Depression Subtypes in Predicting Antidepressant Response: A Report From the iSPOT-D Trial

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Objective: The study aims were 1) to describe the proportions of individuals who met criteria for melancholic, atypical, and anxious depressive subtypes, as well as subtype combinations, in a large sample of depressed outpatients, and 2) to compare subtype profiles on remission and change in depressive symptoms after acute treatment with one of three antidepressant medications.

Method: Participants 18–65 years of age (N=1,008) who met criteria for major depressive disorder were randomly assigned to 8 weeks of treatment with escitalopram, sertraline, or extended-release venlafaxine. Participants were classified by subtype. Those who met criteria for no subtype or multiple subtypes were classified separately, resulting in eight mutually exclusive groups. A mixed-effects model using the intent-to-treat sample compared the groups' symptom score trajectories, and logistic regression compared likelihood of remission (defined as a score ≤5 on the 16-item Quick Inventory of Depressive Symptomatology–Self-Report).

Results: Thirty-nine percent of participants exhibited a pure-form subtype, 36% met criteria for more than one subtype, and 25% did not meet criteria for any subtype. All subtype groups exhibited a similar significant trajectory of symptom reduction across the trial. Likelihood of remission did not differ significantly between subtype groups, and depression subtype was not a moderator of treatment effect.

Conclusions: There was substantial overlap of the three depressive subtypes, and individuals in all subtype groups responded similarly to the three antidepressants. The consistency of these findings with those of the Sequenced Treatment Alternatives to Relieve Depression trial suggests that subtypes may be of minimal value in antidepressant selection.

Am J Psychiatry 2015; 172:743–750; doi: 10.1176/appi.ajp.2015.14020181

Major depressive disorder is a heterogeneous condition in which a wide range of etiologies, risk factors, and symptom profiles may be associated with a threshold diagnosis (1–4). Response to treatment is highly variable. Not only does treatment outcome vary substantially among depressed patients who are treated in a similar fashion (5), but there is little evidence that one treatment is superior to another, whether comparing among antidepressant medications (6), among psychotherapies (7), or between the two (8).

Melancholic, anxious, and atypical symptom features have been used to designate subtypes that could address the heterogeneity among depressed patients and help in selecting from among the different treatment options (9). Data on the clinical utility of these subtypes in treatment selection—that is, whether particular subtypes show different patterns of symptom reduction with any given treatment—are inconsistent. For example, some findings suggest that patients with the melancholic subtype have a significantly less robust response to antidepressant medications than do patients with non-melancholic depression (10), while other findings indicate no differences (11) or higher remission rates among patients with melancholic depression on some outcomes and no differences on others (12). In the initial phase of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, patients with melancholic depression were less likely to remit compared with those with other subtypes when treated with open-label citalopram, but these differences were no longer evident after adjustment for baseline differences (13). A similarly mixed picture has emerged for atypical features. Some findings suggest that patients with atypical depression have lower remission rates than patients without atypical features (14), while other findings indicate no differences (10) or that lower remission rates were no longer significant after adjustment for pretreatment baseline differences (15). In the STAR*D study, participants with anxious depression had significantly lower remission rates

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across treatment steps (16), but a study by Uher et al. (10) found no difference between anxious and nonanxious patients with depression on two of three outcome measures. Russell et al. (17) reported significantly better response and remission rates among chronic depression patients who were highly anxious compared with those without significant anxiety.

Findings are also mixed on whether symptom-based subtypes are useful in the selection of antidepressant medications. Patients with melancholic depression have been found to be more responsive to tricyclic antidepressants than to selective serotonin reuptake inhibitors (SSRIs) in some studies (18, 19) but not in others (10). The evidence is mixed on whether SSRIs are more effective than tricyclics among patients with atypical depression (10, 20, 21). Fewer studies have reported on whether patients with anxious depression respond preferentially to one medication over others, but Russell et al. (17) found no differences in response to an SSRI versus imipramine, and Uher et al. (10) found that patients with anxious depression responded similarly to escitalopram and nortriptyline.

The current literature suffers from additional limitations. First, the three symptom-based subtypes (9) were developed independently and are not necessarily mutually exclusive. Thus, patients characterized as having atypical depression may also meet criteria for anxious or melancholic depression. Failure to account for overlap carries a risk of misclassification and may compromise efforts to determine whether meeting criteria for a specific subtype should inform clinical decision making. Second, many studies examine one subtype at a time using binary classifications (11, 12, 15), which precludes the examination of whether one subtype may be more useful than another in predicting outcome. Third, to our knowledge, no studies have reported on whether patients who do not meet criteria for any of the subtypes respond differently than do those who meet criteria for one or more subtypes.

