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The International Study to Predict Optimized Treatment in Depression (iSPOT-D): Outcomes from the acute phase of antidepressant treatment

Radu Saveanu [a, 1, 2], Amit Etkin [b, c, 1], Anne-Marie Duchemin [a], Andrea Goldstein-Piekarski [b, c], Anett Gyurak [b, c], Charles Debattista [b], Alan F. Schatzberg [b], Satish Sood [d], Claire V.A. Day [e, f, g], Donna M. Palmer [e, f, g], William R. Rekshan [f, g], Evian Gordon [f, g], A. John Rush [h], Leanne M. Williams [b, c, e, *]

[a] Department of Psychiatry, The Ohio State University College of Medicine, Columbus, OH 43210, USA
[b] Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA 94305, USA
[c] Sierra-Pacific Mental Illness Research, Education, and Clinical Center (MIRECC) Veterans Affairs Palo Alto Health Care System, Palo Alto, CA 94304, USA
[d] SHANTI Clinical Trials, Colton, CA 92324, USA
[e] Brain Dynamics Center, Psychiatry, University of Sydney Medical School at Westmead Hospital, Sydney, NSW 2145, Australia
[f] Brain Resource Ltd, 235 Jones Street, Sydney, NSW, Australia
[g] Brain Resource Inc, 1000 Sansome Street, San Francisco, CA 94111, USA
[h] Duke-NUS Graduate Medical School, 8 College Road, Singapore 169857, Singapore

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ABSTRACT

We aimed to characterize a large international cohort of outpatients with MDD within a practical trial design, in order to identify clinically useful predictors of outcomes with three common antidepressant medications in acute-phase treatment of major depressive disorder (MDD). The international Study to Predict Optimized Treatment in Depression has presently enrolled 1008 treatment-seeking outpatients (18–65 years old) at 17 sites (five countries). At pre-treatment, we characterized participants by symptoms, clinical history, functional status and comorbidity. Participants were randomized to receive escitalopram, sertraline or venlafaxine-extended release and managed by their physician following usual treatment practices. Symptoms, function, quality of life, and side-effect outcomes were assessed 8 weeks later. The relationship of anxiety to response and remission was assessed by comorbid Axis I diagnosis, presence/absence of anxiety symptoms, and dimensionally by anxiety symptom severity. The sample had moderate-to-severe symptoms, but substantial comorbidity and functional impairment. Of completers at week 8, 62.2% responded and 45.4% reached remission on the 17-item Hamilton Rating Scale for Depression; 53.3% and 37.6%, respectively on the 16-item Quick Inventory of Depressive Symptoms. Functional improvements were seen across all domains. Most participants had side effects that occurred with a frequency of 25% or less and were reported as being in the "none" to minimal/mild range for intensity and burden.

Outcomes did not differ across medication groups. More severe anxiety symptoms at pre-treatment were associated with lower remission rates across all medications, independent of depressive severity, diagnostic comorbidity or side effects. Across medications, we found consistent and similar improvements in symptoms and function, and a dimensional prognostic effect of comorbid anxiety symptoms. These equivalent outcomes across treatments lay the foundation for identifying potential neurobiological and genetic predictors of treatment outcome in this sample.

* Corresponding author. Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA 94305, USA. Tel.: +1 650 723 3579.
E-mail address: leawilliams@stanford.edu (L.M. Williams).
[1] Equal first authors.
[2] Current address: Department of Psychiatry and Behavioral Sciences, The University of Miami Miller School of Medicine, Miami, FL 33136, USA.

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1. Introduction

Major depressive disorder (MDD) affects 121 million people worldwide (World Health Organization, 2012). It has the highest burden of illness in high-income countries based on disability-adjusted life-years, is the third most disabling medical condition worldwide and is the second-ranked cause of lost quality of life in persons aged 15–44 years (Whiteford et al., 2013; World Health Organization, 2012).

Antidepressant medications (ADMs) are commonly used to treat depression (American Psychiatric Association, 1993; Depression Guideline Panel, 1993; Frank et al., 1993; Thase and Rush, 1995; Rosenbaum et al., 2001; Baghai et al., 2011; Kennedy, 2013), but less than 50% of patients reach remission with any single first-step antidepressant (Frank et al., 1991; Fava and Davidson, 1996; Bileski et al., 2004; Rush et al., 2006; Trivedi et al., 2006; Gartlehner et al., 2008). If the first-step treatment fails, response and remission rates at subsequent steps are even more limited. Greater pre-treatment anxiety, more general medical or psychiatric comorbidity, greater depressive severity, and greater treatment resistance (history of more failed adequately-delivered prior treatments) have been associated with poorer outcomes (Fava et al., 2008; Rush et al., 2009) and poorer daily functioning (Joffe et al., 1993). MDD and anxiety commonly overlap (Joffe et al., 1993; Fava et al., 2008; Rush et al., 2009), but it is not known what form of pre-treatment anxiety influences MDD treatment outcomes. For example, it is unclear whether pre-treatment anxiety *per se* predicts poor outcome across multiple types of antidepressants, independent of other clinical features (e.g., comorbid anxiety disorders, depressive severity) (Fava et al., 1997, 2008; Flint and Rifat, 1997; Nelson, 2008).

Recent efforts have focused on identifying clinical- or laboratory-based measures that help to precisely target treatments for specific patients. While several neurobiological markers have been investigated (Papakostas and Fava, 2008; Kuk et al., 2010; McGrath et al., 2013), none have been of sufficient clinical value to be incorporated into treatment guideline recommendations (Rush et al., 2008).

The international Study to Predict Optimized Treatment in Depression (iSPOT-D) was designed to prospectively identify clinical and neurobiological predictors of ADM outcome in outpatients with non-psychotic MDD treated in their usual clinical care setting (Williams et al., 2011). Outpatients were recruited from academic speciality psychiatry, primary care and community health care settings with the intention of representing the population of treatment seekers and the different clinical settings they are treated in. For example, 42% of participants in the STAR*D validation cohort were treated in primary care settings (Gaynes et al., 2005).

iSPOT-D was designed as a practical trial comparing commonly used active ADMs offered in current typical practice to quantify the rates of response and remission, and the clinical factors that predict and moderate these outcomes, as the necessary foundation for identifying pre-treatment biomarkers of which patients respond and which do not, and why. In other words, iSPOT-D follows current usual care setting clinical practice in the prescription of antidepressant medications, coupled with collection of a broad range of potential predictor measures (e.g. genetics, neurobiological, psychophysiological etc). This was done in order to arrive at a battery of tests that can be used in future prospectively-designed validation studies that will test the proposed individual patient-level treatment optimization algorithm built on these predictors.

With the agreement of treating clinicians (who already include the study medications in their choices for care), participants were randomized to one of three active antidepressant medication arms: escitalopram or sertraline, selective serotonin reuptake inhibitors (SSRIs), or venlafaxine-extended release (venlafaxine-XR), a selective norepinephrine and serotonin reuptake inhibitor (SNRI). There was no placebo option as it is not part of usual treatment in clinical settings, and is not required to identify predictors and moderators of outcomes to ADMs commonly used in real world practice.

