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ARTICLE

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New Aspects in the Treatment of Affective Disorders

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Do atypical features affect outcome in depressed outpatients treated with citalopram?

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Abstract

Depressed patients with atypical features have an earlier onset of depression, a more chronic course of illness, several distinctive biological and familial features, and a different treatment response than those without atypical features. The efficacy and tolerability of selective serotonin reuptake inhibitors (SSRIs) have not been fully evaluated in depression with atypical features. This report evaluates data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study to determine whether depressed outpatients with and without atypical features respond differently to the SSRI citalopram. Treatment-seeking participants with non-psychotic major depressive disorder were recruited from primary- and psychiatric-care settings. The presence/absence of atypical features was approximated using baseline ratings on the 30-item Inventory of Depressive Symptomatology – Clinician-rated. Following baseline assessments, participants received citalopram up to 60 mg/d for up to 14 wk. Baseline sociodemographic and clinical characteristics, and treatment outcomes, were compared between participants with and without atypical features. Of the 2876 evaluable STAR*D participants, 541 (19%) had atypical features. Participants with atypical features were significantly more likely to be female, younger, unemployed, have greater physical impairment, a younger age of depression onset, a longer index episode, greater depressive severity, and more concurrent anxiety diagnoses. Those with atypical features had significantly lower remission rates, although this difference was no longer present after adjustment for baseline differences. Depressed patients with atypical features are less likely to remit with citalopram than those without atypical features. This finding is probably due to differences in baseline characteristics other than atypical symptom features.

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Introduction

Epidemiological studies suggest that atypical depression is common, occurring in 0.7–7.5% of the general population, with 15.7–36.4% of subjects having major depression (Angst *et al*. 2002; Horwath *et al*. 1992; Kendler *et al*. 1996; Matza *et al*. 2003; Sullivan *et al*. 1998). Relative to other depressive illness, atypical depression has been suggested to occur more frequently in women (Davidson *et al*. 1982; Levitan *et al*. 1997; Posternak & Zimmerman, 2002), to have an earlier onset and more chronic course (Angst *et al*. 2002; Horwath *et al*. 1992; Stewart *et al*. 1993), and to be more likely related to bipolar disorder (Benazzi, 2002; Perugi *et al*. 1998). A variety of sociodemographic, clinical, biological, and familial parameters distinguish

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depression with atypical features from melancholia (Stewart *et al*. 1993) and from other non-melancholic depressions (Stewart *et al*. in press). The majority of these validating studies used criteria developed by a group from Columbia University. The 'Columbia criteria' include the requirement of significant mood reactivity plus two of the following four additional characteristics: hyperphagia, hypersomnia, leaden paralysis (feelings of intense lethargy), and pathological rejection sensitivity. Because these were the best validated criteria (Rabkin *et al*. 1996), they were incorporated into DSM-IV (APA, 1994) with the additional requirement that patients do not also meet criteria for melancholic, psychotic or catatonic features.

Other criteria for depression with atypical features also exist. For example, Davidson *et al*. (1982) proposed two types of atypical depression, a V-type indicated mainly by reversed vegetative features (i.e. the hyperphagia/hypersomnia subset of the Columbia/DSM-IV criteria) and an A-type indicated by prominent anxiety but with undefined vegetative features. The latter might today be more akin to the ICD-10 category of anxious depression. Others have also considered reverse vegetative features to be more important than the other Columbia/DSM-IV features (e.g. Himmelhoch *et al*. 1991). Angst *et al*. (2002) has proposed several alternative criteria, and Parker *et al*. (2002) considered rejection sensitivity rather than mood reactivity to be the core feature. While these authors derived their conceptualizations from demographic, symptomatic and comorbidity data, they have not been prospectively validated using biological or treatment differences. Moreover, both groups based their recommendations on groupings that were numerically best without testing whether participants meeting one definition of atypical depression but not another were more similar to those meeting the stricter definition or those not meeting either criteria. Because it has been subjected to a wide variety of proposed validating tests (Klein, 1989; Rabkin *et al*. 1996; Robins & Guze, 1970; Stewart *et al*. 1993) we will focus on the 'Columbia criteria' for depression with atypical features.

One important differentiating feature of depression with atypical features is the relative ineffectiveness of treatment with tricyclic antidepressant (TCA) medications compared to treatment with monoamine oxidase inhibitors (MAOIs) (Liebowitz *et al*. 1988; Quitkin *et al*. 1990). The comparative response of depressed patients with and without atypical features to newer medications, such as the selective serotonin reuptake inhibitors (SSRIs), has not been widely studied. McGrath *et al*. (2000) and Pande *et al*. (1996) were unable to distinguish the efficacy of the SSRI fluoxetine from that of imipramine (a TCA) or phenelzine (a MAOI), respectively, in depressed patients with atypical features. These small studies did not include depressed patients without atypical features. In a study of 195 patients with major depression, Joyce *et al*. (2002) demonstrated fluoxetine to be more efficacious than nortriptyline (a TCA) in patients with atypical features; however, the study included only 16 patients with atypical features. Stratta *et al*. (1991) compared fluoxetine to imipramine in patients with atypical depression and reported a greater efficacy for fluoxetine regarding some atypical symptoms, but not in overall efficacy. Søgaard *et al*. (1999) reported no significant difference in response rates (65% *vs*. 62%) or remission rates (39% *vs*. 30%) between sertraline (an SSRI) and moclobemide (a MAOI) in depressed patients with atypical features. Lonnqvist *et al*. (1994) reported moclobemide to be more efficacious than fluoxetine in depressed patients with atypical features, but the difference was of questionable clinical significance (67% *vs*. 55% responded).

