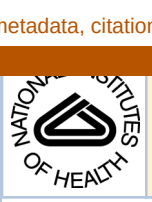

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Does the presence of accompanying symptom clusters differentiate the comparative effectiveness of second-line medication strategies for treating depression?

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Abstract

Background—We explored whether clinical outcomes differ by treatment strategy following initial antidepressant treatment failure among patients with and without clinically relevant symptom clusters.

Methods—The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial was used to examine depression remission and response in patients with coexisting anxiety, atypical features, insomnia, and low energy. We applied propensity scoring to control for selection bias that precluded comparisons between augmentation and switch strategies in the original trial. Binomial regressions compared the likelihood of remission or response among patients with and without symptom clusters for switch versus augmentation strategies (n=269 per arm); augmentation strategy type (n=565); and switch strategy type (n=727).

Results—We found no statistically significant difference in remission or response rates between augmentation or switch strategies. However, symptom clusters did distinguish among augmentation and switch strategies, respectively. For patients with low energy, augmentation with buspirone was less likely to produce remission than augmentation with bupropion (remission Risk

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Ratio [RR]:0.54, 95% CI: 0.35–0.85, response RR:0.67, 95% CI 0.43, 1.03). Also, for patients with low energy, switching to venlafaxine or bupropion was less likely to produce remission than switching to sertraline (RR: 0.59, 95% CI: 0.36–0.97; RR: 0.63, 95% CI: 0.38–1.06, respectively).

Conclusions—Remission and response rates following initial antidepressant treatment failure did not differ by treatment strategy for patients with coexisting atypical symptoms or insomnia. However, some second-step treatments for depression may be more effective than others in the presence of coexisting low energy. Subsequent prospective testing is necessary to confirm these initial findings.

Keywords

Depression; Antidepressant; Propensity Score; Symptom Cluster; Medication Selection

INTRODUCTION

Treatment-resistant depression is a significant burden for the estimated 40% of patients who do not respond to first-line antidepressant treatment.(Gartlehner et al., 2008) Compared with patients whose depression responds adequately to first-line treatment, those with treatment-resistant depression experience poorer quality of life, functional status, and well-being. (Mauskopf et al., 2009) One potential contributor to treatment-resistant depression is the presence of coexisting symptoms, such as anxiety, atypical features (including mood reactivity and reverse neurovegetative symptoms like hyperphagia and hypersomnia), insomnia, and fatigue.(Fava et al., 2008; Fava et al., 1997; Henningsen et al., 2003; Matza et al., 2003; Smith, 1992; Souery D et al., 2006) Such coexisting symptom clusters are believed to contribute to poor response and to increased health care use in depressed patients.(Berman et al., 1997; Charney et al., 1981; Shea et al., 1990; Thompson et al., 1988)

The presence of specific symptom clusters is reported to be the most common factor considered in selecting antidepressants.(Zimmerman et al., 2004) Especially in treatment-resistant depression, selecting a treatment that addresses specific symptoms can improve outcomes.(Fava et al., 1997; Kornstein and Schneider, 2001)For instance, a clinician treating depression with low-energy symptoms might prescribe bupropion because it is believed to be more activating than other antidepressants(Kavoussi et al., 1997; Weihs et al., 2000) Selective Serotonin Reuptake Inhibitors (SSRI) may be selected for patients with depression and comorbid panic or anxiety disorders because these medications are FDA approved for both conditions and are listed as first line treatment options for both conditions under APA practice guidelines.(American Psychiatric Association, 2000; Schoevers et al., 2008) While this approach to selecting an antidepressant may be reasonable, a thorough comparative review of the limited available evidence indicates that when symptom clusters are present, antidepressants do not vary greatly in their efficacy and effectiveness.(Gartlehner et al., 2008) In short, there is not good evidence to support the use of such clusters to guide first-line treatment choice.

In addition to using symptom clusters to guide initial treatment selection,(Zimmerman et al., 2004) clinicians are also likely to use them to guide decisions following initial treatment failure. Namely, clinicians may use the presence of a symptom cluster in deciding whether to add a medication to the existing antidepressant (augment) or switch treatment. In addition, once a strategy is selected, symptom clusters may be used to direct the recommendation of a particular augment or switch agent. To our knowledge, only one study has attempted to examine the role of symptom clusters on subsequent depression treatment decisions following initial treatment failure. This study focused solely on whether or not anxious or atypical symptoms should be considered when switching patients to a new medication.(Rush

et al., 2008) This analysis concluded that for patients with either anxious or atypical features who switch from citalopram, the choice of bupropion SR, sertraline, or venlafaxine XR does not affect the likelihood of remission.

