ORIGINAL RESEARCH

Clinical outcomes of patients with major depressive disorder treated with either duloxetine, escitalopram, fluoxetine, paroxetine, or sertraline

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Purpose: To compare treatment outcomes in patients with major depressive disorder treated with duloxetine, escitalopram, fluoxetine, paroxetine, or sertraline for up to 6 months.

Patients and methods: Data were taken from a 6-month prospective, observational study that included 1,549 major depressive disorder patients without sexual dysfunction in 12 countries. We report the overall results and those from Asian countries. Depression severity was measured using the Clinical Global Impression and the 16-item Quick Inventory of Depressive Symptomatology Self-Report ($QIDS-SR_{16}$). Clinical and functional remissions were defined as having a $QIDS-SR_{16} <6$, and as having a rating of <3 on all three Sheehan Disability Scale items and no reduced productivity, respectively. Mixed effects modeling with repeated measures analysis and generalized estimating equation models were used. Propensity scores were included in the models.

Results: The mixed effects modeling with repeated measures regression models showed that the Clinical Global Impression rating during follow-up was significantly lower in those patients treated with duloxetine compared with escitalopram (0.40, 95% CI 0.25 to 0.56); fluoxetine (0.22, 95% CI 0.05 to 0.38); paroxetine (0.38, 95% CI 0.23 to 0.54); and sertraline (0.32, 95% CI 0.16 to 0.49). The $QIDS-SR_{16}$ of duloxetine-treated patients was significantly lower than those treated with escitalopram (1.58, 95% CI 1.03 to 2.12); fluoxetine (1.48, 95% CI 0.90 to 2.06); paroxetine (1.53, 95% CI 1.00 to 2.07); and sertraline (1.19, 95% CI 0.61 to 1.78). The probability of clinical remission of the patients treated with escitalopram, fluoxetine, paroxetine, and sertraline was lower than those treated with duloxetine (OR 0.46, 95% CI 0.33 to 0.64; OR 0.42, 95% CI 0.29 to 0.61; OR 0.40, 95% CI 0.29 to 0.56; OR 0.50, 95% CI 0.35 to 0.71; respectively). The regression analysis of functional remission also showed more favorable results for duloxetine, with OR ranging from 0.43, 95% CI 0.31 to 0.60 for paroxetine to 0.49, 95% CI 0.35 to 0.70 for sertraline. The results for the Asian countries were generally consistent.

Conclusion: Duloxetine-treated patients had better 6-month outcomes in terms of depression severity and clinical and functional remission, compared with selective serotonin reuptake inhibitor-treated patients.

Keywords: treatment, observational study, health outcomes, functioning

Introduction

Major depressive disorder (MDD) is one of the main causes of disability worldwide, due to its high prevalence and associated impairment.[1] Its lifetime prevalence has been estimated at 14.6% in high-income countries and 11.1% in low- and middle-income countries.[2] Nearly two-thirds of MDD patients report severe impairment in functioning.[3] The 2010 Global Burden of Disease study showed a 37.5% burden

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increase due to MDD between 1990 and 2010.[4] The burden associated with MDD is expected to continue increasing and it is the second projected leading cause of Disability Adjusted Life Years in 2020.[5]

Antidepressant drugs remain the mainstay of treatment of individuals with an MDD. Most international guidelines[6–8] recommend selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) as first-line treatments for MDD. Both, SSRIs and SNRIs, have been proven to be effective in improving the symptoms of depression and preventing recurrences, and have better tolerability than older drugs such as the tricyclic antidepressants or the monoamine oxidase inhibitors.[6,7] However, there is limited information supporting the choice of one of these drugs over others. Many of the trials analyzing the effects of SNRIs are placebo-controlled trials and do not provide direct information on the relative effectiveness of SNRIs when compared with SSRIs. Several head-to-head comparisons between an SNRI and an SSRI have also provided discordant results. Very few studies have been able to analyze more than two antidepressants.[9] There is even less evidence regarding the comparison of the different antidepressants in usual clinical care. Accordingly, evidence on the comparative effectiveness of SSRIs and SNRIs in terms of symptom and functioning improvement is still inconclusive.[7,10,11] Some evidence, however, seems to indicate that SNRIs may be more effective than SSRIs in patients with concurrent pain and depression. Given that the profile of neurotransmitters where they act on are involved in the mechanisms of pain and, accordingly, they may specifically decrease pain.[10,12] Duloxetine,[13] a potent SNRI has been shown to improve pain, which may further help to ameliorate the symptoms of depression.[14,15] However, a specific effect in pain symptoms has not been consistently shown for the SSRIs.[16,17] Additionally, most of these evidence come from western countries, and there is a large knowledge gap with respect to other parts of the world, such as Asian countries.[18,19]

The assessment of treatment outcomes in depression has traditionally focused on the presence of mood symptoms. However, patients report a return to a normal level of functioning as more important than symptom-related outcomes.[20] Severe impairment, affecting areas such as self-care, and family, social, or occupational functioning may be present in ~60% of the MDD patients.[3] Recent studies have also shown that functional impairment may persist after the resolution of mood symptoms[21] and that persistence of functional disability may increase the risk experiencing future MDD episodes.[22–24] In spite of this, many clinical trials do not include patient functioning in assessing treatment outcomes. Evaluating MDD treatment effects without functioning assessment can be considered an unmet need, especially from the patients' perspective.