This report of 1008 MDD participants focuses first on characterizing pre-treatment demographic, social, clinical history, symptom severity, functional capacity, course of illness and comorbidity factors. We then examine rates of response and remission, as well as change in symptom severity and functional status, and side effects, following acute phase treatment. Third, we assess whether pre-treatment characteristics identify which patients remit after acute-phase treatment and which do not, and whether these relationships differ as a function of type of treatment.

2. Materials and methods

2.1. Sites and practitioners

iSPOT-D is a multi-site, randomized practical clinical trial (Williams et al., 2011) conducted at seventeen sites in the United States, Netherlands, Australia, New Zealand and South Africa. These sites include eight academic and nine private clinical settings (Supplementary Table 1). We refer to these as the "study management" sites because they manage recruitment and assessments. Most also act as the hub for a broader network of "care delivery" providers at community general practices and university general health centers, which monitor and manage medication following usual clinical care. This mix was intended to reflect the distribution of how antidepressants are usually managed across services and practices.

2.2. Quality control and training

Quality control and study specific provision of training was overseen by the iSPOT-D Global Coordinating Center.

Inter-rater reliability for the primary outcome measure ($HRSD_{17}$ Hamilton, 1960) was audited for each clinician at each testing site at the beginning, middle and end of recruitment, using an established video-based methodology (Kobak et al., 2008). Clinicians who differed from the average across sites were advised by the head statistician at the Global Coordinating Center of how their rating differed to others, and they were allowed to re-sit the rating exam until they rated within the bounds of the combined group. Internal consistency across raters was measured using an intra-class correlation coefficient (satisfactory at 0.87).

2.3. Participants

The study enrolled adults (aged 18–65 years) with a diagnosis of current nonpsychotic MDD. Fig. 1 outlines the inclusion and exclusion criteria used to recruit participants who would typically receive an ADM in clinical practice. We recognize that ADMs are used in older patients, but in this study we excluded patients over age 65 in order to control for the possible effects of age-related changes on subsequent behavioral and brain imaging recordings, and because symptoms of MDD may be expressed differently in late-life depression (Alexopoulos and Kelly, 2009). Adolescents/

Inclusion Criteria

- Age 18-65
- Fluent and literate in English or Dutch
- Provide written informed consent
- Total $HRSD_{17}$ ≥16
- Meets DSM-IV* criteria for single or recurrent nonpsychotic MDD established by MINI Plus

Exclusion Criteria

- Suicidal ideation and/or tendencies, defined by a score ≥8 on Section C of the MINI Plus
- History of bipolar disorder (I, II, not otherwise specified) (lifetime)
- History of schizophrenia, schizoaffective disorder, or psychosis not otherwise specified (lifetime)
- Current primary diagnosis of anorexia or bulimia, obsessive-compulsive disorder, or primary post-traumatic stress disorder
- Known contra-indication for escitalopram, sertraline and/or venlafaxine-XR, or previous treatment failure at the highest recommended dose
- Taking any medication that is contraindicated with escitalopram, sertraline, or venlafaxine-XR
- Taking escitalopram, sertraline, or venlafaxine-XR in the current episode of MDD
- Use of any non-protocol antidepressant drug or CNS drug (antipsychotic, anticonvulsant anxiolytic, clonidine) that cannot be washed out prior to participation
- Has general medical condition that contraindicates protocol antidepressant treatments or interferes with protocol measurements (such as epileptic condition for EEG recording)
- Substance dependence (including alcohol intake equaling 29 standard alcoholic drinks per week for males; >15 for females) in the past six months
- History of brain injury or blow to the head that resulted in loss of consciousness for greater than five minutes
- Severe impediment to vision, hearing and/or hand movement that is likely to interfere with completion of assessments, or with comprehension of instructions or study requirements
- Participation in an investigational study within four months prior to baseline that could affect symptoms of MDD
- Is pregnant or breast-feeding

Fig. 1. Summary of inclusion and exclusion criteria.

children were excluded because the efficacy and safety of most study ADMs have not been established for this age group.

Participants were recruited through the study management sites or from community general practice clinics and university general health centers. Study management sites oversaw local study recruitment and participation (Supplementary Figure 1). There were no differences in participant characteristics as a function of recruitment site, adding weight to the point that MDD patients in primary care requiring treatment are not less depressed than those in speciality settings.

Inclusion was based on the MINI-Plus to establish a diagnosis of MDD (Sheehan et al., 1998), the $HRSD_{17}$ to assess depressive symptom severity (score ≥16 for inclusion), urine toxicology (to provide data on illicit, or prescribed, drug use) and a pregnancy screen. The initial pre-screen for exclusion and inclusion criteria was made by telephone.

The study was approved by each site's governing Institutional Review Board and was carried out in accordance with the Declaration of Helsinki for human research. All participants provided written informed consent after study procedures had been fully explained.

2.4. Protocol treatments

Participants were randomized (1:1:1) to receive escitalopram, sertraline or venlafaxine-XR, with dose adjustments managed by each participant's usual treating clinician according to their usual clinical practice. The mean duration of treatment was 7.6 weeks for each treatment arm. All other psychotropic medications were discontinued for at least one week, and sleep aids and anxiolytics within 24 h of assessments. 71.6% of patients (n = 722) completed treatment and there was no difference in completion rate across treatment arms: escitalopram, 70.2% (n = 244), sertraline, 74.7% (n = 253) and venlafaxine-XR, 69.9% (n = 240). Mean doses (and ranges) were as follows: escitalopram, 12.3 mg/day (5–20 mg), sertraline, 61.1 mg/day (12.5–200 mg) and venlafaxine-XR, 83.4 mg/day (18.75–225 mg).

Given that we pursued a practical trial design, investigators/raters and participants were not blind to treatment assignment. A blocked randomization procedure was undertaken centrally (block size of 12, across sites).

2.5. Pre-treatment assessments of demographic, social, clinical history, symptom, functional capacity, illness course and comorbidity

Pre-treatment characteristics are summarized in Table 1. Specific self-report items were used to acquire information on demographics and social characteristics (Williams et al., 2011). MINI-Plus data and self-report items were used to acquire clinical history, including family history, information. Established self-report scales were used to assess depressive symptom severity: the 16-item Quick Inventory of Depressive Symptomatology – Self-Report ($QIDS\text{-}SR_{16}$) (Rush et al., 2003; Trivedi et al., 2004) and the Depression, Anxiety and Stress Scales (DASS-42) (Lovibond, 1998). The DASS anxiety subscale is designed to be a specific test of arousal-related anxiety severity. In addition, severity of anxiety was assessed by dimensionally by the $HRSD_{17}$ anxiety/somatization subscale items for psychic anxiety, somatic anxiety, gastrointestinal somatic symptoms, general somatic symptoms, hypochondriasis and insight. (range 0–18) and categorically, based on a previously defined cutoff score of ≥7 (Cleary and Guy, 1977) on this $HRSD_{17}$ anxiety/somatization subscale. To assess functional capacity we used the Social and Occupational Functioning Assessment Scale (SOFAS) (Goldman et al., 1992), the World Health Organization Quality of Life (WHOQoL) scale (World Health Organization Group, 1998), the Satisfaction with Life Scale (SWLS) (Diener et al., 1985) and the Emotion Regulation

Table 1
Demographic, clinical history, symptom, functional status and comorbidity characteristics of MDD at pre-treatment baseline.