The above findings are from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, a large-scale practical clinical trial designed to compare the effectiveness of switching and augmentation strategies following initial treatment failure with citalopram. (Rush et al., 2004) Given the prevalence of coexisting symptom clusters in STAR*D, these data provide a unique opportunity to assess whether symptom clusters are an important factor for clinicians to consider when selecting a second-line treatment. Anxiety, insomnia, and loss of energy, the three clusters with the strongest influence on antidepressant selection, (Zimmerman et al., 2004) were each present in over 50% of STAR*D enrollees. Atypical features, which make depression harder to treat and for which response may vary by psychopharmacologic profile,(American Psychiatric Association, 2000; Berman et al., 1997) were present in over 20% of STAR*D patients.

In this report, we undertake exploratory analyses of the publically available STAR*D data set to evaluate depression remission and response rates for various treatment strategies among patients with specific symptom clusters—anxiety, atypical features, insomnia, and loss of energy—who failed to remit after initial antidepressant treatment with citalopram. Augmentation options for second-line treatments included the addition of bupropion or of buspirone to citalopram, while switch options included changing to bupropion SR, sertraline, or venlafaxine XR. For patients with and without each symptom cluster, we asked:

1. Does the likelihood of remission or response differ as a function of treatment strategy (augmentation vs. switching)?
2. Does the likelihood of remission or response differ by the type of augmentation medication used?
3. Does the likelihood of remission or response differ by the type of switch medication used?

Methods

Study Overview

The original STAR*D trial methods, design and rationale have been detailed previously. (Fava et al., 2003; Rush et al., 2004) Briefly, STAR*D was designed to assess prospectively which of several treatments would be most effective for outpatients with nonpsychotic major depressive disorder who had an unsatisfactory response to initial (and potentially subsequent) treatment. The STAR*D selection criteria were broad and included participants with multiple comorbid medical and psychiatric illnesses. The distribution of depressive severity was reflective of that found in nationally representative samples,(Kessler et al., 2003) and the racial and ethnic composition of enrolled patients approximated the US Census.

Eligible participants who consented to STAR*D were initially given citalopram for 12 weeks unless (1) intolerable side effects required a medication change, (2) optimal dose increase was not possible due to side effects or the participant's choice, or (3) significant symptoms were present after 9 weeks at the maximally tolerated dose. Participants who needed to discontinue citalopram or whose depression did not remit after this initial trial were eligible to participate in a clinical trial involving randomization to a number of treatment options. The present study focuses on participants randomized within the level 2

medication arms for augment (bupropion SR or buspirone added to citalopram) or switch (bupropion SR, sertraline, or venlafaxine XR). We exclude participants who received cognitive behavioral therapy as a second-step treatment. Participants identifying medication augment or switch as acceptable options were randomly assigned within these groups, but not across these groups. In other words, the comparison of augment with switch is not based on random assignment.

Study Population

STAR*D enrolled 4,041 participants 18–75 years of age with a diagnosis of single-episode or recurrent nonpsychotic depression. Of the 4,041 entering initial treatment with citalopram, 1,439 participants did not achieve remission and entered level 2. Excluding the 147 participants who received cognitive behavioral therapy as a second-step treatment, our analyses involved the 1292 patients who were randomized to a medication arm.

Measures

Clinic visits occurred at baseline and at weeks 2, 4, 6, 9, and 12, with an additional visit at week 14 if needed. Primary outcome measures included the Self-Report version of the Quick Inventory of Depressive Symptomatology ($QIDS\text{-}SR_{16}$),(Rush AJ et al., 2006; Rush et al., 2003) the 17-item Hamilton Rating Scale for Depression ($HRSD_{17}$),(Hamilton, 1960, 1967) the Short-Form Health Survey (SF-12),(Gandek et al., 1998) and the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q).(Endicott et al., 1993; Wisniewski et al., 2007) Specific symptom clusters of interest were measured at baseline and months 3, 6, 9, and 12 using the $HRSD_{17}$ and the 30-item Inventory of Depressive Symptomatology - Clinician-Rated (IDS-C-30).(Rush et al., 1996)

Coexisting clusters were identified using standard criteria as follows. Anxious depression was defined as a total score of 7 or more on the $HRSD_{17}$ anxiety/somatic items (psychic anxiety, somatic anxiety, gastrointestinal somatic symptoms, general somatic symptoms, hypochondriasis, and insight).(Fava et al., 2004) Atypical depression was defined, using the IDS-C-30, as having brightening of mood at least when highly desired events occur and having high scores on more than one of the following: hypersomnia, appetite or weight increase, interpersonal sensitivity, or leaden paralysis.(Novick et al., 2005)

Energy loss and insomnia were also defined using the IDS-C-30. Patients were identified as experiencing energy loss if they indicated that they (1) made significant personal effort to initiate or maintain usual daily activities or (2) were unable to carry out most of the usual daily activities due to a lack of energy.(Gaynes et al., 2005) Patients were identified as experiencing insomnia if they indicated that they had a moderate to severe problem with any of the following: (1) insomnia at sleep onset, (2) mid-nocturnal insomnia, or (3) early morning awakening.(Gaynes et al., 2005)