The present study aimed to determine whether patients who have depression with atypical features respond differently to the SSRI citalopram than those without atypical features. To accomplish this, we analysed data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial (www.star-d.org) (Fava *et al*. 2003; Rush *et al*. 2004), which recruited 4041 outpatients with non-psychotic major depressive disorder (MDD) from among those seeking treatment at non-research primary-care and psychiatric-care clinics. While this was not a primary study aim of STAR*D, the study provided a unique opportunity to determine whether patients treated in the community would show differential benefit from treatment with a SSRI depending on the presence or absence of atypical features.

Methods

Study sample

The population and methods of STAR*D including enrolment, inclusion and exclusion criteria, and data collection are detailed elsewhere (Fava *et al*. 2003; Rush *et al*. 2004). Briefly, STAR*D was designed to prospectively define which treatments are most effective for patients with non-psychotic MDD who have an unsatisfactory outcome to an initial and, if necessary, subsequent treatment(s).

From July 2001 to April 2004, STAR*D enrolled 4041 outpatients aged 18–75 yr who were diagnosed by

their clinicians with non-psychotic MDD. This diagnosis was confirmed by a checklist that used criteria from DSM-IV. To enrol a broadly representative group of patients with MDD, participants were recruited from 18 primary-care and 23 psychiatric-care settings across the USA that served either the public or private sectors. Recruitment through advertising was not permitted in STAR*D, since patients recruited via advertising may differ in important ways from treatment-seeking patients (Amori & Lenox, 1989; Bielski & Lydiard, 1997; Parker & Blignault, 1983; Rapaport *et al*. 1996; Thase *et al*. 1984; Zimmerman *et al*. 2005). Trained and certified clinical research coordinators (CRCs) at each clinical site helped implement the treatment protocol and data collection. They also administered some of the clinician-rated instruments.

The STAR*D protocol was developed in accordance with the principles of the Declaration of Helsinki, and it was approved and monitored by the national coordinating centre (University of Texas Southwestern Medical Center, Dallas, TX), the data coordinating center (University of Pittsburgh Epidemiology Data Center, Pittsburgh, PA), the institutional review boards at the 14 regional centers and at each clinical site, and the National Institute of Mental Health Data Safety and Monitoring Board (NIMH; Bethesda, MD). All risks, benefits and adverse events associated with STAR*D were explained to participants, who provided written informed consent prior to study entry.

Inclusion/exclusion criteria

In general, STAR*D used broad inclusion criteria and minimal exclusion criteria to ensure recruitment of a sample representative of treatment-seeking outpatients with MDD who would receive care in everyday practice. For inclusion, patients who were clinically diagnosed with MDD had to have a baseline score of at least 14 (moderate severity) on the 17-item Hamilton Rating Scale for Depression ($HAMD_{17}$; Hamilton, 1967) as rated by the CRC. Patients were excluded if they had schizophrenia, schizoaffective disorder, bipolar disorder, anorexia nervosa, a primary diagnosis of bulimia nervosa or obsessive–compulsive disorder (OCD), or medical contraindications that precluded randomization to any study treatment. Patients with active and clinically significant substance abuse were eligible (unless in-patient detoxification was clinically required at entry), although participation in a substance abuse programme was encouraged by their clinicians. Concomitant medications for current general medical conditions (GMCs) were permitted, as was treatment of anxiety with lorazepam, sedative-hypnotics including trazodone ($\leqslant$200 mg) for insomnia, and medications for sexual side-effects as long as these were not considered to be relatively contraindicated when given with the study medications.

Of the 4041 participants enrolled into STAR*D, 2876 had a research outcomes assessor (ROA)-assessed $HAMD_{17}$ $\geqslant$14 and returned for at least one post-baseline visit (Trivedi *et al*. 2006). These 2876 participants represent the present study's evaluable sample. We chose to limit our analyses to those who took at least one dose of citalopram and had at least one post-baseline visit to limit our focus to participants who were actually treated, while recognizing that a traditional intent-to-treat analysis would include all patients who were given a prescription whether it was filled or not and whether or not they were subsequently evaluated.

A previous study (Novick *et al*. 2005) has been published that used data from the initial 1500 participants who entered STAR*D to make preliminary comparisons of baseline characteristics in participants who have depression with atypical features *vs*. those without atypical features. In the present paper, we present baseline characteristics and treatment outcomes for the full analysable sample of 2876 outpatients enrolled into STAR*D, which includes the subset of the previously reported 1500 who returned for at least one post-baseline visit. Thus, this sample partially overlaps with that of our previously published paper.

Baseline assessments

Sociodemographic and clinical information were collected at the baseline visit, including prior course of illness, current and past substance abuse, prior suicide attempts, family history of mood disorders, current GMCs, and prior history of treatment in the current major depressive episode. The CRC completed the $HAMD_{17}$ and the 16-item Quick Inventory of Depressive Symptomatology – Clinician-rated ($QIDS\text{-}C_{16}$; Rush *et al*. 2003; Trivedi *et al*. 2004), and the participant completed the QIDS self-report ($QIDS\text{-}SR_{16}$; Rush *et al*. 2003; Trivedi *et al*. 2004) for assessment of depressive symptom severity.