In this exploratory study, we examined the first half of a projected sample of 2,016 patients with depression who were participants in the International Study to Predict Optimized Treatment in Depression (iSPOT-D) (22). Our study had two specific aims: 1) to describe the proportions of individuals who met criteria for melancholic, anxious, and atypical depression subtypes, the proportions in which each combination of subtypes overlapped in individual patients, and the proportion in which criteria for any of these subtypes were not met; and 2) to evaluate whether subtype profile predicted general or differential responsiveness to commonly used antidepressants. We hypothesized that 1) among participants who met criteria for a single subtype, melancholic subtype status would be a general predictor of lower remission rate compared with atypical or anxious subtype status (10, 14); 2) the presence of more than one subtype would be a general predictor of a lower remission rate than would be observed among patients with just one subtype; 3) patients who did not meet criteria for any subtype would a have higher remission rate than those who met criteria for a single subtype. No hypotheses were made regarding moderation of treatment effects; analyses related to that question were exploratory. In order to gauge the generalizability of our findings on both subtype distribution and antidepressant outcome, we descriptively compared our results with those derived from an additional analysis of participants in step 1 of the STAR*D trial (5).

METHOD

Study Design

iSPOT-D is a multiple-phase, multisite, open-label, randomized practical clinical trial comparing the outcomes of depressed participants who are randomly assigned to treatment with one of three antidepressants: escitalopram, sertraline, and extended-release venlafaxine. As reported previously (23), average dosages were 12 mg/day for escitalopram, 61 mg/day for sertraline, and 83 mg/day for venlafaxine. Participants were randomized to treatment group in a 1:1:1 ratio (see Figure S1 in the data supplement that accompanies the online edition of this article) using Phase Forward's validated web-based Interactive Response Technology application. A blocked randomization procedure was undertaken centrally (block size=12). The 17 sites (in five countries: the United States, the Netherlands, Australia, New Zealand, and South Africa) consisted of eight academic and nine private sites.

Because iSPOT-D is a practical trial, treating clinicians and participants were necessarily not blind to treatment assignment. However, raters were blind to treatment assignment. Antidepressant medications were prescribed and dosages adjusted by the participant's treating clinician according to routine clinical practice. Psychotropic medication was discontinued for at least 1 week before randomization. Sleep aids and anxiolytics were discontinued 24 hours before assessments. See Williams et al. (22) for further details regarding iSPOT-D's methodology.

Participants

Participants were adults (18–65 years of age) who met DSM-IV criteria for a diagnosis of current single-episode or recurrent nonpsychotic major depressive disorder. Broad inclusion criteria were used to achieve a representative sample of antidepressant treatment seekers. The Mini International Neuropsychiatric Interview (24) was used to establish diagnosis, assess comorbid psychiatric disorders, and identify potential exclusion criteria. The 17-item Hamilton Depression Rating Scale (HAM-D) (25) was used to assess depression severity (a score ≥16 was required for inclusion in the study). Participants provided written informed consent after receiving a complete description of the study. The study was approved by institutional or ethical review boards at each site, and its protocols were in compliance with International Conference on Harmonization and Good Clinical Practice principles, the U.S. Food and Drug Administration Code of Federal Regulations, and country-specific guidelines.

Outcome Measures

Depressive symptom severity was rated using the 16-item Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR). The QIDS-SR was designated a priori as the primary outcome measure because 1) it covers the nine symptom domains used to characterize a major depressive episode, 2) unlike the HAM-D, it does not include items that assess atypical or melancholic symptoms (26), and 3) multiple measurements were available across the study. The QIDS-SR was completed at baseline and at weeks 2, 4, 6, and 8 (study end). Remission was defined as a QIDS-SR score ≤5 at week 8 (26, 27).

Subtype Assessment

Melancholic depression was defined in iSPOT-D as meeting criteria for melancholia on both the Mini International Neuropsychiatric Interview and the Clinical Outcomes in Routine Evaluation scale for measuring psychomotor disturbance (score >7) (28). In the STAR*D study, melancholic features were derived from item scores on the 30-item Inventory of Depressive Symptomatology–Clinician Rating (29), including a score of 2 or 3 on the mood reactivity or pleasure item as well as meeting at least three of the following criteria based on items from the Inventory of Depressive Symptomatology: mood variation, psychomotor retardation, psychomotor agitation, appetite increase or weight decrease, self-outlook, and quality of mood (13).