Statistical Analysis

We examined missing data for the variables necessary for the propensity score and outcomes models. The level of missing information in the analysis dataset was only 5%, but 82% of observations had a missing value on at least one analysis variable. Multiple imputation was performed using SAS PROC MI(SAS Institute Inc., 2008), which replaces missing values based on observed variable distributions and creates multiple analysis datasets to account for the error associated with imputation.(Allison, 2002; Graham, 2009)

Because patients were not randomized to switch and augment strategies, we used propensity score matching to balance covariates between these groups. Propensity scores were developed using multiple logistic regression to estimate each participant’s conditional

probability of receiving medication augmentation. Patients were then matched between the switch group and augment group based on their estimated propensity scores, resulting in the selection of 269 augment participants (on average, across imputed datasets), matched with an equal number of switch participants. Diagnostics indicated acceptable balance between the matched samples (e.g., the standardized difference between groups on each covariate, averaged across 47 covariates and 20 imputations, was 0.035).

We generated incidence proportions and risk ratios (along with corresponding confidence intervals) for remission and response using PROC GENMOD.(Robbins et al., 2002) The following analyses were conducted separately for each symptom cluster and were stratified by presence (vs. absence) of the symptom cluster:

1. Based on the propensity-score-matched sample (n=269 in each arm) we used binomial regression models to estimate for augment and switch patients the proportion in each group experiencing remission and treatment response, as well as the risk ratios (augment/switch) for remission and response.
2. Based on the full sample of patients receiving medication augmentation (n=565), we used binomial regression models to estimate for the two treatment options (citalopram plus bupropion SR, citalopram plus buspirone) the proportion of patients in each group experiencing remission and treatment response as well as the risk ratios (buspirone/bupropion SR) for remission and response. We used the full augmentation sample because the probability of receiving augmentation with buspirone equaled the probability of receiving augmentation with bupropion SR due to randomization.
3. Based on the full sample of patients switching medications (n=727), we used binomial regression models to estimate for the three randomization options (bupropion SR, sertraline, venlafaxine XR) the proportion of patients in each group experiencing remission and treatment response as well as the risk ratios (with sertraline as the reference group) for remission and response.

Results

Sample Description

Table 1 presents comparisons, before and after propensity score matching, between patients whose medication was augmented and those switching to another monotherapy. Prior to matching, there were minimal demographic differences between the 565 patients who received augmentation and the 727 patients who switched treatment. However, the pre-propensity score sample had some notable differences in psychiatric histories between the augment and switch groups. Patients who augmented had fewer major depressive episodes (mean of 5.6 versus 6.8), higher rates of drug abuse (8.7 % versus 5.5% respectively) and less post-traumatic stress disorder (18.9% versus 23.0%) than those who switched medications. Finally, important differences were observed with regard to status at the end of level 1 treatment (i.e., immediately prior to level 2 treatment). Most notably, patients augmenting treatment had significantly lower rates of exit due to side effects (10.3% versus 62.8%), lower side effect scores as indicated by a composite score on the Frequency Intensity and Burden of Side Effects Rating (FIBSER) scale (mean 1.2 versus 2.8), and higher level 1 exit citalopram dose (mean of 55.1 versus mean of 41.4 mg/day) compared with switch patients.

Although the propensity-score-matched sample differed on several variables from the patients for whom no match was found, propensity score matching eliminated important differences between the switch and augment groups which allowed for more meaningful

comparison between treatment strategies. (Table 1). Our matched sample reflects patients who were moderately depressed (QIDS-SR_{16} 12–13)(Rush et al., 2003), were able to tolerate an aggressive level 1 treatment at a relatively high dose of citalopram (mean dose = 53 mg/day), and tended not to exit level 1 because of side effects (approximately 20% of this sample did so). Among excluded patients, those who received augmentation tended to be less severely depressed (QIDS-SR_{16} 10.3 vs. 13.6), remained in level 1 treatment longer (12.8 weeks vs. 6.3 weeks), received a higher dose of citalopram during level 1 treatment (57.1 mg vs. 34.7 mg), and were less likely to exit level 1 because of side effects (1.6% vs. 87.8%) compared to those who received switch treatment.

Augmentation vs. Switch Strategy (Propensity-score-matched Sample): Does the likelihood of remission or response differ as a function of treatment strategy?

Table 2 compares the remission and response rates seen with augmentation to those with switching, by the presence or absence of each symptom cluster. We found no statistically significant difference between the augmentation vs. switch strategies with regard to likelihood of remission or of response. The largest estimated differences were for patients with accompanying anxious symptoms: those who received augmentation were more likely to remit (RR: 1.72, 95%CI 0.69, 4.30) and to respond (RR: 1.81, 95% CI 0.82, 4.00) than those who switched treatment. Among patients with coexisting energy loss there was a similar yet weaker tendency toward better outcomes for augmentation: Patients who augmented were slightly more likely to remit (RR: 1.24, 95% CI 0.74, 2.08) and to respond (RR: 1.30, 95% CI 0.80, 2.11) than patients who switched.