Concurrent GMCs were identified and quantified using the Cumulative Illness Rating Scale (CIRS; Linn *et al*. 1968; Miller *et al*. 1992), which identifies medical conditions according to physiological system. Concurrent psychiatric symptoms were identified using the Psychiatric Diagnostic Screening Questionnaire (PDSQ; Zimmerman & Mattia, 2001*a*) obtained at

baseline. The PDSQ is a self-rated screening questionnaire with which patients rate the presence or absence of current and recent symptoms relevant to 11 Axis I psychiatric disorders. The internal consistency and test–retest reliability of the PDSQ has been validated against structured interviews (Zimmerman & Mattia, 2001*b*).

Within 72 h of the baseline visit, a ROA contacted the participant by telephone to complete the $HAMD_{17}$, the 30-item Inventory of Depressive Symptomatology – Clinician-rated ($IDS\text{-}C_{30}$; Rush *et al*. 1986, 1996; Trivedi *et al*. 2004), and a 5-item Income and Public Assistance Questionnaire (IPAQ). A telephone-based interactive voice response (IVR) system obtained additional participant-reported information not specifically referenced in this article.

Definition of atypical depression

The $IDS\text{-}C_{30}$ items that most closely approximated DSM-IV criteria were chosen by consensus of the authors of our previously published paper (Novick *et al*. 2005), who agreed that several $IDS\text{-}C_{30}$ items best approximated the Columbia criteria for depression with atypical features. Cut-offs for each item were determined from a separate sample of patients by those ratings that produced the best sensitivity and specificity when compared with clinician ratings using the Atypical Depression Diagnostic Scale (ADDS; Novick *et al*. 2005; Stewart *et al*. 1993). These cut-offs provided an operationally defined algorithm for determining which patients had depression with atypical features. Using the ADDS-generated diagnosis as the 'gold' standard, a diagnosis of depression with atypical features made according to the $IDS\text{-}C_{30}$ algorithm had a sensitivity of 78%, a specificity of 71%, a kappa = 0.45, and a diagnostic efficiency of 73%.

All $IDS\text{-}C_{30}$ items are rated 0–3, with higher scores indicating increased symptoms. Depression with atypical features was defined as MDD with the symptom of mood reactivity together with two or more of the following symptoms: hypersomnia, increased appetite or increased weight, interpersonal rejection sensitivity, and leaden paralysis. With regard to scoring the relevant $IDS\text{-}C_{30}$ items, the criteria required a score of 0–2 to indicate mood reactivity (where 0 = high reactivity and 3 = mood non-reactivity), 2–3 to indicate leaden paralysis, 2–3 to indicate weight gain or increased appetite, 2–3 to indicate hypersomnia, and 3 to indicate interpersonal sensitivity.

Melancholic features were defined as MDD with the symptom of non-reactive mood or lack of pleasure/enjoyment together with three or more of the following symptoms: early morning insomnia, mood worsening in the morning, distinct quality of mood, decreased appetite or decreased weight, negative view of self, and psychomotor slowing or psychomotor agitation (Khan *et al*. 2006). Anxious features were ascribed when the participant had a baseline $HAMD_{17}$ somatization-anxiety score $\geqslant 7$ (Fava *et al*. 2004).

Intervention

Eligible participants were started on the SSRI citalopram at 20 mg/d. Protocol recommended increasing citalopram to 40 mg/d by week 4, and to the maximal dose of 60 mg/d by weeks 6–9. Visits were scheduled for weeks 2, 4, 6, 9 and 12, with a week 14 visit if improvement was equivocal at week 12. Treatment was provided using a measurement-based care approach in which the $QIDS\text{-}C_{16}$ (Rush *et al*. 2003, 2006) and the Frequency, Intensity and Burden of Side Effects Rating (FIBSER; Wisniewski *et al*. 2006) were used to ensure that each participant received an adequate dose and duration of treatment while minimizing side-effects (Trivedi *et al*. 2006).

Clinic visit assessments

Depressive symptom severity was determined at each clinic visit using the $HAMD_{17}$, $IDS\text{-}C_{30}$ and the $QIDS\text{-}SR_{16}$. Side-effects were monitored at each clinic visit using FIBSER. Serious adverse events were monitored using a multi-tiered approach involving the CRCs, study clinicians, IVR, safety officers, regional center directors, and the NIMH Data Safety and Monitoring Board.

Outcomes

Remission was defined as an exit $HAMD_{17}$ score $\leqslant 7$ (or last observed $QIDS\text{-}SR_{16}$ score $\leqslant 5$). Response was defined as a reduction of $\geqslant 50\%$ from the baseline $QIDS\text{-}SR_{16}$ at the last assessment. As defined by the original proposal, participants were designated as not having achieved remission when their exit $HAMD_{17}$ score was missing. Treatment intolerance was defined *a priori* as either leaving treatment before 4 wk or leaving at or after 4 wk with intolerance as the identified reason.

Statistical methods

Summary statistics are presented as means and standard deviations for continuous variables, and percentages for discrete variables. Student's *t* tests and Mann–Whitney *U* tests were used to compare

continuous baseline sociodemographic and clinical features, treatment features, and side-effect and serious adverse-event rates among those with and without atypical features. χ^2 tests compared discrete characteristics in those with and without atypical features.

Logistic regression models were used to compare remission and response rates, after adjusting for the effect of regional center and baseline characteristics that were not equally distributed in those with and without atypical features. Times to first remission and to first response were defined as the first clinic visit at which the definition was met. Log-rank tests were used to compare the cumulative proportion of participants with remission or response in those with and without atypical features. Cox proportional-hazards models were used to estimate the effect of atypical features on time to remission and response after controlling for the effects of regional centre and baseline depressive severity (QIDS-SR_{16}). Statistical significance was defined as a two-sided p value <0.05. Because we considered the analyses of treatment outcome to be exploratory, no adjustments were made for multiple comparisons. Therefore, results must be interpreted accordingly.

