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A Description of Next-Step Switching Versus Augmentation Practices for Outpatients with Treatment-Resistant Major Depressive Disorder Enrolled in an Academic Specialty Clinic

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Background. *There is a paucity of naturalistic studies from depression specialty clinics describing the next-step (augmentation versus switching) practices of clinicians for outpatients with major depressive disorder (MDD) resistant to an antidepressant trial of adequate dose and duration.*

Methods. *Eighty-five MDD outpatients enrolled in one of two specialty clinics, who had not achieved remission after a first adequate prospective antidepressant trial conducted at the clinic underwent either augmentation (n = 36) or switching (n=49) of their antidepressant regimen. Outcome was defined with the use of the Clinical Global Impressions (CGI) Scale.*

Results. *Nonresponders (CGI-I>3) following the first antidepressant trial were more likely to have their treatment switched than patients who experienced incomplete response (CGI-I<4, CGI-S>1) (67.2% versus 28.5%, p = 0.001). Incomplete responders during the first trial who went on to receive augmentation had higher remission rates (60.0% versus 0%, p=0.01), lower endpoint depression severity scores (1.8 ± 1.1 versus 3.3 ± 0.8, p = 0.01) and greater clinical improvement scores (1.6 ± 1.1 versus 3.0 ± 0.0, p=0.03) than incomplete responders who had their antidepressant regimen switched. Although nonresponders to the first treatment who were switched experienced greater symptom improvement than nonresponders who were augmented (2.7 ± 1.1 versus 3.4 ± 1.2, p=0.03), there was no significant difference (p>0.05) between these two groups with respect to remission rates (18.6% versus 14.2%, respectively) and endpoint depressive severity (3.0 ± 1.4 versus 3.4 ± 1.4, respectively).*

Conclusions. *In this nonrandomized, naturalistic treatment setting, nonresponders to an adequate, prospective antidepressant trial were more likely to have their antidepressant regimen switched, while patients with incomplete response during the first trial were more likely to have their regimen augmented. In addition, patients with incomplete response who had their treatment augmented had better outcome than patients with incomplete response who had their treatment switched.*

Keywords Naturalistic, Non-randomized, Treatment, Resistant, Augmentation, Switch

INTRODUCTION

Studies suggest that 29% to 46% of depressed patients show only partial or no response to antidepressants, with most taking a selective serotonin reuptake inhibitor (SSRI) as an initial treatment (1,2). Among responders to antidepressant treatment, residual symptoms are rather common (3) and have been shown to be associated with greater likelihood of relapsing and

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perhaps having a poorer long-term prognosis (4). When one surveys psychiatrists to assess their perceptions of what works in refractory depression, it is clear that the most popular antidepressant strategies, particularly newer ones, are not those that are best supported by evidence (5). The results of a survey of clinicians (6) suggests that clinicians are more likely to increase the dose (82%), than augment (14%) or switch (4%) treatment in SSRI partial responders, and more likely to switch (61%) or augment treatment (12%) than increase the dose (27%) in SSRI nonresponders. However, whether clinicians who regularly treat depression are more likely to switch or augment the treatment regimen of nonresponders versus incomplete responders in naturalistic treatment settings for MDD is unknown. The purpose of the present study was to 1) describe the practices of clinicians regarding their next-step treatment strategy choice (switch versus augmentation) in patients with MDD resistant to a single antidepressant trial, and 2) to compare the outcome of these two strategies overall as well as in nonresponders versus incomplete responders in a nonrandomized, naturalistic treatment sample.

METHODS

Psychiatrists (ASY, DVI, MAP, GIP) from two academic sites (the Massachusetts General Hospital Depression Clinical and Research Program and the Department of Psychiatry and Human Behavior, Brown University School of Medicine) received IRB approval to review the charts of all patients on their caseload for possible inclusion in the analysis. Inclusion criteria included: all charts of adult patients seen within the last three years with a documented diagnosis of major depressive disorder (DSM-IV criteria). Exclusion criteria included: documented (current or history of) bipolar disorder, schizophrenia, or psychosis. Severity of depression and clinical response to treatments were measured with the Clinical Global Impressions – Severity (CGI-S) and Clinical Global Impressions – Improvement (CGI-I) scales (7). Charts that did not use CGI scores as a measure of severity and outcome were excluded. Although clinicians used a variety of measures to document illness severity and symptoms, the CGI was selected because it was the most consistently used measure among the participating clinicians. Clinicians reviewed the charts of their patients and entered basic demographic, clinical and treatment data into a Statview (SAS product) database. These databases contained no patient identifiers (names, initials, medical record number, social security number or date of birth). These anonymous data were collected by two pre-designated investigators (TJP and GIP), who then conducted the statistical analyses.