Feature	Total (n = 1008)		Escitalopram (n = 336)		Sertraline (n = 336)		Venlafaxine-XR (n = 336)	
Demographic	N	%	N	%	N	%	N	%
Gender (Female)	571	56.6	178	53.0	191	56.8	202	60.1
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age (years)	37.8	12.6	38.3	12.6	37.9	12.3	37.4	12.8
Education (years)	14.5	2.8	14.4	2.9	14.7	2.7	14.5	2.8
Race								
White	625	62.0	216	64.3	205	61.0	204	60.7
Black	167	16.6	54	16.1	61	18.2	52	15.5
Other	212	21.0	65	19.3	69	20.5	78	23.2
Unknown	4	0.4	1	0.3	1	0.3	2	0.6
Hispanic ethnicity	83	8.2	27	8.0	25	7.4	31	9.2
Social factors								
Employment								
Employed	506	50.2	187	55.7	157	46.7	162	48.2
Unemployed	66	6.5	25	7.4	20	6.0	21	6.2
Retired	43	4.3	10	3.0	19	5.7	14	4.2
Student	189	18.8	49	14.6	66	19.6	74	22.0
Other[a]	73	7.2	24	7.1	29	8.6	20	6.0
Unknown	131	13.0	41	12.2	45	13.4	45	13.4
Marital status								
Single[b]	614	60.9	195	58.0	198	58.9	221	65.8
Married/cohabiting	193	19.1	60	17.9	74	22.0	59	17.6
Divorced/separated	142	14.1	56	16.7	49	14.6	37	11.0
Widowed	17	1.7	5	1.5	3	0.9	9	2.7
Unknown	42	4.2	20	6.0	12	3.6	10	3.0
Clinical history								
Family history of MDD	232	23.0	81	24.1	77	22.9	75	22.3
First episode ≤18 years	478	47.4	154	45.8	154	45.8	170	50.6
Age at first episode (years)	22.9	12.0	23.4	12.6	23.2	11.9	22.1	11.5
Duration of MDD (years)	14.9	12.2	14.7	12.0	14.7	12.1	15.2	12.5
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Prior treatment failure	288	28.6	100	29.8	88	26.2	100	29.8
Symptom severity								
$HRSD_{17}$ score/52[c]	21.9	4.1	21.8	4.1	21.9	4.2	22.0	4.1
$QIDS\text{-}SR_{16}$ score/27[c]	14.5	3.8	14.5	4.0	14.6	3.7	14.3	3.8
DASS depression/42[c]	22.2	9.5	22.2	9.8	21.7	9.2	22.7	9.7
DASS anxiety/42[c]	8.8	6.7	8.9	6.8	8.9	6.8	8.6	6.5
DASS stress/42[c]	18.2	8.4	18.2	8.6	18.0	8.3	18.4	8.2
Functional capacity								
SOFAS/100[d]	55.9	9.1	55.7	8.9	56.4	9.1	55.6	9.3
SWLS/35[d]	11.6	5.4	11.6	5.5	11.3	5.2	11.9	5.5
WHOQoL-Physical/100[d]	51.8	14.4	52.0	14.0	51.7	15.3	51.7	14.0
WHOQoL-Psychological/100[d]	34.6	13.8	34.6	14.1	34.7	14.3	34.6	13.2
WHOQoL-Social/100[d]	38.6	19.9	38.5	19.4	39.0	19.2	38.3	21.1
WHOQoL-Environmental/100[d]	51.7	15.8	51.5	15.9	51.2	15.3	52.4	16.1
ERQ Reappraisal/7[d]	4.3	1.2	4.4	1.2	4.3	1.2	4.3	1.3
ERQ Suppression/7[d]	4.2	1.3	4.1	1.4	4.2	1.3	4.1	1.4
Illness course and comorbidity	***N***	***%***	***N***	***%***	***N***	***%***	***N***	***%***
Number of MDD episodes								
1	105	10.4	43	12.8	36	10.7	26	7.8
2	85	8.6	27	8.3	27	8.2	31	9.3
3	105	10.7	37	11.4	34	10.3	34	10.2
4	129	12.2	31	9.6	38	11.6	51	15.4
5 or more	570	57.9	186	57.4	194	59.0	190	57.2
Dysthymia	219	21.7	79	23.5	77	22.9	63	18.8
Panic disorder	85	8.4	31	9.2	26	7.7	28	8.3
Agoraphobia	74	7.3	29	8.6	23	6.8	22	6.6
Social phobia	93	9.2	31	9.2	23	6.8	39	11.6
Specific phobia	55	5.5	17	5.1	21	6.2	17	5.1
Generalized anxiety disorder	69	6.8	29	8.6	17	5.1	23	6.8
No comorbidities	636	63.1	200	59.5	212	63.1	224	66.7
Previous suicide attempt	117	11.6	38	11.3	37	11.0	42	12.5
General medical condition								
0	569	56.4	181	53.9	201	59.8	187	55.7
1	233	23.1	70	20.8	81	24.1	82	24.4
2	96	9.5	33	9.8	28	8.3	35	10.4
3	49	4.9	24	7.1	11	3.3	14	4.2

Table 1 (*continued*)

Feature	Total (n = 1008)		Escitalopram (n = 336)		Sertraline (n = 336)		Venlafaxine-XR (n = 336)	
Demographic	N	%	N	%	N	%	N	%
4	31	3.1	14	4.2	10	3.0	7	2.1
≥5	50	3.0	14	4.2	5	1.5	11	3.3
MDD recurrence								
Recurrent MDD	880	87.3	281	83.6	293	87.2	306	91.1
Non-recurrent MDD	105	10.4	43	12.8	36	10.7	26	7.7
Unknown	23	2.3	12	3.6	7	2.1	4	1.2

*p < 0.05, **p < 0.01, ***p < 0.001.
Abbreviations: DASS: Depression, Anxiety, Stress Scale (0–42); ERQ: Emotion Regulation Questionnaire (1–7); $HRSD_{17}$: 17-item Hamilton Rating Scale for Depression (0–52); MDD: Major Depressive Disorder; $QIDS\text{-}SR_{16}$: 16-item Quick Inventory of Depressive Symptomatology – Self Report (0–27); SOFAS: Social Functioning and Adjustment Scale (0–100); SWLS: Satisfaction With Life Scale (5–35); WHOQoL: World Health Organization Quality of Life, Overall score is rated from 1 to 5, and subscale scores from 0 to 100; XR: Extended Release.
[a] Includes homemaker.
[b] The category of "single" includes patients who are cohabiting but identify as single consistent with the legal definition of married versus single in the country in which testing was completed. Consistent with legal definition of country in which tested. Category of married/cohabiting comprises minimum estimation for cohabiting component.
[c] Higher scores for these scales indicate greater symptom severity.
[d] Higher scores for these scales indicate better functioning.