Atypical depression was defined in iSPOT-D as mood reactivity plus at least two items of hypersomnia, hyperphagia, leaden paralysis, and/or rejection sensitivity on the Columbia Atypical Depression Diagnostic Scale (30). In the STAR*D study, atypical depression was defined as having mood reactivity on the Inventory of Depressive Symptomatology–Clinician Rating as well as two or more of the following symptoms: hypersomnia, increased appetite or increased weight, interpersonal rejection sensitivity, and leaden paralysis (15).

Anxious depression, consistent with the STAR*D study (31), was defined in iSPOT-D as a HAM-D anxiety-somatization factor score ≥7.

Statistical Analysis

Participants were classified by subtype. Individuals who met criteria for more than one subtype were classified into a group defined by the specific combination. This resulted in eight mutually exclusive subtype groups: none, atypical, melancholic, anxious, anxious/atypical, melancholic/anxious, melancholic/atypical, and all. For the intent-to-treat sample, a mixed model for repeated measurements was used to estimate and compare the trajectories of symptom change, based on QIDS-SR scores for each subtype group, adjusting for age, gender, and baseline depression severity. To compare remission rates in the eight groups, a logistic regression model was used including the following predictors: subtype, age, gender, and baseline symptom severity. For categorical covariates, p values were derived from the Wald test. Logistic regression was also used to compare remission among those with no subtype, those with one subtype, and those with more than one subtype. To test whether subtype moderated the effects of medication on remission, a logistic regression model was used that included medication (three levels), subtype group (eight levels), and the subtype-by-treatment interaction.

Descriptive statistics regarding the distribution of subtypes and antidepressant outcome gathered from step 1 of the STAR*D data set are also presented. Intention-to-treat remission data used last observation carried forward, with remission based on the study exit QIDS-SR score. Participants in the completer analysis were restricted to those who had at least 9 weeks of treatment, and remission was based on study exit score. See Trivedi et al. (5) for a detailed description of the STAR*D study's methodology.

RESULTS

Of the 1,008 iSPOT-D participants, subtype data were missing for two. The demographic and clinical characteristics of the eight subtype groups are summarized in Table 1. Baseline depression scores on the QIDS-SR were comparable across subtypes.

Subtype Classification

As shown in Figure 1A, 75% of the iSPOT-D sample met criteria for at least one of the three depressive subtypes, and 25% did not meet criteria for any of the subtypes. Of those who met criteria for at least one subtype, 52% (N=390/753) qualified for a single subtype, and 48% (363/753) met criteria for more than one subtype. The most common "pure" depression subtype in the sample was atypical, with 15% of participants meeting criteria. Thirteen percent of participants met criteria for the anxious subtype, and 11% for the melancholic subtype. More than one-third of the participants in the study (36%) met criteria for two or more subtypes, and 11% met criteria for all three subtypes. Figure 1B illustrates the percentages of STAR*D participants who met criteria for the same subtypes and their combinations.

Symptom Reduction

Using the intent-to-treat sample, a mixed model for repeated measurements compared the response trajectories of each of the eight groups (Figure 2). All groups exhibited a statistically significant reduction in depressive symptoms as assessed by the QIDS-SR ($p<0.001$). After adjustment for group differences in age, gender, and baseline depression severity, the subtype groups did not differ in their response to antidepressant medications. Participants with no subtype had a flatter response trajectory (Figure 2), but their mean QIDS-SR score at the end of the study did not differ significantly from those of participants who met criteria for one or more subtypes.

Remission

Remission rates for each of the eight subtype groups in the intent-to-treat and completer samples of both the iSPOT-D and STAR*D studies are summarized in Figure 3 (see also Table S1 in the online data supplement). Among iSPOT-D participants, logistic regression revealed no differences between the eight groups. Patients who did not meet criteria for

TABLE 1. Demographic Characteristics of Depression Subtypes in the iSPOT-D Trial[a]