Definition of Outcome and Data Analysis

Clinical response was defined as a CGI-I of 2 or 1 ("much" or "very much improved"), partial response was defined as a CGI-I of 3 ("minimally improved"), and nonresponse as a CGI-I>3. Remission was defined as a CGI-S of 1. The Massachusetts General Hospital Antidepressant Treatment Questionnaire (8) was used to define minimal dose and duration for an antidepressant trial to be considered inadequate, adequate or optimal. Chi-square and t-tests were used to compare groups on the basis of nominal or continuous variables, respectively. A .05 two-tailed level of significance was used.

RESULTS

Results of the First Trial

One hundred and fifteen patient records were included in the analysis (44.3% female, 40.6 ± 13.0 years of age). The mean age of first onset of MDD was 27.0 ± 13.7 years, the mean duration of the current major depressive episode (MDE) 31.4 ± 45.5 months, the mean number of lifetime major depressive episodes (MDEs) 4.3 ± 5.6, and the mean CGI-S score at baseline 4.0 ± 0.8 (before beginning initial treatment). The mean duration of the initial treatment was 17.4 ± 23.7 weeks. The first treatments employed are listed in Table 1. Of the 115 patients enrolled, 26 remitted (22.6%), 4 responded (3.4%), 19 experienced a partial response (16.5%), and 66 did not respond (57.3%). 4 patients discontinued after the first trial (3.4%).

Results of the Second Trial

Eighty five nonremitters following a first adequate antidepressant trial received either augmentation (36 or 42.3%) or were switched to a different treatment (49 or 57.7%). There were no statistically significant differences in CGI-S scores at the end of treatment 1 (baseline for treatment 2) (3.5 ± 0.7 versus 3.7 ± 0.8, p>0.05) between patients who received augmentation or were switched. Overall 43/64 (67.2%) nonresponders, 5/17 (29.4%) partial responders, and 1/4 (25.0%) responders to the first treatment had their treatment switched. In contrast, 21/64 (32.8%) nonresponders, 12/17 (70.6%) partial responders and 3/4 (75.0%) responders to the first treatment had their treatment augmented. Nonresponders (CGI-I>3) were more likely to have their treatment switched than patients who experienced incomplete symptom response (CGI-I<4, CGI-S>1) (43/64 or 67.2% versus 6/21 or 28.5%, respectively, p=0.001).

Table 1 First Prospective Treatment Choices

Initial Agent	%	(n)
SSRI	62.2%	(72)
Bupropion	14.7%	(17)
Nefazodone	7.8%	(9)
Mirtazapine	5.2%	(6)
TCAs	4.3%	(5)
Venlafaxine	4.3%	(5)

Patients who received augmentation had slightly lower CGI-I scores corresponding to the first antidepressant trial (CGI-I scores at the end of treatment 1), reflecting greater symptom improvement, than patients switched (3.5 ± 0.6 versus 3.8 ± 0.4, p<0.01).

Results of the Second Trial: Overall Outcome

The mean duration of the second treatment was 9.7 ± 5.6 weeks. The second treatments employed are listed in Table 2. Of the 85 patients who received a second adequate treatment, 20 remitted (23.5%), 14 responded (16.4%), 16 experienced a partial response (18.8%), and 35 did not respond (41.1%). There were no statistically significant differences in endpoint (post-treatment 2) CGI-S (2.8 ± 1.1 versus 2.7 ± 1.4, p>0.05) and -I (3.0 ± 1.4 versus 2.6 ± 1.5, p>0.05) scores between patients who had their treatment switched versus those who had their treatment augmented. There was a trend towards statistical significance in the proportion of remitters between patients who had their treatment switched versus those who had their treatment augmented (8/49 or 16.3% versus 12/36 or 33.3%, respectively, p=0.06).

Results of the Second Trial: Partial Responders and Responders

There were no differences in CGI-S (3.0 ± 0.7 versus 3.1 ± 0.4, respectively) or -I (2.8 ± 0.5 versus 2.8 ± 0.4, respectively) scores at the end of treatment 1 (baseline for treatment 2) in patients who had shown incomplete improvement during the first trial (CGI-I<4, CGI-S>1) who received either augmentation or were switched (p>0.05). There was a statistically significant difference in the proportion of remitters to the second trial among patients who had shown incomplete improvement during the first trial who received either augmentation (remission rate 9/15 or 60.0%) or were switched (0/6 or 0.0%) (p=0.01). There were statistically significant differences in the CGI-S scores (1.8 ± 1.1 versus 3.3 ± 0.8, p=0.01) and CGI-I scores at the end of treatment 2 (1.6 ± 1.0 versus 3.0 ± 0.0, p=0.03) among patients who had shown incomplete improvement during the first trial who received either augmentation or were switched favoring augmentation.