Within the randomized augmentation arm (full sample): Does the likelihood of remission or response differ by the type of augmentation medication used?

We also assessed whether, for each symptom cluster, the likelihood of remission and response differed by the augmenting agent (bupropion SR or buspirone) among the full sample of patients (N = 565) receiving augmentation (Table 3). The only statistically significant effect was that patients with coexisting energy loss were approximately half as likely to remit if augmented with buspirone than bupropion SR (RR: 0.54, 95% CI 0.35, 0.85). Although not significant, patients with energy loss also appeared less likely to respond when augmenting with buspirone than bupropion SR (RR: 0.67, 95% CI 0.43, 1.03). Similar tendencies were seen among patients with atypical features who were less likely to remit (RR: 0.55, 95% CI 0.27, 1.13) and to respond (RR: 0.63, 95% CI 0.31, 1.27) when augmented with buspirone compared with bupropion. Differences were less clear for the other two symptom clusters.

Within the randomized switch arm (full sample): Does the likelihood of remission or response differ by the type of switch medication used?

Finally, we assessed whether, for each symptom cluster, the likelihood of remission and response differed by the switch agent (bupropion SR, sertraline or venlafaxine XR) among the full sample of patients switching treatment (n = 727) (Table 4). As with augmentation, the only statistically significant finding was seen for patients with coexisting low energy. Compared with sertraline, those switched to venlafaxine were less likely to remit (RR: 0.59, 95%CI 0.36, 0.97). Those switched to bupropion also tended toward lower remission rates (RR: 0.63, 95%CI 0.38, 1.06). Similarly, there was a trend toward lower likelihood of response with venlafaxine (RR: 0.82, 95%CI 0.53, 1.26) and bupropion (RR: 0.70, 95%CI 0.43, 1.14) compared to sertraline. The only other notable effects differentiating switch treatments were seen for patients with co-existing anxiety. Compared to sertraline, patients tended to be less likely to remit if switched to venlafaxine (RR: 0.65, 95%CI 0.32, 1.30) or to bupropion (RR: 0.67, 95%CI 0.33, 1.33). Patients also tended to be less likely to respond

with venlafaxine (RR: 0.79, 95%CI 0.43, 1.47) or bupropion (RR: 0.74, 95%CI 0.39, 1.39) than with sertraline.

Discussion

Symptom clusters have been associated with more persistent depressive illness, and the selection of a particular medication or medication strategy in treatment-resistant depression management is often guided by identification of coexisting symptom clusters. However, for those with such clusters, no direct evidence on the comparative effectiveness of augmentation vs. switch strategies exits; no direct evidence of the comparative effectiveness of various augmentation strategies exists; and limited direct evidence of the comparative effectiveness of various medication switches exists. The purpose of this study was to begin to fill in these gaps.

Within the propensity score matched sample, we found no statistically significant differences in remission or response rates for augmentation vs. switching among patients with coexisting atypical symptoms, insomnia, loss of energy, or anxiety. However, for patients with coexisting anxiety symptoms, the risk ratio estimates and their confidence intervals were more compatible with a benefit of augmentation over switching than with any other interpretation.

It is important to clarify to whom the propensity score matched results generalize. The matched sample does not reflect the full STAR*D trial population. Rather, it reflects patients who were mildly to moderately depressed; tolerated an aggressive, relatively high dose of a standard selective serotonin reuptake inhibitor (citalopram) during an initial treatment attempt for approximately 11 weeks; and tended not to discontinue the initial treatment because of side effects. Although the propensity score matched sample no longer reflects the original STAR*D study population, it minimized selection bias that was inherent in the original study design and allowed us to make comparisons across the different treatment strategies (augmentation and switching).

Among patients within the randomized augmentation arm, treatment strategies appeared to have different effects depending on the presence of low energy as a symptom. Patients with coexisting low energy who augmented with bupropion SR were nearly twice as likely to remit compared to those augmented with buspirone. This finding is consistent with the activating properties commonly attributed to bupropion which may increase their likelihood of remission among patients with low energy. For patients with coexisting atypical features, there was a statistically non-significant trend toward greater remission rates with bupropion SR augmentation than with buspirone. For these two symptom clusters we also found that the relative risks for response, while not statistically significant, were similar to those for remission and favored bupropion augmentation.