Results

Baseline sociodemographic and clinical characteristics

Table 1 shows the baseline sociodemographic and clinical characteristics for the full evaluable sample and by the presence/absence of atypical features. Of the 2876 participants, 64% were women, 76% were Caucasian, and the mean age at study entry was 41 ± 13 yr. Despite the low entry $HAMD_{17}$ requirement, the modal patient had moderate to severe depression. In total, 541 (19%) participants had depression with atypical features. These participants were significantly younger, more likely to be female, less likely to be currently married or employed, and had lower income than those without atypical features. Participants with atypical features had greater symptom severity (by the $HAMD_{17}$, IDS-C_{30} and QIDS-SR_{16}), an earlier age of onset, and a longer current episode.

Participants with atypical features were more likely to have a positive family history of suicide, MDD onset before age 18 yr, anxious features or chronic depression (Table 2). Regarding comorbid Axis I psychiatric disorders, participants with atypical features were more likely to have panic disorder, social phobia, post-traumatic stress disorder, agoraphobia, drug abuse, hypochondriasis or bulimia than those without. Participants with atypical features were also more likely to have a greater number of comorbid psychiatric disorders than those without atypical features.

Treatment features and outcomes

Participants with and without atypical features did not differ in maximal citalopram dose, dose at exit, number of visits, or time in treatment (Table 3). Overall, participants with atypical features were significantly less likely to reach remission by $HAMD_{17}$ ($\leqslant 7$) or QIDS-SR_{16} ($\leqslant 5$) than those without (Table 4). Given the lack of treatment differences between the two groups, these outcome differences cannot be explained by differential treatment. After the analyses were adjusted for important baseline differences, remission rates did not differ between the two groups

Remission occurred significantly later in participants with atypical features than for those without atypical features (Fig. 1), but time to response was not different (Fig. 2). This disconnect possibly resulted from the higher pre-treatment QIDS-SR_{16} scores in the atypical group having to decrease more in order to meet remission criteria. Thus, after controlling for the effects of regional centre and baseline depressive severity (measured by QIDS-SR_{16}), neither time to remission (hazard ratio 0.976, $p=0.7473$) nor time to response (hazard ratio 0.995, $p=0.9411$) differed between those with atypical features and those without. Figure 3 shows the likelihood of remission by week among those who eventually remitted. Those without atypical features were more likely to remit between weeks 2 and 6, while comparatively more participants with atypical features remitted at week 10 and after week 12.

Remission rates between those with and without atypical depression were not moderated by gender; that is, there was no significant interaction between atypical depression and gender for either $HAMD_{17}$ or $QIDS_{16}$. Although unadjusted remission rates were lower in those with atypical depression, the magnitude of this effect was consistent among men and women (Table 5).

Participants with atypical features had a greater side-effect intensity and burden than those without atypical features (Table 6). There were no differences between the two groups with regard to the number of serious adverse events or psychiatric serious adverse events, or in treatment intolerance.

Discussion

Important baseline differences were found between outpatients with depression who had atypical features

Table 1. Baseline demographic characteristics associated with atypical/non-atypical features

		Atypical features		
	Total sample	No ($n=2334$) (81.2%)	Yes ($n=541$) (18.8%)	
Characteristic	%	%	%	p value
Setting				0.4488
Primary care	37.9	37.6	39.4	
Speciality care	62.1	62.4	60.6	
Race				0.9621
White	75.8	75.7	76.2	
African-American	17.6	17.7	17.2	
Others	6.6	6.6	6.6	
Ethnicity, Hispanic	13.0	12.5	15.0	0.1179
Sex, female	63.7	61.9	71.7	<0.0001
Marital status				0.0378
Never married	28.7	27.5	33.6	
Married	41.7	42.2	39.5	
Divorced	26.5	27.0	24.5	
Widowed	3.1	3.3	2.4	
Employment status				0.0441
Employed	56.2	57.1	52.3	
Unemployed	38.2	37.1	42.9	
Retired	5.6	5.8	4.8	
Insurance status				0.1589
Private insurance	51.1	52.0	47.3	
Public insurance	14.3	14.0	15.2	
No insurance	34.7	34.0	37.5	
Family history of depression	55.6	55.7	55.2	
	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)	
Age (yr)	40.8 (13.0)	41.1 (13.0)	39.5 (13.0)	0.0083
Education (years of schooling)	13.4 (3.2)	13.5 (3.3)	13.3 (3.1)	0.2086
Income ($/month)	2358 (3030)	2428 (3134)	2060 (2524)	0.0068
General medical comorbidities				
Categories endorsed	3.1 (2.3)	3.1 (2.3)	3.2 (2.2)	0.3236
Total score	4.4 (3.7)	4.4 (3.8)	4.5 (3.6)	0.5059
Severity index	1.2 (0.6)	1.2 (0.6)	1.3 (0.6)	0.2609
Age at onset of first episode	25.3 (14.4)	22.0 (35–15)	19.0 (31–13)	<0.0001
Number of episodes	6.0 (11.4)	3.0 (5–1)	3.0 (5–2)	0.1208
Length of current episode (months)	24.6 (51.7)	8.0 (24–3)	9.0 (27–3)	0.0418
Length of illness (yr)	15.5 (13.2)	12.0 (25–4)	13.0 (24–5)	0.0589
$HAMD_{17}$ (ROA)	21.8 (5.2)	21.6 (5.2)	22.6 (5.1)	<0.0001
IDS-C_{30} (ROA)	38.6 (9.6)	37.4 (9.4)	43.3 (8.8)	<0.0001
QIDS-SR_{16}	16.2 (4)	15.9 (4.0)	17.5 (3.7)	<0.0001

$HAMD_{17}$, 17-item Hamilton Rating Scale for Depression; IDS-C_{30}, 30-item Inventory of Depressive Symptomatology – Clinician-rated; QIDS-SR_{16}, 16-item Quick Inventory of Depressive Symptomatology – Self-Rated; ROA, Research Outcome Assessor; S.D., standard deviation.