Table 2 Second Prospective Treatment Choices

Switch Agent	%	(n)	Augmentation	%	(n)
SSRI	40.8%	(20)	Bupropion	25.0%	(9)
Bupropion	14.2%	(7)	Lithium	16.6%	(6)
Venlafaxine	14.2%	(7)	Mirtazapine	11.1%	(4)
Mirtazapine	12.2%	(6)	SSRI	11.1%	(4)
TCAs	08.1%	(4)	Atyp.Anti.*	11.1%	(4)
Nefazodone	06.1%	(3)	Psychostim**	08.3%	(3)
MAOIs	04.0%	(2)	TCAs	05.5%	(2)
			T3	05.5%	(2)
			Modafinil	02.7%	(1)
			Venlafaxine	02.7%	(1)

*Atypical antipsychotic agents.
**Psychostimulants.

Results of the Second Trial: Nonresponders

There was no difference in CGI-S (3.8 ± 0.6 versus 3.8 ± 0.6, respectively) or -I (4.0 ± 0.0 versus 4.0 ± 0.2, respectively) scores at the end of treatment 1 (baseline for treatment 2) in nonresponders (CGI-I>3) during the first trial who received either augmentation or switch (p>0.05). There was no difference in remission rates among nonresponders to the first antidepressant trial (nonresponders) who received either augmentation (remission rate 3/21 or 14.2%) or were switched (8/43 or 18.6%) (p>0.05). There was no statistically significant difference in the CGI-S scores at the end of treatement 2 (3.4 ± 1.4 versus 3.0 ± 1.4, p>0.05) among nonresponders to the first trial who went on to receive either augmentation or were switched. However, there was a statistically significant difference in the CGI-I scores corresponding to treatment 2 (3.4 ± 1.2 versus 2.7 ± 1.1, respectively, p=0.03) among nonresponders during the first trial who received either augmentation or were switched.

DISCUSSION

The present results are interesting from two viewpoints. On one hand, although there have been prior reports of surveys of clinician practices (5,6), this is the first study to report on actual clinician practices with respect to the selection of the next-step treatment in patients who have not sufficiently responded after an adequate, prospective antidepressant trial. In the present sample, patients were much more likely to receive an augmentation strategy if they had experienced incomplete symptom improvement, while nonresponders were more likely to have their antidepressant regimen switched. Specifically, more than two thirds of nonresponders to the first antidepressant trial were switched, while almost 3 out of 4 patients who experienced incomplete symptom improvement during the first antidepressant trial subsequently received an augmentation strategy. This is in contrast to the practices reported during a recent survey of practitioners who attended a psychopharmacology course in which only 14% of respondents stated they would choose to augment SSRIs in partial responders (6).

On the other hand, this is also the first study to report that, in a naturalistic treatment sample, incomplete responders to an adequate, prospective antidepressant trial who then had their treatment regimen augmented had better outcome than incomplete responders who had their regimen switched. Specifically, patients who had experienced incomplete response during the first trial and subsequently had their treatment augmented had greater remission rates, greater symptom improvement and

lower endpoint depression severity scores than incomplete responders who subsequently had their treatment switched. However, whether there was a difference in outcome in nonresponders who underwent augmentation versus switching is not clear. While there was no difference in remission rates or endpoint depression severity between the two groups, patients who had their treatment switched did improve more than those who received augmentation.