Questionnaire (ERQ) (Gross and John, 2003). The MINI-Plus was also used to assess course of illness (recurrent versus non-recurrent MDD) and to establish comorbid diagnoses. Comorbid diagnoses included current anxiety disorders (including diagnosis of generalized anxiety disorder, social anxiety disorder, panic disorder or agoraphobia) and dysthymia.

2.6. Symptom-derived treatment outcome measures

Primary outcome measures were obtained at the week-8 visit, following ADM treatment. Monitoring of ADM dosage, compliance, concomitant medications, and adverse events was done by telephone at day 4 and weeks 2, 4 and 6, and in person at the week 8 visit. Self-reported depressive symptom severity ($QIDS\text{-}SR_{16}$) and Frequency, Intensity and Burden of Side Effects Rating (FIBSER) (Wisniewski et al., 2006) data were obtained by web-based questionnaires at the same time points. The primary outcome was rate of response and remission to treatment (clinician-rated $HRSD_{17}$). Response rate was defined as a ≥50% decrease in severity from baseline to week 8, and remission by an $HRSD_{17}$ score ≤7. The secondary outcome was self-reported response and remission on the $QIDS\text{-}SR_{16}$, for which response rate was a ≥50% decrease in severity from baseline to week 8, and remission a score ≤5. These outcome measures are summarized in Table 2.

2.7. Functional capacity, side effects and adverse event treatment outcome measures

Secondary outcomes also included re-test on the measures of functional capacity (WHOQoL, SOFAS, SWLS, ERQ), symptom severity ($HDRS_{17}$, $QIDS_{16}$-SR, DASS), side effects (FIBSER self-report) and any adverse events. See the Supplementary Methods for details on data quality control. These outcome measures are summarized in Table 3.

2.8. Statistical analyses

Summary statistics for baseline demographic, social, clinical history, symptom, functional capacity, illness course and comorbidity data are presented as means (±SD) for continuous variables and percentages for discrete variables (Table 1). Chi-squared analysis was used to compare discrete variables, and analysis of variance to compare continuous variables, across the three treatment arms.

To test treatment outcomes as a function of medication arm at week 8, we conducted analyses that could deal with missing outcome data. We used mixed-linear models to account for time dependencies and the nested longitudinal structure of the data. To implement these models we used the PROC MIXED procedure in

Table 2
Response and Remission outcomes in MDD at 8-week post-medication follow-up.[a]

Outcome variable	Total		Escitalopram		Sertraline		Venlafaxine-XR	
	N	%	N	%	N	%	N	%
Treatment completers (n = 722)								
Clinician defined								
$HRSD_{17}$ response	443/712	62.2	141/233	60.5	163/246	66.3	139/233	59.7
$HRSD_{17}$ remission	323/712	45.4	112/233	48.1	114/246	46.3	97/233	41.6
Self-report defined								
$QIDS\text{-}SR_{16}$ response	359/674	53.3	123/221	55.7	130/234	55.6	106/219	48.4
$QIDS\text{-}SR_{16}$ remission	263/700	37.6	93/227	41.0	93/245	38.0	77/228	33.8
Patients with missing exit scores defined as not responsive and not in remission (n = 1008)								
Clinician defined								
$HRSD_{17}$ response	443/1008	43.9	141/336	42.0	163/336	48.5	139/336	41.4
$HRSD_{17}$ remission	323/1008	32.0	112/336	33.3	114/336	33.9	97/336	28.9
Self-report defined								
$QIDS\text{-}SR_{16}$ response	359/1008	35.6	123/336	36.6	130/336	38.7	106/336	31.5
$QIDS\text{-}SR_{16}$ remission	263/1008	26.1	93/336	27.7	93/336	27.7	77/336	22.9

Abbreviations: $HRSD_{17}$: 17-item Hamilton Rating Scale for Depression (0–54); MDD: Major Depressive Disorder; $QIDS\text{-}SR_{16}$: 16-item Quick Inventory of Depressive Symptomatology – Self-Rated (0–27); XR: Extended Release.
[a] Following the protocols of STAR*D, we report the % rates of response and remission using the non-missing data, since we could not include the missing data points.

Table 3
Secondary treatment outcomes in MDD at 8-week post-medication follow-up (n = 722).

Secondary outcome variable	Total		Escitalopram		Sertraline		Venlafaxine-XR	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Symptom severity change from baseline								
$HRSD_{17}$[a]	−12.2	6.5	−12.4	7.1	−12.5	6.4	−11.5	5.8
$QIDS\text{-}SR_{16}$[a]	−6.9	5.2	−7.0	5.5	−7.0	5.0	−6.6	5.0
Functional capacity change from baseline								
SOFAS/100[b]	13.7	10.4	13.6	10.3	14.3	10.8	13.2	10.2
SWLS/35[b]	4.3	6.0	4.4	6.2	4.6	6.1	4.0	5.6
WHOQoL-Physical/100[b]	12.4	15.2	13.0	15.7	12.9	15.1	11.3	15.0
WHOQoL-Psychological/100[b]	16.6	16.7	16.7	18.2	17.6	17.1	15.5	14.7
WHOQOLD-Social/100[b]	12.1	20.3	11.9	19.5	13.2	21.7	11.1	19.5
WHOQoL-Environmental/100[b]	7.8	13.8	8.0	14.0	8.1	13.7	7.4	13.7
WHOQoL-Overall/5	0.5	1.0	0.6	0.9	0.5	1.0	0.5	0.9
ERQ-Reappraisal/7[b]	0.4	1.3	0.3	1.2	0.5	1.3	0.5	1.3
ERQ-Suppression/7[b]	−0.4	1.3	−0.4	1.3	−0.5	1.2	−0.2	1.2
DASS Depression/42	−12.45	10.3	−12.78	10.8	−12.07	10.4	−12.54	9.8
DASS Anxiety/42	−3.55	6.2	−3.46	6.0	−3.99	6.6	−3.18	6.1
DASS Stress/42	−7.63	8.8	−7.54	9.3	−7.74	9.1	−7.62	8.1
Side effects for treatment completers	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Frequency								
No side effects	285	41.3	113	50.9	95	39.3	77	34.1
10–25% of the time	296	42.9	76	34.2	114	47.1	106	46.9
50–75% of the time	78	11.3	17	7.7	23	9.5	38	16.8
90–100% of the time	31	4.5	16	7.2	10	4.1	5	2.2
Intensity								
None	273	39.6	108	48.9	91	37.6	74	32.7
Minimal to mild	288	41.8	81	36.7	103	42.6	104	46.0
Moderate to marked	118	17.1	29	13.1	45	18.6	44	19.5
Severe to intolerable	10	1.50	3	1.4	3	1.2	4	1.8
Burden								
None	383	55.5	142	64.0	128	52.9	113	50.0
Minimal to mild	231	33.5	65	29.3	86	35.5	80	35.4
Moderate to marked	69	10.0	14	6.3	26	10.7	29	12.8
Severe to intolerable	7	1.0	1	0.5	2	0.8	4	1.8
Discontinuation due to intolerance	36	3.6	13	3.9	10	3.0	13	3.9
Adverse events								
Serious adverse events								
Hospitalization	6	0.6	3	0.9	0	0.0	3	0.9
Hospitalization for suicidal planning/attempt	2	0.2	1	0.3	0	0.0	1	0.3
Psychiatric hospitalization for worsening depression	–	–	–	–	–	–	–	–
Psychiatric hospitalization for other condition	–	–	–	–	–	–	–	–
Suicidal ideation without hospitalization								
Medical event without hospitalization	431	42.8	146	43.5	136	40.5	149	44.3