Table 2. Clinical and family characteristics according to atypical/non-atypical features

	Atypical features			
	No ($n=2334$) (81.2%)	Yes ($n=541$) (18.8%)		
	%	%		p value
Clinical feature				
Family history of depression	55.7	55.1		0.8142
Family history of alcohol abuse	41.1	42.8		0.4740
Family history of drug abuse	24.4	23.8		0.7775
Family history of mood disorder	57.7	57.9		0.9398
Family history of suicide	3.2	5.4		0.0114
Attempted suicide	17.3	20.7		0.0590
Present suicide risk	2.9	3.9		0.2171
Age at onset				<0.0001
⩽18 yr	36.0	45.5		
>18 yr	64.0	54.5		
Anxious depression	51.7	59.7		0.0008
Melancholic depression	23.9	21.5		0.2226
Chronic depression	24.3	29.2		0.0187
Recurrent depression	75.2	77.5		0.2875
CIRS count				0.4671
0	10.4	8.1		
1	15.4	15.0		
2	18.0	17.0		
3	14.6	15.5		
4	41.6	44.4		
Psychiatric disorder			OR	
Anxiety disorder	22.9	26.6	1.22	0.0726
OCD	13.9	16.3	1.21	0.1527
Panic	12.3	16.3	1.38	0.0146
Social phobia	28.4	43.9	1.98	<0.0001
PTSD	19.8	23.9	1.27	0.0351
Agoraphobia	10.6	17.1	1.74	<0.0001
Alcohol abuse	12.3	11.0	0.89	0.4214
Drug abuse	6.8	9.6	1.44	0.0289
Somatoform	2.5	2.1	0.83	0.5845
Hypochondriasis	3.9	6.8	1.79	0.0039
Bulimia	11.2	20.6	2.04	<0.0001
PDSQ count				<0.0001
0	37.0	25.4		
1	26.9	25.2		
2	15.2	22.1		
3	9.1	9.7		
4	11.8	17.6	1.65	

CIRS, Cumulative Illness Rating Scale; OCD, obsessive–compulsive disorder; OR, odds ratio; PDSQ, Psychiatric Diagnostic Screening Questionnaire; PTSD, post-traumatic stress disorder.

Table 3. Treatment characteristics in relation to symptomatic outcome by atypical/non-atypical features

		Atypical features		
	Total ($n=2875$)	No ($n=2334$) (81.2%)	Yes ($n=541$) (18.8%)	
Dose and treatment	*n* (%)	*n* (%)	*n* (%)	*p* value
Maximum dose of citalopram (mg/d)				0.5600
<20	63 (2.2)	47 (2.0)	16 (3.0)	
20–39	694 (24.2)	565 (24.3)	129 (23.9)	
40–49	862 (30.1)	705 (30.3)	157 (29.1)	
⩾50	1249 (43.5)	1011 (43.4)	238 (44.0)	
Dose of citalopram at study exit (mg/d)				0.7204
<20	105 (3.7)	81 (3.5)	24 (4.4)	
20–39	784 (27.3)	635 (27.3)	149 (27.6)	
40–49	856 (29.8)	700 (30.1)	156 (28.9)	
⩾50	1123 (39.2)	912 (39.1)	211 (39.1)	
Time in treatment (wk)				0.1307
<4	322 (11.2)	250 (10.7)	72 (13.3)	
4 to <8	485 (16.9)	404 (17.3)	81 (15.0)	
⩾8	2067 (71.9)	1679 (72.0)	388 (71.7)	
	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)	
Number of visits	4.8 (1.5)	4.8 (1.5)	4.8 (1.5)	0.7028
Time to first treatment visit (wk)	2.3 (1.1)	2.3 (1.1)	2.3 (0.9)	0.7915
Time in treatment (wk)	10.0 (4.2)	10.0 (4.1)	10.0 (4.3)	0.9703
Time from final dose to study exit (wk)	5.0 (3.8)	5.0 (3.9)	5.0 (3.8)	0.9017

S.D., Standard deviation.

and those who did not. These included an earlier onset, a more chronic course, a more severe illness, more Axis I comorbidities, and a greater likelihood of having a family history of suicide in participants with atypical features. These findings reprise our previously published findings (Novick *et al*. 2005), not surprisingly, since the earlier findings were based on a partially overlapping population.