Characteristic	No Subtype (N=253)		Atypical (N=153)		Melancholic (N=107)		Anxious (N=130)		Anxious/ Atypical (N=131)		Melancholic/ Anxious (N=54)		Melancholic/ Atypical (N=71)		All Three Subtypes (N=107)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	39	12	39	13	39	12	39	13	35	13	39	13	36	12	36	13
Education (years)	14	3	15	3	14	3	15	3	15	3	14	3	14	3	14	3
Duration of major depression (years)	14	12	14	12	15	13	16	13	13	12	14	12	15	11	15	12
Baseline HAM-D score	19	3	20	3	22	3	23	4	24	4	27	5	21	3	26	4
Baseline QIDS-SR score	14	4	14	4	15	4	14	4	15	3	17	4	14	4	15	4
Dosage at week 8 (mg/day)																
Escitalopram	12	8	11	5	14	16	13	8	12	4	10	6	13	5	12	8
Sertraline	64	41	56	29	54	20	69	37	53	32	54	23	60	31	46	20
Venlafaxine (extended release)	80	46	69	35	90	51	75	39	82	50	68	42	66	33	71	36
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Female	142	56	90	59	55	51	73	56	83	63	29	54	35	49	64	60
Race/ethnicity																
Black	40	16	28	18	25	23	17	13	12	9	11	20	15	21	19	18
Hispanic	38	15	8	5	7	7	3	2	8	6	5	9	6	9	7	7
White	149	59	106	69	61	57	85	65	79	60	30	56	44	62	65	61
Other	25	10	13	8	14	13	24	18	32	24	8	15	5	7	15	14
Unknown	0	0	0	0	1	1	1	1	0	0	0	0	1	1	1	1
Employment																
Employed	137	54	80	52	55	51	65	50	66	50	21	39	32	45	50	47
Unemployed	15	6	9	6	5	5	12	9	9	7	3	6	5	7	9	8
Retired	10	4	9	6	7	7	7	5	5	4	3	6	1	1	2	2
Student	43	17	31	20	14	13	27	21	30	23	11	20	20	28	24	22
Other	25	10	14	9	11	10	4	3	5	4	5	9	2	3	9	8
Unknown	25	10	31	20	1	1	16	12	16	12	11	20	11	16	15	14
Marital status																
Married or cohabitating	61	24	29	19	20	19	26	20	25	19	7	13	6	9	19	18
Divorced or separated	43	17	23	15	12	11	25	19	14	11	6	11	8	11	11	10
Single	139	55	23	62	61	57	72	55	90	69	35	65	52	73	68	64
Widowed	5	2	2	1	5	5	3	2	0	0	1	2	1	1	2	2
Unknown	5	2	5	3	9	8	5	4	3	2	5	9	4	6	7	7

[a] iSPOT-D=International Study to Predict Optimized Treatment in Depression; HAM-D=17-item Hamilton Depression Rating Scale; QIDS-SR=16-item Quick Inventory of Depressive Symptomatology–Self-Report.

any subtype were more likely to remit compared with those who did meet criteria for one or more subtypes (40% compared with 37%), but this difference was not statistically significant. Those who met criteria for more than one subtype had a lower remission rate (34%), but again this difference was not statistically significant.

Moderation of Treatment Effect

Logistic regression indicated no main effect for treatment: participants who received escitalopram, sertraline, and venlafaxine all had a similar likelihood of achieving remission. There was no statistically significant subtype-by-treatment interaction, which indicates that subtype was not a moderator of treatment effect.

