been formulated. Furthermore, since few scientific data exist concerning predictors of response to augmentation or switching, it is unknown which factors would predict favorable outcomes in one treatment versus the other.

It should also be pointed out that the median duration of the current depressive episode was somewhat longer in the cohort whose antidepressant was switched (104 weeks vs. 45 weeks), and this may have in part conveyed a worse prognosis for this group. Another limitation is that, as a naturalistic study, we were unable to control or account for patients concurrently engaged in psychotherapy.

Notwithstanding these limitations, the present study suggests that for patients who do not respond to an initial antidepressant trial, augmentation may be somewhat more effective than switching antidepressants. However,

larger, controlled studies are needed to confirm this conclusion. It remains unclear whether the likelihood of response decreases with each subsequent trial, but our results suggest a relatively high percentage will continue to respond. Future studies may shed light on predictors of response to one strategy versus another and, with the use of a control group, can more accurately assess the overall response rates to these 2 interventions.

Drug names: amitriptyline (Elavil and others), bupropion (Wellbutrin), buspirone (BuSpar), citalopram (Celexa), clomipramine (Anafranil and others), desipramine (Norpramin and others), dextroamphetamine (Dexedrine and others), fluoxetine (Prozac), methylphenidate (Ritalin and others), mirtazapine (Remeron), nefazodone (Serzone), nortriptyline (Pamelor and others), paroxetine (Paxil), phenelzine (Nardil), phentermine (Adipex-P, Fastin), sertraline (Zoloft), venlafaxine (Effexor).

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, the following agents mentioned in this article are not approved by the U.S. Food and Drug Administration for the treatment of depression: buspirone, methylphenidate, and moclobemide.

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1. For depressed patients who have responded to an antidepressant trial, the relapse rate during the first 12 months of maintenance therapy has been estimated to be:
a. 10%
b. 20%
c. 30%
d. 50%

2. Which of the following can be inferred from the overall outcomes of double-blind studies that have assessed the effectiveness of switching antidepressants in patients who fail to respond to an initial trial?
a. Switching antidepressants is effective in a relatively small percentage of patients.
b. Switching antidepressants is effective in a relatively large percentage of patients.
c. It is uncertain how effective switching antidepressants is.
d. No double-blind studies have been performed evaluating the effectiveness of switching antidepressants.

3. Which of the following statements is most accurate regarding the effectiveness of switching from one serotonin reuptake inhibitor to another for refractory depression?
a. It has never been studied.
b. It has been studied and has not been found to be effective.
c. It is supported by open-label studies.
d. It is supported by double-blind studies.

4. Which of the following is true regarding prior studies that have directly compared the effectiveness of augmentation and switching strategies?
a. Augmentation has generally been found to be more effective.
b. Switching has generally been found to be more effective.
c. The two strategies have been found to be equally effective.
d. The two strategies have never been directly compared with each other.

5. Based on prior literature, the decision of whether to switch or augment antidepressants should probably be determined by:
a. Which antidepressant the patients initially failed
b. How long the initial trial lasted
c. Whether the patient was a nonresponder, partial responder, or relapser
d. Side effects, cost, and ease of administration

6. In the present report, of the 74 patients who failed an initial antidepressant trial, what percentage responded to a switch or augmentation in the acute phase?
a. 33%
b. 50%
c. 67%
d. 71%

7. In the present report, of the patients who did not respond to an initial switch or augmentation, what percentage responded to a second trial switch or augmentation?
a. 10%
b. 20%
c. 30%
d. 50%

8. From a power analysis, it was determined that the sample size in the present study was probably:
a. Too small to detect differences between the two strategies assuming a small effect size
b. Sufficient to detect differences between the two strategies assuming a small effect size
c. Too large to detect differences between the two strategies assuming a small effect size
d. A power analysis could not be performed because the study was open-label.

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