Similarly, within the randomized switch arms, we assessed whether, for those with particular symptom clusters, the likelihood of remission varied by type of switch medication used. Similar to previous findings from STAR*D, we found no statistical difference in the likelihood of remission between the three switch medication options in patients with anxious or atypical features.(Rush et al., 2008) Of note, for those with anxious features, our estimates were compatible with a range of explanations, but most compatible with increased chances of remission with sertraline compared with bupropion and venlafaxine. Our risk ratios were similar in size and direction to those found in the STAR*D anxious depression analyses.(Fava et al., 2008; Rush et al., 2008)

We also extended previous results by including two additional symptom clusters, insomnia and low energy. Among patients with insomnia, we found no differences among the three

medication switch options. However, for those with coexisting low energy, switching to venlafaxine was 59% as likely to produce remission as switching to sertraline, and switching to bupropion was 63% as likely to produce remission compared to sertraline. Of note, these exploratory estimates were not precise, and in the case of bupropion vs. sertraline, the confidence interval included a risk ratio of 1 (95%CI 0.38, 1.06)

These findings extend the clinical application of STAR*D results by identifying symptom clusters that may be useful in the future for guiding treatment selection. Initial STAR*D outcome analyses at level 2 found no significant differences in remission or response rates among patients receiving medication augmentation(Trivedi et al., 2006) or among patients who switched medication.(Rush et al., 2006) However, if one considers symptom clusters as potential effect modifiers, some potential differences among treatments emerge. For those considering augmentation, having coexisting low energy appears to favor selection of bupropion SR over buspirone (NNT = 7). Similarly, for those with coexisting low energy who switch, sertraline is preferred over venlafaxine XR (NNT = 10). Of note, these analyses involved the full STAR*D population. Therefore, unlike the propensity score sample, these observations maintain the generalizability of the STAR*D trial.

The results from this study should be interpreted in light of its limitations. First, these analyses were exploratory and the findings are most appropriately seen as preliminary. Prospective testing of these findings, involving adequate sample sizes, is necessary to formally test the hypotheses generated. Second, while the propensity-score-matched sample eliminated potential confounding from our comparisons, it also reduced the sample for the augment vs. switch comparison. For example, those patients excluded from the analysis who switched medications had more side effects than those who were included, and those eliminated from the augmentation group had lower depression severity scores. Third, although the propensity score matching balanced groups on observable characteristics, it did not necessarily balance them on potential unobservable confounders. Consequently, other interventions that were occurring, such as unreported psychotherapy differentially occurring between compared groups, might explain differences seen. Fourth, we were unable to control for dosing differences in the within-augment and within-switch comparisons because of small sample sizes. It is possible that differences in dosing of the respective medications (e.g., a higher dosing of bupropion relative to a lower dosing of buspirone) may explain differences in benefits. Fifth, it is possible that the symptom clusters identified at the beginning of level 2 treatment are related to citalopram side effects rather than a distinct symptom cluster, a quandary that clinicians face frequently in deciding next step treatments. Finally, the treatment options in STAR*D are not inclusive of all available treatments including other SSRIs, tricyclic antidepressants, and atypical antipsychotic medications. Our results, then, apply only to the use of specific augment and switch options after a failed initial SSRI trial and do not apply to other commonly used medications.

Conclusion

In the absence of direct evidence to guide treatment selection, clinicians make use of the highest quality evidence available, which may involve non-experimental data and preliminary findings. Our findings must be interpreted in that context. In these exploratory analyses of patients failing an initial antidepressant trial, we found that augmentation and switching do not yield different remission or response rates among patients with coexisting atypical symptoms, insomnia, or loss of energy. However, there is a suggestion that for those with coexisting anxiety, augmentation may be preferred. Further, low energy may guide medication selection when selecting among augmentation or switch medications. If one receives augmentation as the second step treatment, the presence of coexisting low energy may favor augmentation with bupropion SR over buspirone, and if switching

treatment, low energy may favor sertraline over venlafaxine. The role of the other clusters in guiding augmentation or switch selection was less certain. Further investigation is necessary to confirm the associations seen in these initial exploratory analyses.

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Table 1

Covariate Balance Pre and Post Propensity Score Matching

	Without Propensity Score		After Propensity Score Matching		Unmatched Patients	
	Augment N = 565	**Switch N = 727**	**Augment N = 269**	**Switch N = 269**	**Augment N = 296**	**Switch N = 458**
Demographic Characteristics						
Age – yr	41.6 ± 12.7	42.4 ± 12.8	41.7 ± 12.8	41.8 ± 12.9	41.5 ± 12.6	42.7 ± 12.7
Female sex - %	58.8	58.7	59.0	58.4	58.5	58.9
Race - %						
White	78.0	75.8	77.4	77.0	78.6	75.1
Black	18.0	18.7	18.4	18.9	17.7	18.6
Hispanic ethnic group	13.6	11.0	13.1	13.0	14.1	9.8
Education - %						
More than High School	22.3	23.1	20.4	21.2	24.1	24.2
Employment status - %						
Employed	64.0	63.1	65.1	64.7	63.0	62.2
Monthly income - $	1,055 ± 1,607	963 ± 1,281	937 ± 1,538	918 ± 1,185	1,164 ± 1,660	990 ± 1,334
Medical insurance - %						
Private	49.0	43.9	46.3	47.2	51.5	42.0
Public	13.4	14.9	15.8	15.9	11.3	14.3
Marital status - %						
Married or cohabitating	43.8	43.0	44.7	44.4	43.0	42.2
Divorced, separated or widowed	28.2	30.7	28.6	28.7	27.8	31.8
Psychiatric History (baseline)						
No. of major depressive episodes	5.6 ± 8.8	6.8 ± 11.1	6.5 ± 10.4	6.3 ± 10.1	4.8 ± 7.0	7.1 ± 11.6
Duration of index major depressive episode						
Mean - mo	27.8 ± 56.1	30.3 ± 66.7	25.8 ± 52.0	25.9 ± 58.1	29.6 ± 59.6	33.0 ± 71.1
≥ 2 Years - %	27.6	27.6	26.2	25.7	28.9	28.7
Psychiatric Comorbidities - %						
Drug Abuse	8.7	5.5	7.0	7.1	10.4	4.6
Alcohol Abuse	13.0	11.9	11.7	11.9	14.2	12