DISCUSSION

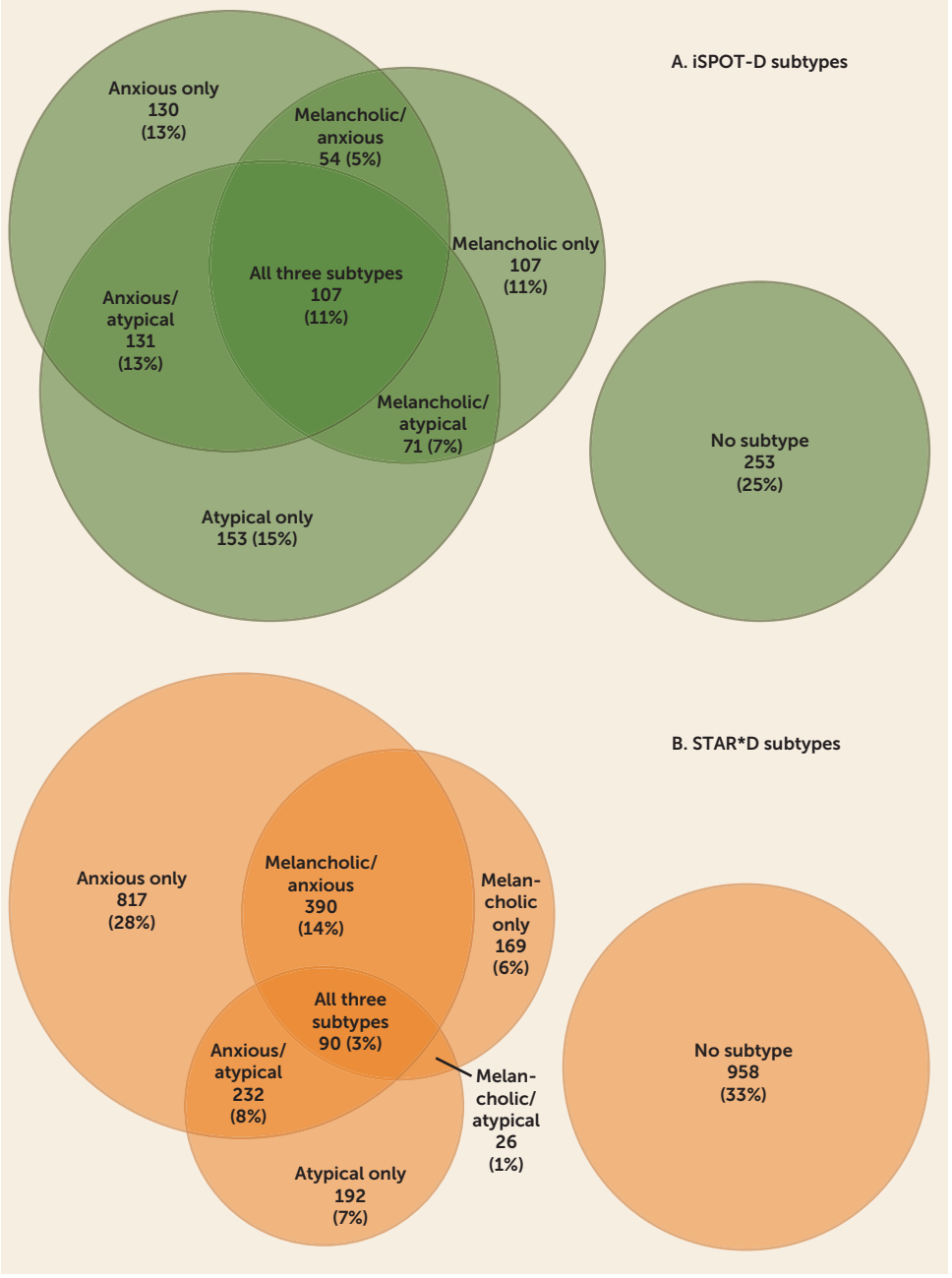
This study revealed two main findings. First, there was substantial overlap among the three subtypes of major depressive disorder in both the iSPOT-D and STAR*D samples, indicating that the subtypes are not "pure." Second, subtype status in the iSPOT-D sample did not predict antidepressant outcome overall or differentially, whether assessed categorically or continuously; results were similar for the STAR*D sample.

Specifically, in terms of subtype overlap, 25% of the iSPOT-D participants did not meet criteria for any subtype, 39% exhibited a pure-form single subtype, and 36% met criteria for more than one subtype. Among STAR*D participants, 33% did not meet criteria for any subtype, 41% met criteria for a single subtype, and 26% met criteria for more than one subtype. Put differently, among those who met criteria for a subtype, 48% and 39% in the iSPOT-D and STAR*D studies, respectively, met criteria for more than one subtype.

In terms of outcomes, after adjustment for age, gender, and baseline severity, remission rates and symptom reduction in the iSPOT-D sample did not differ among the pure melancholic, anxious, and atypical subtypes, nor did remission rates or change from baseline in depression symptom score differ among participants who met criteria for one, more than one,

or no subtype. The slope of change was flatter among those who met criteria for no subtype and differed from the other groups because of the lower mean baseline score in this group. This group's outcome at trial completion was similar to the outcomes of the other subgroups. These results were partially but not fully consistent with those from the STAR*D data set. Although the two trials had considerably different sampling frames, recruitment and eligibility criteria, comorbidities, and medications and dosages, remission rates in the two studies did not differ among the three pure subtypes in either the intent-to-treat or the completer analysis. Remission rates (and their 95% confidence intervals) were similar among the mixed subtypes as well. The only difference in remission rates was observed in the no-subtype groups, where the intent-to-treat STAR*D rates were higher than the iSPOT-D rates.