Abbreviations: DASS: Depression, Anxiety, Stress Scale (0–42); ERQ: Emotion Regulation Questionnaire (1–7); $HRSD_{17}$: 17-item Hamilton Rating Scale for Depression (0–54); MDD: Major Depressive Disorder; $QIDS\text{-}SR_{16}$: 16-item Quick Inventory of Depressive Symptomatology – Self-Rated (0–27); SOFAS: Social Functioning and Adjustment Scale (0–100); SWLS: Satisfaction with Life Scale (5–35); WHOQoL: World Health Organization Quality of Life, Overall score is rated from 1 to 5, and subscale scores from 0 to 100; XR: Extended Release.

[a] Negative change scores for these scales indicate improved (lessened) symptom severity.

[b] Positive change scores for these scales indicate improved functional capacity.

SAS (Version 9.3 for Windows, SAS Institute Inc., Cary, NC). This method enabled us to include non-completers as their predicted values were calculated based on the whole dataset (Fitzmaurice, 2003). In the Proc Mixed procedure we used the MIVQUE0 specification to estimate starting points (noting that MIVQUE0 is also the default option for estimating starting points in maximum likelihood and restricted maximum likelihood specifications). Because MIVQUE0 is a non-iterative method it is computationally efficient. The MIVQEU0 specification produces unbiased estimates that are invariant with respect to the fixed effects of the model and that are locally the best quadratic unbiased estimates given that the true ratio of each component to the residual error component is zero. The technique is similar to the TYPE1 specification except that the random effects are adjusted only for the fixed effects (which were the focal effects of interest in our analytic design).

The parameter estimates were set up as follows: intercepts for each participant were modeled as a random effect, and time (pre–post treatment) was modeled as a fixed effect under a repeated unstructured covariance matrix. Predictors were dummy-coded treatment arm (Escitalopram: 0/1, Sertraline: 0/1, Venlafaxine: 0/1) or SSRIs (escitalopram & sertraline) versus SNRI (venlafaxine-XR): 0/1. We first tested symptom-derived treatment outcomes, and secondly we tested "functional and side-effect treatment outcome measures". In addition, these analyses were adjusted for the covariates of site (categorical variable with 7 levels) and $HRSD_{17}$ symptom severity as a continuous variable.

A third set of analyses addressed whether pre-treatment characteristics contributed to determining which patients achieved remission, and the contribution of these characteristics differed by treatment arm. To test whether pre-treatment demographic, social, clinical history and illness course contributed to remission we used the above described mixed model in SAS, with these pre-treatment variables as predictors, and symptom-defined remission as the outcome variable. Given prior evidence, we focused on the

contribution of comorbid anxiety disorder in these mixed models. Analyses were first conducted without adjusting for covariates, and then adjusting for site, in subsequent steps.

Statistical significance for analyses was set at an alpha level of $p < 0.05$, so results must be interpreted accordingly.

3. Results

3.1. Participants

Of 1008 randomized participants, 12.4% were accrued directly from internal services at the site, 78.9% were recruited via advertisement within the network of care delivery sites and 8.7% were recruited from other sources (Supplementary Table 2).

3.2. Pre-treatment characteristics

3.2.1. Demographic and social factors

The gender distribution was 56.6% women and 43.4% men. Mean age was 37.8 ± 12.6 years (Table 2). The racial distribution reflected that of the participating countries (Supplementary Table 2). There were no significant differences in demographic or social characteristics between the three treatment arms.

3.2.2. Clinical history and symptoms

Mean age at MDD onset was about 23 years. Almost half the participants had their first episode at ≤18 years of age, over 10% reported a suicide attempt and almost 25% reported a family history (first-degree relatives) of MDD (Table 1). Participants had moderate-to-severe depression based on their average $HRSD_{17}$ and $QIDS\text{-}SR_{16}$ scores. DASS Depression scores also reflected moderate-to-severe depression severity. Participants also had moderate symptoms of generalized distress, based on their average DASS Stress scores, and mild-to-moderate symptoms of anxious arousal based on the DASS Anxiety scores (Table 1). 29% of the sample had a prior failure of treatment. These clinical and symptom characteristics did not differ significantly among the three treatment arms.

3.2.3. Functional capacity

The sample had a moderate-to-severe level of functional impairment on the SOFAS, SWLS and WHOQoL (Table 2). Quality of life was reported as especially low for psychological and social domains. Cognitive reappraisal and expressive suppression (per ERQ) were used equally as strategies for regulating positive and negative emotions (Table 2).

3.2.4. Illness course and comorbid conditions

Almost 90% of participants had at least one prior episode and more than half of the sample had five episodes or more of MDD (Table 1). Approximately one-third of participants had at least one current comorbid diagnosis, including panic disorder, agoraphobia, social phobia, specific phobia, and generalized anxiety disorder. Over 40% also had a comorbid general medical condition. The proportion of recurrent MDD and comorbidity did not differ significantly among the three treatment arms (Table 2).

3.3. Treatment outcomes

3.3.1. Treatment features

The average duration of treatment was 7.6 ± 0.8 weeks at the time of follow-up assessment (Table 1). Average daily ADM dosages were escitalopram: 12.0 ± 6.4 mg, (recommended 5–20 mg); sertraline: 61.3 ± 32.4 mg, (recommended 50–200 mg); venlafaxine-XR: 83.4 ± 38.1 mg (recommended 75–225 mg) (Table 1). Only 8% of participants used concomitant psychotropic medications, mostly anxiolytics (3.8%) and sleep aids (1.2%). Except for dosing, treatment characteristics did not significantly differ between the three treatment arms.

3.3.2. Symptom-derived treatment outcomes

Rates of response and remission reported in Fig. 2 and Table 2 were based on participants who completed the week 8 rating scale. 71.6% (722/1008) completed the full 8 weeks and at least one outcome measure at Week 8. By the $HRSD_{17}$, >60% of these participants met criteria for response at week 8, of which 45.4% were in remission. Response and remission rates did not significantly differ between the treatment arms (Fig. 2, Table 2). By the $QIDS\text{-}SR_{16}$, 53.3% of participants had responded, of which 37.6% were in remission at week 8.