	Without Propensity Score		After Propensity Score Matching		Unmatched Patients	
	Augment N = 565	**Switch N = 727**	**Augment N = 269**	**Switch N = 269**	**Augment N = 296**	**Switch N = 458**
Post Traumatic Stress Disorder	18.9	23.0	21.5	20.6	16.5	24.4
Generalized Anxiety Disorder	23.4	22.2	23.0	22.8	23.8	21.9
Level 1 Exit Characteristics						
Clinical Measures						
Depressive Severity:						
QIDS-SR_{16} score	11.4 ± 4.9	13.2 ± 4.9	12.5 ± 5.1	12.6 ± 4.9	10.3 ± 4.5	13.6 ± 4.9
$HRSD_{17}$ score	16.0 ± 7.1	19.0 ± 7.3	17.6 ± 7.2	17.6 ± 7.3	14.6 ± 6.7	19.9 ± 7.2
SF-12						
Mental	32.4 ± 9.2	29.7 ± 9.6	31.0 ± 8.9	30.8 ± 9.4	33.7 ± 9.2	29.1 ± 9.6
Physical	46.9 ± 11.8	45.6 ± 12.0	46.1 ±12.1	46.2 ± 11.8	47.7 ± 11.4	45.3 ± 12.2
Q-LES-Q score	45.7 ± 16.3	41.1 ± 16.9	43.0 ± 16.5	43.1 ± 16.5	48.1 ± 15.7	39.9 ± 17.0
CIRS						
Total score	4.7 ± 4.0	5.1 ± 4.1	5.2 ± 4.3	5.1 ± 4.2	4.2 ± 3.7	5.1 ± 4.0
Side Effect Measures						
FIBSER score	1.2 ± 1.3	2.8 ± 1.9	1.4 ± 1.4	1.4 ± 1.5	1.0 ± 1.2	3.7 ± 1.6
PRISE score	6.2 ± 3.2	7.8 ± 3.6	6.6 ± 3.3	6.5 ± 3.6	5.8 ± 3.1	8.6 ± 3.4
Exited due to side effects - %	10.3	62.8	19.9	20.2	1.6	87.8
Experienced a serious adverse event - %	4.6	2.6	3.5	3.5	5.6	2.1
Symptom Measures						
Anxious features - %	32.3	46.6	38.0	37.7	27.1	51.9
Atypical features - %	19.1	23.0	21.3	20.6	17.0	24.4
Insomnia - %	74.4	80.1	76.6	75.6	72.5	82.8
Energy Loss - %	49.0	58.2	56.7	56.6	50.0	59.1
Management Features						
Duration of level 1 treatment - wk	11.9 ± 2.9	8.0 ± 4.2	10.9 ± 3.2	10.9 ± 3.0	12.8 ± 2.4	6.3 ± 3.8
Citalopram dose - mg/day	55.1 ± 10.9	41.4 ± 17.7	52.8 ± 12.8	52.9 ± 12.4	57.1 ± 8.4	34.7 ± 16.8
Medication Adherence - %						

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	Without Propensity Score		After Propensity Score Matching		Unmatched Patients	
	Augment N = 565	**Switch N = 727**	**Augment N = 269**	**Switch N = 269**	**Augment N = 296**	**Switch N = 458**
Never/Rarely Missing	89.6	82.6	88.9	87.4	90.1	79.7

Plus–minus values are means ± SD.

QIDS-SR16, the 16-item Quick Inventory of Depressive Symptomatology, Self-Rated (scores can range from 0 to 27; higher scores indicate increased severity of depressive symptoms); HRSD17 the 17-item Hamilton Rating Scale for Depression (scores can range from 0 to 52; higher scores indicate increased severity of depressive symptoms); SF-12 Short Form Health Survey, two SF-12 subscales (Mental and Physical) range from 0 to 100, with higher scores indicating increased perceived functioning. The population norm for each is 50 ± 10; QLESQ Quality of Life Enjoyment and Satisfaction Questionnaire (scores can range from 0 to 100; higher scores indicate greater satisfaction); FIBSER (Frequency Intensity and Burden of Side Effect Rating), is a global measure of the intensity and the burden of side effects. Scores were averaged to calculate a composite score. PRISE, Patient-Rated Inventory of Side Effects assesses the presence of specific side effects in nine biologic systems.