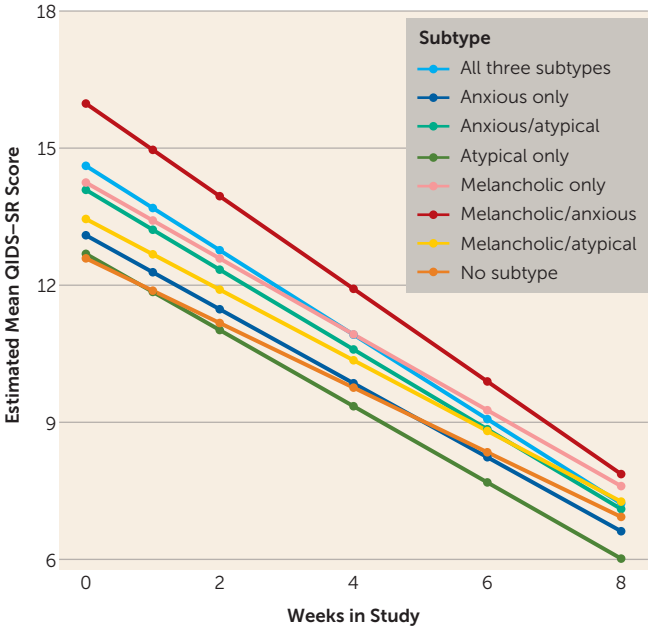
FIGURE 1. Proportions of Patients Meeting Criteria for Each Major Depressive Disorder Subtype Classification in the iSPOT-D and STAR*D Trials[a]



[a] iSPOT-D=International Study to Predict Optimized Treatment in Depression; STAR*D=Sequenced Treatment Alternatives to Relieve Depression. The STAR*D data are from step 1 of the trial.

Our finding that remission rates and symptom reduction were similar in the melancholic, atypical, and anxious subgroups diverges from several other reports. Uher et al. (10), who included an anxious-somatizing group as well as the three subgroups that we examined here, found that the melancholic subgroup had lower symptom reduction than the other groups, although the difference was judged not to be clinically significant. The Uher et al. study involved a different drug regimen (escitalopram or nortriptyline) and longer treatment duration (12 weeks). Gili et al. (14), in a naturalistic investigation of depressed patients in which clinicians were free to prescribe medications as they saw fit, found that patients with melancholic depression had lower rates of remission than those without melancholic depression, and that patients with atypical depression had lower remission rates than those without atypical depression. However, in addition to differences in the medications prescribed, baseline symptom values were not collected in that study, and it is unclear whether the same results would have been obtained with baseline severity as a covariate, as was done in our study. Yang et al. (12) found that patients with melancholic depression did not differ significantly from those with non-melancholic depression on remission or response as assessed by the HAM-D but had a higher remission rate as assessed by the Clinical Global Impressions Scale. However, in addition to differences between that study and ours in the medications prescribed and the length of the study period (12 weeks compared with 8 weeks), Yang

FIGURE 2. Mean Score Trajectories on the 16-item Quick Inventory of Depressive Symptomatology–Self-Report in the iSPOT-D Trial, From Mixed-Effects Regression Model (N=1,006)[a]



[a] iSPOT-D=International Study to Predict Optimized Treatment in Depression. The Ns for the various subtype classifications are as follows: all three subtypes, N=107; anxious/atypical, N=131; anxious only, N=130; atypical only, N=153; melancholic/anxious, N=54; melancholic/atypical, N=71; melancholic only, N=107; no subtype, N=253.

et al. did not statistically adjust for the influence of baseline depression severity.

Our findings on melancholic depression are consistent with those of McGrath et al. (13) in the open-label phase of the STAR*D trial, Rush et al. (32) in step 2 of the STAR*D trial, and Bobo et al. (11) in the Combining Medications to Enhance Depression Outcomes study. Our finding of no significant difference in outcome between the atypical subtype group and the other subtype groups is consistent with the findings of Stewart et al. (15), who reported no differences between participants with and without atypical depression after adjusting for baseline variables in the open-label phase of the STAR*D trial, and with the findings of Uher et al. (10), who also found no differences in outcome between participants with atypical and non-atypical depression.

In the iSPOT-D sample, we found no difference in outcome between any of the anxious subtypes and the other groups, which is not consistent with Fava et al. (16), who found anxious depression to have lower remission rates than nonanxious depression in both steps 1 and 2 of the STAR*D trial. However, the STAR*D authors compared all patients who met criteria for anxious depression (53% in step 1) to all nonanxious patients. As our findings reveal, a large proportion of those who met criteria for anxious depression in step 1 of the STAR*D trial also met criteria for other subtypes, with only 28% meeting criteria for the pure anxious subtype.