The proportion of patients identified as having MDD with atypical features (18.8%) was lower than what has been found in other clinical samples (Asnis *et al*. 1995; Benazzi, 1999; Perugi *et al*. 1998; Posternak & Zimmerman, 2002), but was in line with the findings of epidemiological studies (Horwath *et al*. 1992; Kendler *et al*. 1996; Matza *et al*. 2003; Sullivan *et al*. 1998). Several reasons may account for this. The IDS-C_{30}-derived algorithm may have under-diagnosed patients. Excessive numbers of patients having MDD with atypical features may have been excluded from the study by the use of a $HAMD_{17}$ cut-off since the $HAMD_{17}$ under-represents atypical relative to melancholic features. Additionally, the exclusion of bipolar disorder may have excluded potential subjects having atypical features, which has been linked to bipolar disorder (e.g. Benazzi, 1999; Perugi *et al*. 1998). Finally, the participants evaluated for most of the prior reports came from research clinics or speciality private practice, while STAR*D recruited a more general sample which may, therefore, have been more representative of patients that clinicians can expect to see in their practices.

Unadjusted analyses demonstrated that STAR*D participants who had MDD with atypical features were significantly less likely to reach remission with

Table 4. Remission and response status by atypical/non-atypical features

		Atypical features					
	Total ($n=2875$)	No ($n=2334$) (81.2%)	Yes ($n=541$) (18.8%)	Unadj.	Unadj.	Adj.	Adj.
Outcome	%	%	%	OR	*p* value	OR[a]	*p* value[a]
$HAMD_{17}$ remission				0.78	0.0217	1.04	0.7437
No	72.6	71.6	76.5				
Yes	27.4	28.4	23.5				
$QIDS\text{-}SR_{16}$ remission				0.79	0.0214	1.11	0.3929
No	67.2	66.2	71.4				
Yes	32.8	33.8	28.6				
$QIDS\text{-}SR_{16}$ response					0.9328		
No	53.1	53.2	53.0				
Yes	46.7	46.8	47.0				
	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)				
Exit $QIDS\text{-}SR_{16}$	9.1 (5.9)	9 (5.9)	9.7 (6)		0.0098		
$QIDS\text{-}SR_{16}$ Change	−7 (5.9)	−6.9 (5.9)	−7.8 (6.1)		0.0009		
$QIDS\text{-}SR_{16}$ Change (%)	−42.8 (35)	−42.5 (35.6)	−44 (33.9)		0.5711		

Adj, Adjusted; $HAMD_{17}$, 17-item Hamilton Rating Scale for Depression; OR, odds ratio; $QIDS\text{-}SR_{16}$, 16-item Quick Inventory of Depressive Symptomatology – Self-Rated; S.D., standard deviation; Unadj, Unadjusted.

[a] Adjusted for regional centre, gender, marital status, employment status, age, total income, baseline severity, $HAMD_{17}$, $QIDS\text{-}SR_{16}$, $IDS\text{-}C_{30}$.

citalopram treatment than those without atypical features. This difference disappeared in subsequent analyses that adjusted for baseline variables that differed between the two groups. Determining which of the two analyses is relevant depends on whether one considers the various between-group differences to be inherent aspects of atypical depression, or random between-group differences due to sampling variation. If the differences are random, then the analysis that adjusts for them is more applicable; conversely, if the differences are inherent in the illness, the unadjusted analysis would seem more relevant. Several of the adjusted variables have been proposed as being characteristic of atypical depression. For example, early onset and chronicity have been proposed for consideration as additional criteria for atypical depression in DSM-V (Stewart *et al*. 2007), while several prior reports remark on increased rates of women in those diagnosed as having depression with atypical features (Angst *et al*. 2002; Davidson *et al*. 1982; Posternak & Zimmerman, 2002). If these differences between patients with and without atypical depression are indeed inherent differences between illnesses, then adjusting for them removes variance attributable to the disorder rather than variance attributable to random differences between groups. From a practical standpoint, it may be simplest for a clinician to consider whether a patient has atypical features rather than paying close attention to age of onset and chronicity when determining expectation of how helpful citalopram will be.

Depressed patients with atypical features have been considered to have a more mild illness than other depressed populations (Anisman *et al*. 1999; Kendel *et al*. 2004; Parker *et al*. 2002). However, in the STAR*D sample, depressed participants with atypical features were more severely depressed, whether severity was measured by $HAMD_{17}$, $IDS\text{-}C_{30}$, $QIDS\text{-}SR_{16}$, functional impairment (marital status, employment status, income), or comorbid Axis I psychiatric disorders; findings that are consistent with other reports of increased severity and/or functional impairment in atypical depression (Angst *et al*. 2006; Matza *et al*. 2003; Posternak & Zimmerman, 2002). The finding of increased $HAMD_{17}$ scores is particularly surprising since this rating scale does not include items that rate

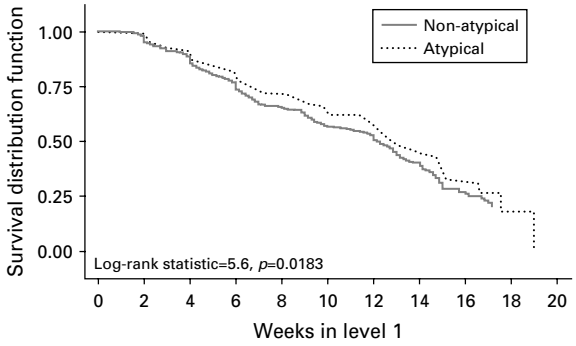

Fig. 1. Time to remission (i.e. first week Quick Inventory of Depression Symptoms, Self-Rated, 16-item version, $\leqslant 5$) by presence or absence of depression with atypical features. 'Non-atypical' indicates major depression without atypical features; 'Atypical' indicates major depression with atypical features. Curves represent Kaplan–Meier survival curves until the occurrence of remission, with patients who dropped out of the study censored, uncorrected for baseline group differences.