Level 1 refers to initial treatment with citalopram. Level 2 refers to second-step treatment with either medication augmentation or switching.

Table 2

Comparison of Remission and Response by Treatment Strategy for Patients With and Without Symptom Clusters

	Augment (N = 269)			Switch (N = 269)			Augment vs. Switch	
QIDS-SR$_{16}$ - Remission	**N (%)**	**IP**	**95% CI**	**N (%)**	**IP**	**95% CI**	**RR**	**95% CI**
Anxious Features								
Yes	99 (36.8)	0.15	0.06, 0.24	99 (36.8)	0.09	0.02, 0.15	1.72	0.69, 4.30
No	170 (63.2)	0.35	0.27, 0.44	170 (63.2)	0.34	0.26, 0.41	1.05	0.76, 1.45
Atypical Features								
Yes	53 (19.7)	0.23	0.11, 0.35	51 (19.0)	0.25	0.10, 0.40	0.92	0.43, 1.98
No	216 (80.3)	0.29	0.22, 0.36	218 (81.0)	0.24	0.18, 0.31	1.20	0.83, 1.73
Insomnia								
Yes	206 (76.7)	0.23	0.16, 0.31	204 (75.6)	0.20	0.14, 0.27	1.14	0.75, 1.73
No	63 (23.4)	0.43	0.28, 0.58	66 (24.4)	0.37	0.24, 0.50	1.16	0.70, 1.92
Energy Loss								
Yes	153 (56.7)	0.22	0.15, 0.30	152 (56.5)	0.18	0.11, 0.25	1.24	0.74, 2.08
No	117 (43.3)	0.35	0.24, 0.47	117 (43.5)	0.33	0.24, 0.42	1.07	0.70, 1.62
QIDS-SR$_{16}$ - Response	N (%)	IP	95% CI	N (%)	IP	95% CI	RR	95% CI
Anxious Features								
Yes	99 (36.8)	0.21	0.11, 0.31	99 (36.8)	0.12	0.04, 0.19	1.81	0.82, 4.00
No	170 (63.2)	0.30	0.22, 0.38	170 (63.2)	0.30	0.23, 0.38	0.99	0.69, 1.41
Atypical Features								
Yes	53 (19.7)	0.28	0.14, 0.41	51 (19.0)	0.28	0.12, 0.43	1.01	0.49, 2.09
No	216 (80.3)	0.26	0.20, 0.33	218 (81.0)	0.23	0.16, 0.29	1.18	0.80, 1.72
Insomnia								
Yes	206 (76.7)	0.25	0.18, 0.32	204 (75.6)	0.21	0.14, 0.27	1.20	0.81, 1.79
No	63 (23.4)	0.33	0.19, 0.47	66 (24.4)	0.32	0.20, 0.45	1.01	0.58, 1.76
Energy Loss								
Yes	153 (56.7)	0.26	0.18, 0.34	152 (56.5)	0.20	0.13, 0.27	1.30	0.80, 2.11
No	117 (43.3)	0.28	0.19, 0.36	117 (43.5)	0.28	0.19, 0.37	0.99	0.63, 1.54

Total sample size averaged over 20 imputations so numbers may not add to total sample size.

Remission on the QIDS-SR16 is defined as a level 2 exit score of ≤ 5. Response was defined as ≥ 50% decrease in QIDS-SR16 score from level 2 entry to level 2 exit. IP= Incidence Proportion; RR=Risk Ratio

Table 3

Comparison of Remission and Response Within Augmentation Strategies for Patients With and Without Symptom Clusters

	Citalopram plus Bupropion SR (N = 279)		Citalopram plus Buspirone (N = 286)		Citalopram plus Buspirone vs Citalopram plus Bupropion SR	
QIDS-SR16 - Remission	**N (%)**	**IP**	**N (%)**	**IP**	**RR**	**95% CI**
Anxious Features						
Yes	81 (29.0)	0.21	95 (33.2)	0.16	0.77	0.39, 1.51
No	198 (71.0)	0.41	191 (66.8)	0.39	0.93	0.73, 1.19
Atypical Features						
Yes	42 (15.1)	0.35	57 (19.9)	0.19	0.55	0.27, 1.13
No	237 (84.9)	0.36	229 (80.1)	0.34	0.96	0.74, 1.23
Insomnia						
Yes	207 (74.2)	0.30	213 (74.5)	0.29	0.96	0.71, 1.30
No	72 (25.8)	0.51	73 (25.5)	0.37	0.74	0.49, 1.11
Energy Loss						
Yes	137 (48.9)	0.33	140 (49.0)	0.18	**0.54**	**0.35, 0.85**
No	143 (51.1)	0.38	146 (51.0)	0.44	1.16	0.87, 1.55
QIDS-SR16 - Response	N (%)	IP	N (%)	IP	RR	95% CI
Anxious Features						
Yes	81 (29.0)	0.23	95 (33.2)	0.20	0.89	0.49, 1.60
No	198 (71.0)	0.31	191 (66.8)	0.27	0.87	0.64, 1.20
Atypical Features						
Yes	42 (15.1)	0.35	57 (19.9)	0.22	0.63	0.31, 1.27
No	237 (84.9)	0.28	229 (80.1)	0.26	0.93	0.68, 1.26
Insomnia						
Yes	207 (74.2)	0.27	213 (74.5)	0.24	0.86	0.61, 1.21
No	72 (25.8)	0.33	73 (25.5)	0.29	0.87	0.51, 1.49
Energy Loss						
Yes	137 (48.9)	0.31	140 (49.0)	0.21	0.67	0.43, 1.03
No	143 (51.1)	0.27	146 (51.0)	0.29	1.08	0.73, 1.60