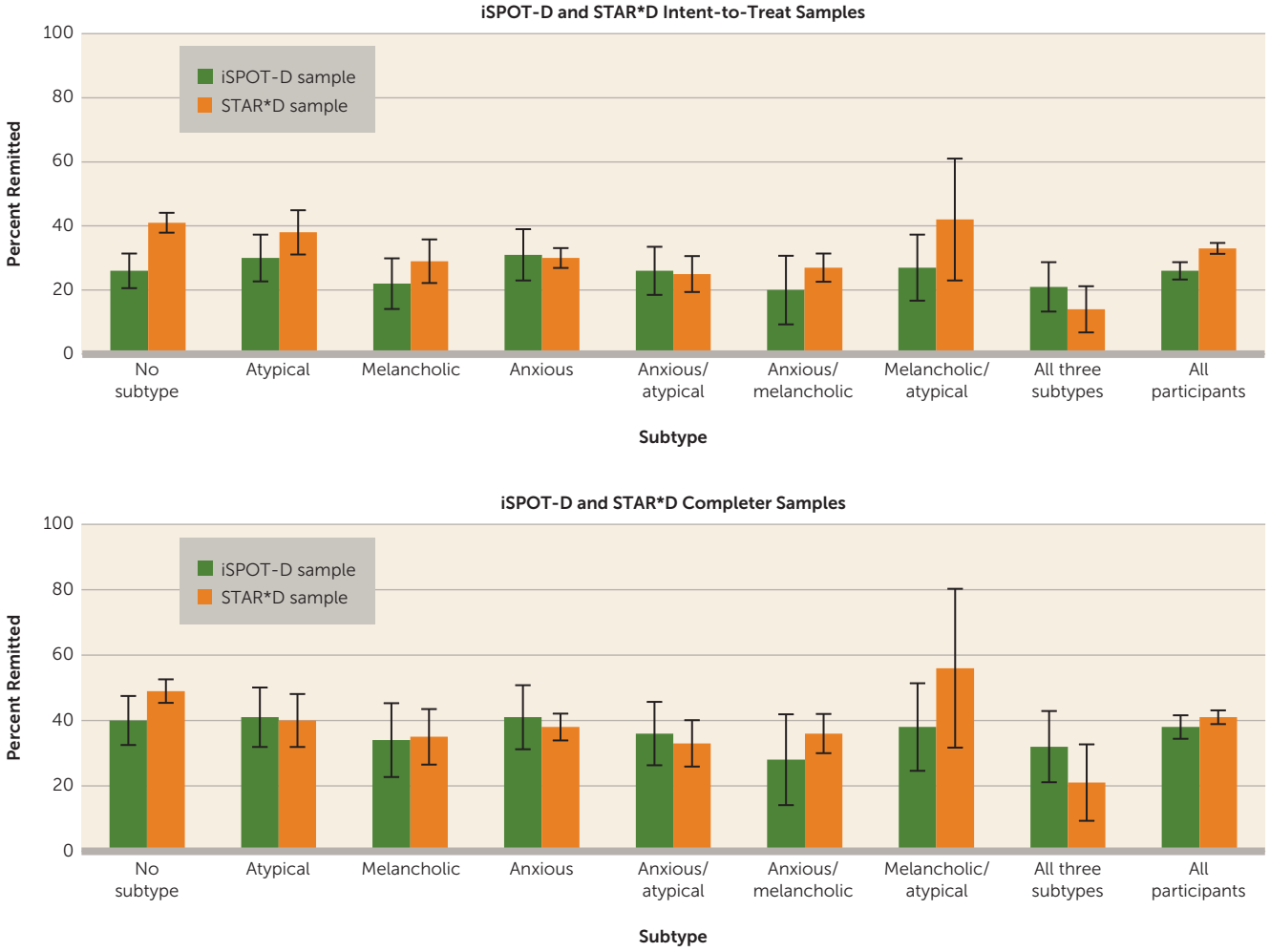
The statistical approach we employed to examine the relationship between depressive subtype and antidepressant outcome is different from those used in previous studies, which typically have compared one subgroup to all other members of a sample. Our analysis compared each of the eight subgroups to every other subgroup individually rather than to the sample as a whole. Our findings suggest that comparing one subtype to all other members of a sample in a two-group comparison will inevitably involve misclassification, as some participants in the reference subtype group will also meet criteria for other subtypes. Furthermore, studies that compare one subtype to all others in a large sample (14, 16) are likely to be sufficiently powered to find differences that may be statistically significant but may or may not be clinically significant (10).

We found no evidence that any subtype, whether mixed or "pure," moderated outcome with the three medications used in this trial. The medications in iSPOT-D were chosen based on their frequency of use as well as their approval in five countries (22). Because tricyclic antidepressants were not included as a study medication, we were unable to confirm or disconfirm whether patients with melancholic depression respond preferentially to tricyclics (18, 19) or whether patients with atypical depression respond preferentially to SSRIs compared with tricyclics (20, 21). Still, our findings are consistent with those reported in step 2 of the STAR*D trial, in which atypical, anxious, and melancholic features did not predict response to one antidepressant medication versus another (32).