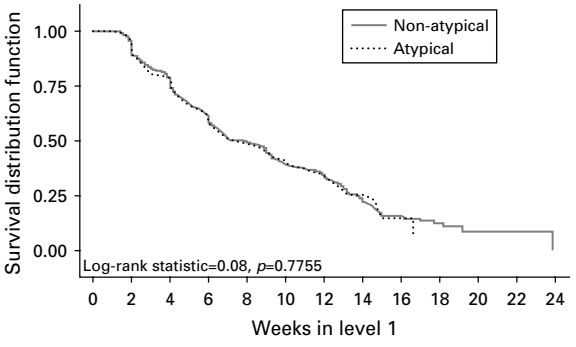

Fig. 2. Time to response (i.e. first week Quick Inventory of Depression Symptoms, Self-Rated, 16-item version, $\leqslant 50\%$ of baseline) by presence or absence of depression with atypical features. 'Non-atypical' indicates major depression without atypical features; 'Atypical' indicates major depression with atypical features. Curves represent Kaplan–Meier survival curves until the occurrence of remission, with patients who dropped out of the study censored, uncorrected for baseline group differences.

atypical features. While concomitant anxiety symptoms or formal anxiety disorders can explain the higher $HAMD_{17}$ and IDS-C_{30} ratings for the atypical group, the higher QIDS-SR_{16} ratings are not confounded with anxiety symptom items. The QIDS-SR_{16} only measures the nine core symptom domains that define a DSM-IV major depressive episode, while measuring the reverse vegetative symptoms of depression with atypical features.

Table 5. Percent (n) remission by atypical by gender

Gender	With atypical features	Without atypical features
$HAMD_{17} \leqslant 7$		
Male	16 (25)	25 (226)
Female	26 (102)	30 (436)
$QIDS_{16} \leqslant 5$		
Male	24 (37)	33 (288)
Female	30 (118)	35 (499)

$HAMD_{17}$ remission: gender × atypical interaction ($p < 0.17$).
$QIDS_{16}$ remission: gender × atypical interaction ($p < 0.35$).

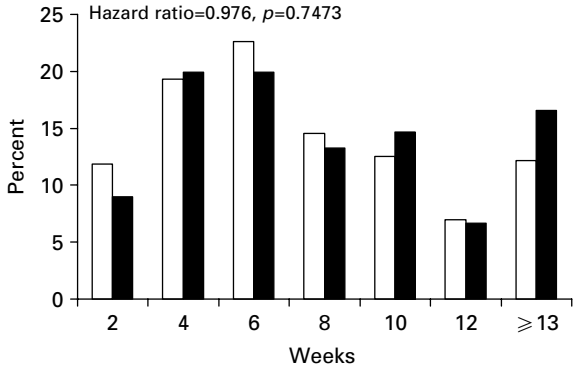

Fig. 3. Percent remitting by study week of patients with and without major depression with atypical features, among patients who remitted (Quick Inventory of Depressive Symptoms, Self-Rated, 16-item version, $\leqslant 5$). □, Patients without atypical features; ■, patients with atypical features.

Because more change must occur in patients beginning with higher entry scores in order for them to meet the remission criterion, it is not surprising that the more severely ill group was significantly slower and less likely to reach remission criteria at study exit. Two analyses suggest that these observations did not result from inferior delivery of citalopram. First, response rates and time to reach response did not differ between groups, suggesting that the trajectory of improvement did not differ between those with and those without atypical features. Second, exit scores did not differ when differences in severity were included as covariates in the outcome analysis.

Most participants took 40 mg/d citalopram for over a month, and were in treatment for at least 8 wk, so most participants received an adequate pharmacological trial. It is noteworthy that about 20% of participants who remitted did not do so until week 12 or

Table 6. Adverse events, side-effects by atypical/non-atypical features

		Atypical features		
	Total ($n=2875$)	No ($n=2334$) (81.2%)	Yes ($n=541$) (18.8%)	
Side-effects, adverse events	*n* (%)	*n* (%)	*n* (%)	*p* value
Maximum side-effect frequency				0.1718
None	448 (15.7)	376 (16.2)	72 (13.3)	
10–25% of the time	807 (28.2)	664 (28.6)	143 (26.5)	
50–75% of the time	914 (32.0)	730 (31.5)	184 (34.1)	
90–100% of the time	691 (24.1)	550 (23.7)	141 (26.1)	
Maximum side effect intensity				0.0430
None	442 (15.5)	371 (16.0)	71 (13.2)	
Trivial	793 (27.7)	659 (28.4)	134 (24.8)	
Moderate	1172 (41.0)	936 (40.3)	236 (43.7)	
Severe	453 (15.8)	354 (15.3)	99 (18.3)	
Maximum side effect burden				0.0398
No impairment	583 (20.4)	488 (21.0)	95 (17.6)	
Minimal-mild impairment	1173 (41.0)	962 (41.5)	211 (39.1)	
Moderate-marked impairment	864 (30.2)	687 (29.6)	177 (32.8)	
Severe impairment-unable to function	240 (8.4)	183 (7.9)	57 (10.5)	
Serious adverse events	116 (4.0)	95 (4.1)	21 (3.9)	0.8403
Death, non-suicide	3	3	0	
Hospitalization for GMCs	58	48	10	
Medical illness without hospitalization	4	2	2	
Psychiatric hospitalization				
Substance abuse	8	6	2	
Suicidal ideation	36	30	6	
Worsening depression	6	6	0	
Other	2	2	0	
Suicidal ideation (without hospitalization)	6	4	2	
Any psychiatric serious adverse events	57 (2.0)	47 (2.0)	10 (1.9)	0.9688
Intolerance[a]	490 (17.0)	386 (16.5)	104 (19.2)	0.1345

GMC, General medical condition.