Total sample size averaged over 20 imputations so numbers may not add to total sample size.

Remission on the QIDS-SR_{16} is defined as a level 2 exit score of ≤ 5. Response was defined as ≥ 50% decrease in QIDS-SR_{16} Score from level 2 entry to level 2 exit. IP= Incidence Proportion; RR=Risk Ratio

Table 4

Comparison of Remission and Response Within Switch Strategies for Patients With and Without Symptom Clusters

	Bupropion SR (N = 239)		**Sertraline (N = 238)**		**Venlafaxine XR (N = 250)**		**Bupropion vs Sertraline**		**Venlafaxine vs Sertraline**	
QIDS-SR16 - Remission	**N (%)**	**IP**	**N (%)**	**IP**	**N (%)**	**IP**	**RR**	**95% CI**	**RR**	**95% CI**
Anxious Features										
Yes	104 (43.5)	0.11	114 (47.9)	0.17	114 (45.6)	0.11	0.67	0.33, 1.33	0.65	0.32, 1.30
No	135 (56.5)	0.30	124 (52.1)	0.30	136 (54.4)	0.32	0.98	0.67, 1.43	1.05	0.72, 1.52
Atypical Features										
Yes	43 (18.0)	0.20	53 (22.3)	0.25	61 (24.4)	0.23	0.80	0.36, 1.78	0.91	0.45, 1.84
No	196 (82.0)	0.22	185 (77.7)	0.24	189 (75.6)	0.22	0.94	0.64, 1.36	0.94	0.64, 1.37
Insomnia										
Yes	186 (77.8)	0.19	197 (82.8)	0.22	199 (79.6)	0.19	0.86	0.57, 1.28	0.87	0.58, 1.29
No	53 (22.2)	0.33	41 (17.2)	0.34	51 (20.4)	0.36	0.95	0.52, 1.72	1.04	0.57, 1.91
Energy Loss										
Yes	128 (53.6)	0.15	140 (58.8)	0.24	154 (61.6)	0.14	0.63	0.38, 1.06	**0.59**	**0.36, 0.97**
No	111 (46.4)	0.29	98 (41.2)	0.24	96 (38.4)	0.35	1.24	0.77, 1.99	1.50	0.95, 2.36
QIDS-SR16 - Response	N (%)	IP	N (%)	IP	N (%)	IP	RR	95% CI	RR	95% CI
Anxious Features										
Yes	104 (43.5)	0.14	114 (47.9)	0.19	114 (45.6)	0.15	0.74	0.39, 1.39	0.79	0.43, 1.47
No	135 (56.5)	0.28	124 (52.1)	0.27	136 (54.4)	0.35	1.03	0.68, 1.54	1.27	0.87, 1.86
Atypical Features										
Yes	43 (18.0)	0.25	53 (22.3)	0.25	61 (24.4)	0.29	1.01	0.48, 2.09	1.15	0.60, 2.21
No	196 (82.0)	0.21	185 (77.7)	0.23	189 (75.6)	0.24	0.93	0.63, 1.37	1.09	0.75, 1.58
Insomnia										
Yes	186 (77.8)	0.20	197 (82.8)	0.23	199 (79.6)	0.23	0.86	0.58, 1.27	1.00	0.70, 1.45
No	53 (22.2)	0.29	41 (17.2)	0.25	51 (20.4)	0.36	1.19	0.59, 2.40	1.47	0.74, 2.91
Energy Loss										
Yes	128 (53.6)	0.17	140 (58.8)	0.25	154 (61.6)	0.20	0.70	0.43, 1.14	0.82	0.53, 1.26
No	111 (46.4)	0.27	98 (41.2)	0.21	96 (38.4)	0.34	1.30	0.78, 2.16	1.65	1.01, 2.70

Total sample size averaged over 20 imputations so numbers may not add to total sample size.

Remission on the QIDS-SR_{16} is defined as a level 2 exit score of ≤ 5. Response was defined as ≥ 50% decrease in QIDS-SR_{16} Score from level 2 entry to level 2 exit. IP= Incidence Proportion; RR=Risk Ratio