Among the strengths of this study were that we utilized a large sample from an effectiveness trial (iSPOT-D), with broad inclusion and exclusion criteria enhancing the external validity of the study's findings. The sample size was adequate for subtype classification estimations and for the formal testing of a priori hypotheses with full statistical power.

The iSPOT-D study had several limitations. First, although antidepressant dosages were similar between subtypes, they were at the lower end of the recommended ranges. It is unknown whether higher dosages might have been associated with better response in one or two of the subtypes, revealing a different pattern of remission or symptom reduction than was observed in our investigation. Moreover, it could be argued that the dosage of extended-release venlafaxine (83 mg/day) in iSPOT-D is sufficient only to test its serotonin reuptake inhibitor properties but not its efficacy as a dual-action agent and that the findings in this report cannot be generalized to medications with different mechanisms of action. Second, the length of treatment in iSPOT-D was 8 weeks, and it is possible that a different pattern of findings would have emerged over a longer course of treatment. In the longer-duration STAR*D trial, trajectories of symptom reduction indicated that about two-thirds of patients who achieved remission did so within the first 8 weeks of treatment (5). Third, not all depression subtypes were examined (e.g., we did not include psychotic depression). Fourth, our findings pertain specifically to the relationship between categorical subtypes and antidepressant treatment outcome. It is possible, for example, that dimensional assessments of anxious, atypical, or melancholic symptoms correlate directly with amount of symptom change.

FIGURE 3. Intent-to-Treat and Completer Remission Rates for the iSPOT-D and STAR*D Trials[a]



[a] iSPOT-D=International Study to Predict Optimized Treatment in Depression; STAR*D=Sequenced Treatment Alternatives to Relieve Depression. The STAR*D data are from step 1 of the trial. Error bars indicate 95% confidence intervals.

CONCLUSIONS

This exploratory study revealed substantial overlap among anxious, atypical, and melancholic depression subtypes, a finding consistent with observations from the STAR*D data set. Whether pure or mixed, subtypes were not differentially predictive of overall acute treatment outcomes or differentially predictive of efficacy among the three antidepressant medications. If replicated, these findings would suggest that the clinical utility of these subtypes in treatment selection is minimal.

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Supported by Brain Resource, Ltd.

The authors acknowledge the editorial support of Jon Kilner, M.S., M.A.

Clinicaltrials.gov identifier: NCT00693849.

Dr. Blasey has received consulting fees from Brain Resource, Ltd. Dr. Williams has received consulting fees from and has been a stockholder in Brain Resource, Ltd. Dr. Palmer is employed by and has received stock options from Brain Resource, Ltd. Mr. Rekshan is employed by and has received stock options from Brain Resource, Ltd. Dr. Schatzberg has served as a consultant to Bay City Capital, BrainCells, CeNeRx, Cervel, Depomed, Eli Lilly, Forum, Genentech, Gilead, Jazz, Lundbeck/Takeda, McKinsey, Merck, MSI, Neuronetics, Novadel, One-Carbon, Pharma-NeuroBoost, Sunovion, Synosia, and Xhale; he has received honoraria from Merck; he has equity in Amnestix, BrainCells, CeNeRx, Corcept (co-founder), Delpor, Forest, Merck, Neurocrine, Novadel, Pfizer, Pharma-NeuroBoost, Somaxon, Synosis, Titan, and Xhale; and he receives royalties from Stanford University for patents on mifepristone use and the pharmacogenetics of antidepressant response. Dr. Etkin has received research funding from Brain Resource, Ltd. Dr. Kulkarni has received research support from AstraZeneca, the Department of Human Services (Victoria, Australia), Eli Lilly, Janssen-Cilag, the National Health and Medical Research

Council of Australia, Mayne Pharma, Neurosciences Australia, Servier, and the Stanley Medical Research Institute; she has received speaking honoraria from AstraZeneca, Bristol-Myers Squibb, Janssen-Cilag, and Lundbeck; and she is an advisory board member for Janssen-Cilag, Lundbeck, Pfizer, and Roche. Dr. Rush has received consulting fees from Brain Resource, Ltd., Eli Lilly, Lundbeck A/S, Medavante, NIDA, Santium, and Takeda USA; speaking fees from the University of California at San Diego, Hershey Penn State Medical Center, the American Society for Clinical Psychopharmacology, and New York State Psychiatric Institute; royalties from Guilford Publications and the University of Texas Southwestern Medical Center; a travel grant from the International College of Neuropsychopharmacology; and research support from Duke–National University of Singapore. The other authors report no financial relationships with commercial interests.

Received Feb. 11, 2014; revision received Nov. 26, 2014; accepted Jan. 16, 2015; published online March 27, 2015.

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