[a] Intolerance: participants exited within the first 4 wk of level or exited after 4 wk and indicated unacceptable side-effects.

later despite the protocol raising citalopram to the maximal dose by weeks 6–9. It appears, then, that the maximal tolerated dose should be continued for at least 4 wk before declaring citalopram ineffective.

The STAR*D sample included several important features that add to the generalizability of its results. First, participants were recruited from among those attending the offices and clinics of general and family practitioners, internists and general psychiatrists. None were recruited through advertising or from research clinics. Second, the only exclusions were for safety reasons. For example, it would be inappropriate to enrol a patient with substance abuse who needed acute detoxification, or a patient with a history of a seizure or eating disorder (since bupropion is contraindicated for such patients and it was both an augmentation and a switch option for STAR*D participants who did not remit with citalopram). Third, STAR*D actively recruited minorities and recruited from clinical settings across the USA. These three features suggest that the STAR*D results can be generalized to patients with non-psychotic unipolar depression who are entering a wide variety of clinical settings.

Several caveats temper enthusiasm about generalizing the results. First, STAR*D had no placebo control. It is possible that citalopram was ineffective for all participants and that any observed changes were entirely due to non-pharmacological treatment and environmental effects. Contrary to this possibility, STAR*D remission rates did mimic those reported in meta-analyses of placebo-controlled studies (Smith *et al*. 2002; Thase *et al*. 2001) and were within the range of other published open-label studies (range 23–51%, mean 40%) (Corey-Lisle *et al*. 2004; McGrath *et al*. 2006; Stewart *et al*. 1998). Further, research outcome raters were masked to diagnosis and treatment, which adds legitimacy to the findings, at least with the $HAMD_{17}$. Moreover, these blind ratings were highly correlated with the self-reported $QIDS\text{-}SR_{16}$, which suggests that both ratings were unbiased. However, lower entry HAMD ratings than in most pharmaceutical industry studies may have increased placebo response (Brown *et al*. 1992; Wilcox *et al*. 1992) resulting in more apparent efficacy than true effectiveness (Paykel *et al*. 1988; Stewart *et al*. 1983; Tedlow *et al*. 1998). A second tempering caveat is that atypical features were inferred from rating scales intended to measure symptomatology and severity of illness, rather than from structured diagnostic interviews. Factors that support the use of our $IDS\text{-}C_{30}$ algorithm include its demonstrated correlation with ratings determined in structured diagnostic interviews, and the STAR*D findings of differences between participants with and without atypical features that are similar to differences reported previously. Nevertheless, ascertainment errors could have clouded true between-group differences, and the $\kappa = 0.45$ between diagnoses based on the $IDS\text{-}C_{30}$ algorithm and diagnoses based on psychiatric interview may have been inflated by using the most discriminatory cut-offs, so a replication study might demonstrate a lower κ. A further issue is whether statistically significant differences based on a large sample are clinically meaningful. Some, such as a $HAMD_{17}$ difference of 1 point, seem clinically trivial; while others such as a 3-point mean difference on the $IDS\text{-}C_{30}$ seem more substantive. Finally, DSM-IV criteria stipulate that patients with depression not be considered to have atypical features in the presence of melancholic features. Our analyses did not remove participants who may have had melancholic features. STAR*D did develop an algorithm to assess the presence of melancholic features (Khan *et al*. 2006). Because this algorithm has not been validated, while the algorithm we used for atypical features has been validated against diagnoses made by experienced clinicians, we chose to present findings based solely on the algorithm for atypical features without excluding participants who may have also met STAR*D algorithm criteria for melancholic features. Additional analyses were conducted that excluded those who met STAR*D criteria for melancholic features. These analyses showed relatively minor differences in baseline differences between participants with and without atypical features while not demonstrating unadjusted treatment outcome differences. That is, in the analyses presented, participants with atypical features were less likely to remit, and their remissions occurred later than in participants without atypical features; however, these two differences were no longer significant when baseline covariates were included. Timing and likelihood of remission were also not different between patients with and without atypical features when patients with algorithm-derived melancholic features were removed from the analyses [analyses available from the first author (J.W.S.) upon request].

Significant numbers of the participants who reached remission only did so after 8 wk of citalopram treatment. This suggests that treatment should be provided for at least 12 wk before declaring citalopram ineffective. It might be beneficial to consider even longer treatment durations, particularly for patients who have depression with atypical features. The present study's data suggest that patients with atypical features take longer to reach remission than those without atypical features, although the longer times to remission and lower remission rates found in patients with depression who have atypical features may be attributable to their increased severity (there was no main effect for atypical features in analyses in which severity was a covariate). However, this suggestion should be tempered by recognizing that faster remissions might occur if the dose is increased more rapidly than provided for by the STAR*D protocol.

In conclusion, patients who have depression with atypical features have a number of distinct baseline sociodemographic features and greater depressive severity. Those with atypical features are also less likely to remit with citalopram and take longer to remit with citalopram, but these differences do not remain after adjustment for baseline differences. Therefore, these differential findings are probably due to those baseline differences rather than the atypical features themselves. Given the finding that most participants who remitted did not do so until after 8 wk treatment, it might be beneficial to continue citalopram treatment for at least 12 wk (and perhaps longer) before declaring citalopram ineffective, particularly

when treating depressed patients who have atypical features.

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