3.3.3. Functional capacity outcomes

Most domains of function showed improvement on the order of one standard deviation, a clinically meaningful shift over the acute treatment phase (Fig. 3, Table 3). A similar level of improvement was observed for symptoms of depression and anxiety (Fig. 2, Table 3). None of the score changes differed significantly between the three treatment arms.

3.3.4. Side effects and adverse events

Adverse events (any medical symptom or condition occurring or worsening after the baseline visit) were reported by 44.8% (452/1008) of participants, 88.3% (399/452) of whom experienced events likely to be related to the antidepressants (Table 3). All six serious adverse events involved hospitalization, with two for active suicidal planning or attempt. Adverse and serious adverse event rates did not significantly differ across treatment arms.

Among completers at 8 weeks, according to the FIBSER, 41.3% of participants reported no side effects and 42.9% reported side effects

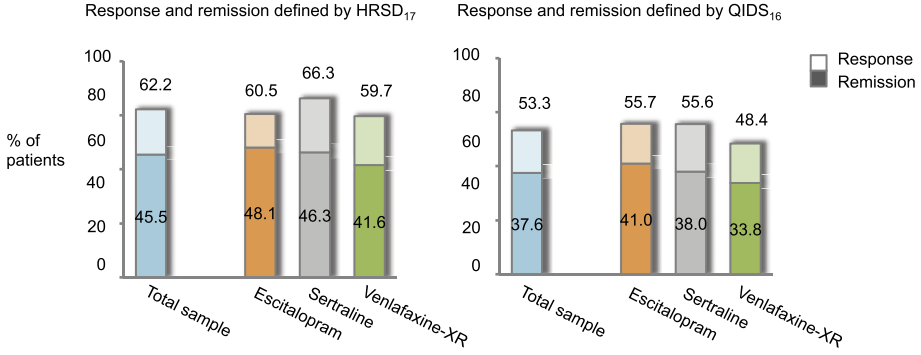

Fig. 2. Rates of response and remission following 8 weeks of antidepressant treatment.

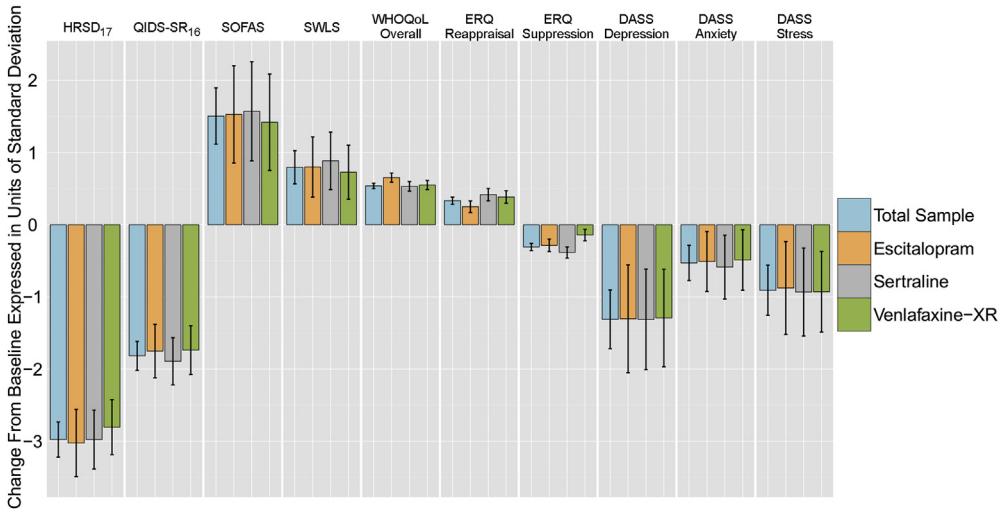

Fig. 3. Changes in symptom and functional status from baseline to week 8, expressed in units of standard deviation. The raw change scores for each measure are presented in Table 2. Abbreviations: DASS: Depression, Anxiety, Stress Scale; ERQ: Emotion Regulation Questionnaire; $HRSD_{17}$: 17-item Hamilton Rating Scale for Depression; $QIDS\text{-}SR_{16}$: 16-item Quick Inventory of Depressive Symptomatology – Self-Rated; SOFAS: Social Functioning and Adjustment Scale; SWLS: Satisfaction with Life Scale; WHOQoL: World Health Organization Quality of Life; XR: Extended Release.

occurring 10–25% of the time (Table 3). Correspondingly, side effect intensity was reported as "none" in 39.6% and minimal to mild in 41.8% of participants and side effect burden was reported as "none" in 55.5% and minimal to mild in 33.5% of participants (Table 3). Overall, 3.6% of participants discontinued due to intolerance, defined as the presence of an adverse event related to a study medication that resulted in its permanent discontinuation.

3.4. The contribution of demographic and social factors to remission

There were no differences in the rates of remission as a function of pre-treatment demographic and social factors (Table 4).

3.5. The contribution of clinical history to remission

There were also no differences in the rates of remission as a function of clinical history (Table 4).

3.6. The contribution of comorbid anxiety disorder to remission

In this sample, 41.9% of participants (n = 422/1008) met criteria for at least one comorbid anxiety diagnosis, with no significant difference among treatments (escitalopram, 39.6%; sertraline, 43.2%; venlafaxine-XR, 42.9%) (Table 1).

The only observed relationship between anxiety and outcome was an association between greater dimensional scores on the DASS anxiety subscale and lower remission rates on the $QIDS\text{-}SR_{16}$ (Fig. 4; $F(1,918) = 14.05$, $p = 0.0002$). This effect was also significant after controlling for site ($F(1,912) = 14.04$, $p = 0.0002$).

Given prior evidence for a role of anxiety in poorer remission outcomes, additional analyses were conducted to explore other potential contributing factors. First, we tested whether this relationship between anxiety severity and poorer remission might simply reflect greater depressive severity in participants with greater anxiety. We controlled for either total $HRSD_{17}$ score or DASS depression subscale scores (along with site); DASS anxiety still predicted poor remission ($HRSD_{17}$: $F(1,916) = 8.31$, $p = 0.004$; DASS depression: $F(1,916) = 4.76$, $p = 0.03$). No significant interaction was evident between medication arm and anxiety scores, (i.e., the effects of anxiety were consistent across all medications [$F < 1$, n.s.]). We also found no difference in final medication dose as a function of anxiety, or in rate of attrition (Supplemental Table 3). To examine whether effects of anxiety on remission were due to differences in side effects, we controlled for intensity, frequency and burden of side effects, along with site. Side effects did not affect the relationship of greater baseline anxiety to poor treatment outcome ($F(1,917) = 14.70$, $p = 0.0001$).

4. Discussion

The goal of this iSPOT-D study is to characterize a large international cohort of outpatients with MDD within a practical trial design, in order to identify clinically useful predictors and moderators of response to three of the most commonly used first-line antidepressant medications (ADMs). Our initial cohort of 1008 participants was treated primarily in the community. Pre-treatment results suggest that substantial functional impairments accompany moderate-to-severe. Improvements in both symptoms and functional capacity were equivalent across all three ADMs. Response rates were around 60% based on completers and were also consistent across treatment arms. Greater severity of anxious arousal symptoms was associated with lower remission rates overall, independent of depressive severity.