There are many reasons that could explain why incomplete responders who received augmentation had better outcome than those who had their treatment switched. However, given the naturalistic, open-label design, and the lack of randomization in the present study it is not possible to draw any further conclusions regarding the nature of this relationship. For example, although there was no statistical difference in the mean CGI-S and –I scores immediately before treatment 2 for partial responders who received augmentation versus switch, given the lack of randomization, we cannot exclude that there may have been slight differences in the trajectory of improvement between the two groups prior to the treatment decision that influenced the outcome. In addition, full response during the first trial is predictive of achieving remission when the patient is continued on the same treatment through a consolidation of response. Furthermore, clinician and patient expectation favoring one strategy over another may have influenced the outcome. Definitive data regarding next step treatments, based on a large-scale effectiveness trial, will be available at the conclusion of the National Institute of Mental Health-funded Sequential Treatment Alternatives to Relieve Depression study (www.edc.gsph.pitt.edu/stard). When completed, this study will generate important answers to questions centered on what treatment strategy work best after nonresponse, partial response or response to an initial, adequate trial of an antidepressant. However, it will be interesting to note similarities and discrepancies when comparing findings for such a large, randomized, controlled trial with the present as well as other naturalistic treatment studies since both similarities as well as discrepancies between such studies can shed further light on factors inherent in randomized trials versus naturalistic treatment settings that influence differential response to switching versus augmentation strategies. In turn, identifying such factors may further improve the standard of care for depression.

There is a paucity of naturalistic or randomized studies comparing switching versus augmentation strategies for the treatment of MDD. In a naturalistic, open-label design, *Posternak and Zimmerman* (9) compared switching versus augmenting the antidepressant regimen for patients with treatment-resistant depression (TRD), defined as inadequate response to an antidepressant trial at minimum effective dosage for 4 weeks and, similar to our study, reported a numerical but not statistical difference in favor of augmentation (55.6% versus 44.7%) when the entire sample was examined. However, the authors did not report on how many TRD patients were partial or non-responders, and how many nonresponders versus partial/full responders had their antidepressant regimen switched versus augmented. In an earlier work, Hylan et al. (10) reported 160 patients who received naturalistic treatment with SSRIs and found that patients who remained on their initial antidepressant regimen for at least two months with no switching, augmentation or dose titration were 1.63 times more likely to experience clinical response that patients who had an adjustment to therapy within that initial time period. Although the relationship between premature switching and poorer outcome may indicate that these patients were less likely to receive treatment of optimal duration, it is much more difficult to explain why augmenting an agent or increasing the dose would be related to poorer outcome. The latter relationships may simply reflect that patients who do not improve during the 8-week interval are more likely to have their antidepressant dose increased or their treatment augmented, and more likely to have a poorer outcome than patients who improve during the first 8 weeks. In the present report, we avoided such pitfalls by only examining patients who had failed to achieve remission after an adequate trial of dose and duration.

The major limitation of the present naturalistic study is its relatively small sample size, making it possible that the present findings are due to chance. Several other limitations of our study also deserve mention. First, the chart review method utilized for data collection carries with it the possibility of inaccurate documentation of treatments. Clinicians who practice in academic settings are typically very busy, and it is a challenge to document treatments provided and clinical response as accurately as in clinical trials. In addition, in the present study we only relied on a single clinician rating to assess clinical improvement, and could not replicate our findings with other clinician or patient-rated scales. Furthermore, as this was not a traditional clinical trial, reliability assessments were not conducted to ensure adherence to a common standard for assigning CGI ratings while randomization and subject and rater blinding was not performed.

Although commonly used as the primary outcome measure in other naturalistic studies and chart reviews (9, 10–14), and recently reported as a sensitive measure of early global improvement in clinical trials (15), the CGI certainly does not assess specific symptom change as do measures used in other clinical trials (e.g., Hamilton Depression Rating Scale; 16). Without the consistent use among clinicians of more sensitive measures, we are unable to determine where change in symptoms occurred (e.g., sleep, mood, etc.). Similarly, no formal measures of medication adherence were utilized. However, all participating clinicians indicated that adherence was checked through interview at each clinical visit.

With respect to diagnosis, clinicians did not uniformly and consistently utilize structured interview instruments (e.g. SCID-P; 17) to make the diagnosis of major depressive disorder. Rather, the diagnosis was most often assigned based on clinical judgment with DSM IV criteria as the reference point. While this could be viewed as a limitation of this study, the investigators participating in this study are highly experienced psychiatrists who have each conducted hundreds of structured

diagnostic interviews, and work in specialized depression research programs located in hospital-based academic centers.

Patient clinical history available for the study was limited. In particular, structured interviews were not consistently conducted to determine psychiatric comorbidity. Therefore, the extent to which chronicity and comorbidity impacted response to the treatments examined is difficult to accurately assess.

CONCLUSION

In this non-randomized, naturalistic treatment setting, MDD patients who were nonresponders during their first adequate, prospective antidepressant trial were more likely to have their antidepressant regimen switched, while incomplete responders were more likely to have their regimen augmented. In addition, incomplete responders who had their treatment augmented had better outcome than incomplete responders who had their treatment switched.

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