We first characterized the cohort on pre-treatment demographic, social, clinical history, symptom severity, functional status and comorbidity factors. Demographic and social characteristics of the iSPOT-D sample were similar to those of other large MDD outpatient samples. Participant characteristics suggest a sample broadly representative of the community of antidepressant treatment seekers, with a generally high level of education and employment despite active symptoms and functional impairment. The iSPOT-D emphasis on recruitment through advertisement and management of medication in general practice community settings may account for these characteristics. For example, the iSPOT-D sample was 56.6% women compared to 62.2% in STAR*D (Young, 2009), 68.0% in CO-MED (Rush et al., 2011), and 71.8% in naturalistic observations (Rush and Rose, 2005). This difference may reflect many factors, such as recruitment sources or differences in gender prevalence based on community versus tertiary

Table 4
Rates of remission as a function of pre-treatment demographic, social, clinical history and comorbidity factors.[a]

	Remission defined by HDRS%	Remission defined by QIDS-SR%
Gender		
Female	47.3%	36.82%
Male	42.76%	38.59%
Age		
18–30 years	47.69%	42.13%
31–50 years	48.69%	36.42%
≥51	34.25%	31.94%
Education		
Pre-High School (<9 years)	40.00%	25.00%
HS Less than College (≥9 to ≤ 12)	46.24%	30.12%
College plus (>12 years)	45.33%	40.59%
Clinical history		
Family history of MDD		
Yes	42.01%	33.54%
No	46.41%	38.81%
First episode ≤18 years		
Yes	43.62%	38.25%
No	47.40%	37.05%
Duration of MDD		
<2 years	48.46%	38.63%
≥2 years	35.10%	34.00%
Illness course and comorbidity		
Comborbid anxiety disorder		
Yes	46.67%	38.53%
No	40.76%	34.19%
General medical condition		
≥5 (reference group)	29.17%	24.00%
General medical condition <5	45.93%	38.07%
MDD recurrence		
Recurrent MDD, Yes	44.99%	37.70%
No (exclude Unknown)	51.47%	38.81%

[a] Given so few patients had a history of a previous suicide attempt we did not include this variable in the analyses.

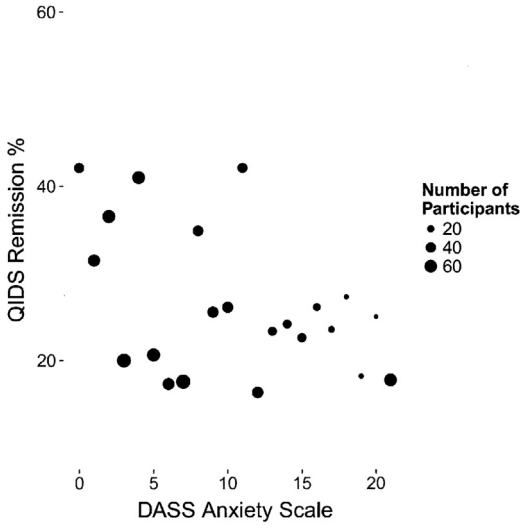

Fig. 4. Greater levels of anxiety using DASS anxiety scores predict lower remission on the secondary outcome of QIDS-SR_{16}. Abbreviations: DASS: Depression Anxiety Stress Scale; QIDS-SR_{16}: 16-item Quick Inventory of Depressive Symptomatology – Self-Rated.

care samples. Almost half (47%) of the cohort experienced their first episode of MDD prior to the age of 18 years, and a smaller proportion (23%) had a family history of MDD. This profile is consistent with the moderate-to-severe levels of depressive symptoms rated by clinicians, and endorsed by patients across the self-report measures.

We included a set of measures of functional capacity (spanning occupational and social functioning quality of life, satisfaction with life and emotion regulation), not included previously in treatment trials of MDD. Our findings suggest that MDD outpatients being treated in the community have a substantive pre-treatment level of impairment in functional capacity, which is well below the normative average. Quality of life was reported as especially low for psychological and social domains. Cognitive reappraisal and expressive suppression were used equally as strategies for regulating positive and negative emotions. It is likely that these impairments contribute to the enormous burden of illness and rates of disability associated with MDD (Whiteford et al., 2013; World Health Organization, 2012). Comorbid general medical conditions occurred with higher frequency (44%) than psychiatric comorbidities (37%); however, one third of outpatients met diagnostic criteria for an anxiety disorder. In the overall cohort, levels of anxiety severity assessed dimensionally were at mild-to-moderate levels. The rate of comorbid psychiatric disorders was lower than that for STAR*D (62%) (Rush et al., 2005), which may also reflect community sampling and the exclusion of substance dependence. The high rate of general medical comorbidities is consistent with previous reports that MDD and other chronic conditions frequently co-occur (Gaynes et al., 2005; Rush et al., 2005; Yates et al., 2004).

At the pre-treatment baseline there were no differences in demographic, social, clinical history, symptom severity, functional capacity or comorbidity factors across the three treatment arms. These findings suggest that the randomization protocol used in iSPOT-D was appropriate, and that post-treatment findings may be interpreted with confidence.

Post-treatment we observed response rates of 62%, defined by symptom improvement of ≥50% on the clinician-rated $HDRS_{17}$. The self-reported $QIDS_{16}$-SR response rates were 53.3%, which is consistent with other reports (Trivedi et al., 2006; Rush et al., 2006).

The overall rate of clinician-defined remission was 45.4% and by self-report, 37.6%. These rates of response and remission are in line with those reported in primary care settings (Yeung et al., 2012; Rush and Rose, 2005; Sicras-Mainar et al., 2012; Gates et al., 2007) and with a meta-analysis of 203 studies (second-generation antidepressants, samples of >100) published between 1987 and 2000 (Gartlehner et al., 2008). Response and remission rates of 69% and 52% respectively have been found in naturalistic studies of inpatients (Seemuller et al., 2010). Response rates did not significantly differ for treatment with escitalopram, sertraline and venlafaxine-XR. Demographic, social and clinical history factors associated with antidepressant response rates—such as gender (Young, 2009; Thiels et al., 2005), age (Morishita and Kinoshita, 2008), depression subtype (McGrath et al., 2008; Howland et al., 2008; Silverstein and Patel, 2011) and comorbidity (Howland et al., 2009; Kim et al., 2011)— also did not differ for treatments.

These findings for similar rates of response and remission across treatment arms support previous effectiveness and efficacy trials that show consistency across antidepressants (Eckert and Falissard, 2006). They depart from findings that suggest escitalopram has a higher response rate than other SSRIs and SNRIs (Kennedy et al., 2009), or that venlafaxine produces higher response and remission rates than SSRIs (including sertraline and escitalopram) (Bauer et al., 2009). Thus, while one explanation for our findings of similar outcome with each of the medications could be the relatively low average final doses for these medications in this study, prior work

has demonstrated similar responses across SSRIs and SNRIs or differences at effect sizes that we would be unlikely to detect with our sample size. Our finding of consistent rates of response across treatments reflects the outcomes following clinical treatment management in the community.

There was also a consistent improvement in secondary functional capacity and symptom severity outcomes post-treatment. Most domains of function showed improvements on the order of one standard deviation, a clinically meaningful shift over the acute treatment phase. Similarly, the degree of symptom improvement was in the order of one standard deviation. None of the score changes differed significantly between the three treatment arms.

Our third set of analyses tested whether pre-treatment characteristics contribute explaining which patients achieve remission and which patients do not. None of the pre-treatment demographic, social, clinical history or comorbidity factors contributed to differences between remitters and non-remitters. Specifically, we did not find that rates of remission differed between patients with a comorbid diagnosis of anxiety disorder and those without such comorbidity. However, dimensional degree of anxious arousal was found to contribute to remission outcomes. These findings support the clinical relevance in recognizing and quantifying the level of anxiety symptoms in patients with MDD (Fava et al., 2008). Though in this study the overall magnitude of anxiety's association with outcome was modest, it has now been consistently implicated across several studies and can be readily assessed in routine clinical care. Moreover, our data suggest that it is anxious arousal symptoms more specifically that predict outcome, and that these can be assessed readily with a brief self-report scale (unlike most prior studies, which examined anxiety using the anxiety/somatization subscale on the clinician-administered $HRSD_{17}$ scale). The effects of anxiety on remission were also not related to overall depression severity, medication dose, study completion or side effects. The similar anxiety effects in each treatment arm suggest that merely using a serotonin/norepinephrine antidepressant instead of a serotonin-only antidepressant will not improve outcome for anxious patients. Finally, these results also illustrate that anxiety is a prognostic dimension of dysfunction in depression and not a specific consequence of meeting criteria for a particular anxiety disorder. This finding carries broader implications as it supports recent efforts to disassemble psychopathology into impairments on dimensional aspects of brain function (Insel et al., 2010).

One explanation for our findings of similar outcome with each of the medications could be the relatively low average final doses for these medications in this study. However, prior work has demonstrated similar responses across SSRIs and SNRIs or differences at effect sizes that we would be unlikely to detect with our sample size. Our findings of consistent rates of response across treatments were observed for depressed patients with symptoms in the upper mild to severe range, who received standard care treatment mainly in primary care and community settings. We recognize that the efficacy of the medications may vary for each individual patient, and that for some patients response may not have been due to the medication *per se*. Meta-analyses have suggested that antidepressant efficacy may greater (relative to placebo) in depressed patients with severe symptoms (Fournier et al., 2010), although a synthesis of complete longitudinal data of published and unpublished studies suggests that there is no particular association pre-treatment symptom severity (Gibbons et al., 2012).

Limitations of this study include reliance on only three first-step ADMs, though they are commonly used in practice. Doses were lower than midrange of the recommended range, perhaps because the response and remission rates were large enough that further dose escalation was not warranted in many patients. Furthermore, since dose ranges were reflective of usual management practices and since primary care physicians prescribe about two-thirds of antidepressants (Mark et al., 2009), these ranges are an appropriate starting point for identifying predictors of outcome in real-world management settings. A review of >1000 primary care patients found that only 37.7% were prescribed full doses of medication (Gill et al., 2010). The finding that response rates were robust and did not significantly differ across treatment arms suggests that dose did not differentially impact these rates. We note that outcome assessments were not blinded, but that assessments were done by study personnel and not by treating clinicians.

In conclusion, in a broad community sample of people with depression, approximately 45% were found to remit and 60% to respond following randomization to 8 weeks of treatment with one of three commonly used antidepressants. These antidepressants had not previously been used to treat the participants' current episode of depression prior to taking part in the study. These same participants also showed acute improvements in functional capacity following treatment with one of the three antidepressants. Among the clinical characteristics of the sample, when assessed dimensionally comorbid symptoms of anxious arousal made a small contribution to poorer rates of remission.

Role of the funding source

Brain Resource Ltd is the sponsor for iSPOT-D. Brain Resource managed the operations of the study via a central management team. The academic functions of the study were managed by a publication committee and by investigators at each participating site.

Contributors

Authors AFS, EG, AJR and LMW designed the study and LMW wrote the protocol. Author LMW oversaw the academic functions across sites as the Academic Principal Investigator. Author CD coordinated the running of the study and managed the sites and data quality control. Author DM managed the data processing and quantification system. Authors RS, AE, A-MD, AJR and LMW wrote the drafts of the manuscript. Authors AG and AG designed the statistical models for the analysis. Authors AG, AG and WR undertook the statistical analyses and wrote the statistical analysis sections. All authors contributed to and have approved the final manuscript.

Conflict of interest

Dr. Saveanu has received research funding from Brain Resource.
Dr. Etkin has received research funding from Brain Resource.
Dr. Duchemin has received research funding from Brain Resource.
Dr. Goldstein has no disclosures to declare.
Dr. Gyurak has no disclosures to declare.
Dr. DeBattista has received research funding from Brain Resource, Takeda, CNS response, St Jude Medical, Aztra Zeneca, and Roche. He has served as a consultant to Genentech and Pfizer.

Dr. Schatzberg has served as a consultant to BrainCells, CeNeRx, CNS Response, Eli Lilly, Forest Labs, GSK, Jazz, Lundbeck, Merck, Neuronetics, Novadel, Novartis, Pathway Diagnostics, Pfizer, PharmaNeuroBoost, Quintiles, Sanofi-Aventis, Sunovion, Synosia, Takeda, Xytis and Wyeth. Dr. Schatzberg has equity in Amnestix, BrainCells, CeNeRx, Corcept (co-founder), Delpor, Forest, Merck, Neurocrine, Novadel, Pfizer, PharaNeuroBoost, Somaxon and Synosis, and was named an inventor on pharmacogenetic use

patents on prediction of antidepressant response. Dr. Schatzberg has also received speaking fees from GlaxoSmithKline and Roche.

Dr. Sood has received research funding from Brain Resource.

Ms. Day is employed by Brain Resource.

Dr. Palmer is employed by Brain Resource.

Mr. Rekshan is employed as a biostatistician at Brain Resource, Inc.

Dr. Gordon is the Chairman of Brain Resource.

Dr. A.J. Rush has received consulting fees from Brain Resource Ltd,,H. Eli Lilly, Lundbeck A/S, Medavante, Inc; National Institute of Drug Abuse, Santium Inc.,Takeda USA,; speaking fees from the University of California at San Diego, Hershey Penn State Medical Center, and the American Society for Clinical Psychopharmacology; royalties from Guilford Publications and the University of Texas Southwestern Medical Center; a travel grant from CINP and research support from Duke-National University of Singapore.

Dr. Williams has previously received fees as a consultant for Brain Resource Ltd and in the last 3 years and was a stockholder in Brain Resource Ltd.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpsychires.2014.12.018.

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