This study aims to produce evidence on the comparative effectiveness of distinct antidepressants in usual clinical practice, analyzing both clinical severity and functional impairment. Using data from a 6-month, prospective, observational study conducted mostly in Asia and Mexico, this post-hoc analysis aims to examine the comparative effectiveness of duloxetine, escitalopram, sertraline, fluoxetine, and paroxetine on clinical course and functioning in a naturalistic clinical setting in non-Western countries. Specifically, we will compare the clinical and functioning outcomes of patients treated with duloxetine with the outcomes of patients treated with escitalopram, sertraline, fluoxetine, and paroxetine. We also examine whether the comparative effectiveness of these antidepressants differs between patients with and without painful physical symptoms (PPS). Finally, since the largest proportion of patients in this study comes from Asian countries, we repeat the analyses including only those patients.

Patients and methods
Patients
This post-hoc analysis is based on data obtained from a 24-week prospective, observational study which was primarily aimed at examining treatment-emergent sexual dysfunction (TESD) and other clinical outcomes in patients with MDD. Patients were treated with either an SSRI or an SNRI. Prescription of the medication was completely at the discretion of the participating psychiatrists. The study was conducted between November 15, 2007, and November 28, 2008, at 88 sites. Of the 1,647 MDD patients who were initially enrolled, 1,549 patients were classified as "sexually active patients without sexual dysfunction at study entry" and included in the study. Patients were recruited in Asia (China [n=205, 13.2%], Hong Kong [n=18, 1.2%], Malaysia [n=33, 2.1%], the Philippines [n=113, 7.3%], Taiwan [n=199, 12.8%], Thailand [n=17, 1.1%], Singapore [n=2, 0.1%], Saudi Arabia [n=179, 11.6%], and United Arab Emirates [n=135, 8.7%]); Mexico (n=591, 38.2%); and other regions (Israel [n=9, 0.6%] and Austria [n=48, 3.1%]). This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and is consistent with the *International Conference on Harmonization Guideline for Good Clinical Practice*. Local ethical committee approval was obtained following every countries regulation. All patients provided written informed consent for participation. Supplementary

materials include the list of Ethics Committees that approved the study. Further details about the study design have been published elsewhere.[25–27]

Study population

The inclusion criteria of the study were 1) adult patients; 2) presenting within the normal course of care; 3) being diagnosed with MDD according to the International Statistical Classification of Diseases, 10th revision[28] or *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition text revision[29] criteria; 4) at least moderately depressed as assessed with the Clinical Global Impression-Severity (CGI-S) scale with a score of ≥ 4;[30] 5) initiating or switching to any available SSRI or SNRI antidepressant; 6) being sexually active with no sexual dysfunction, as defined by Arizona Sexual Experience Scale;[31] 7) not being enrolled in any other study; and 8) providing written consent. Patients were excluded if they had 1) a history of treatment-resistant depression (lack of response to two antidepressants from distinct classes at therapeutic doses for ≥ 4 weeks); 2) a past or current diagnosis of another major mental disorder (eg, schizophrenia, schizophreniform or schizoaffective disorder, bipolar disorder, dysthymia, mental retardation, or dementia); or 3) received any antidepressant within 1 week (1 month for fluoxetine [Eli Lilly and Company, Indianapolis, IN, USA]) prior to study entry, with the exception of patients receiving an ineffective treatment. Patients were followed regardless of maintaining or not the medication started at the baseline visit.

Study therapy

Patient treatment, including medication prescribed at baseline, dosage, use of concomitant medication, changes in dose or in medication, was solely at the discretion of the participating psychiatrist.

Data collection and outcome assessment

Data were collected prospectively by treating psychiatrists during visits within the normal course of care. Patient demographics and clinical history were recorded at baseline. Follow-up assessments were planned at weeks 8, 16, and 24 from the baseline visit.

The CGI-S scale and 16-item Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR$_{16}$) were used to measure clinical severity.[32] The presence of pain and its severity was assessed with the items of the Somatic Symptom Inventory (SSI) which evaluate pain (abdominal pain, lower back pain, joint pain, neck pain, pain in the heart or chest, headaches, and muscular soreness).[33] Patients were classified as those with PPS (PPS+) if they had a mean score of ≥ 2 for the seven pain-related items from the SSI, or without PPS (PPS−) if the mean score was <2.

The Sheehan Disability Scale (SDS) was used to measure patient functioning. The SDS is a brief self-report inventory with three domains of functioning, namely work/school, social life, and family life.[34] On each of them, the patient rated his/her functioning from 0 to 10. Anchor scores were 0: no impairment; 1–3: mild impairment; 4–6: moderate impairment; 7–9: marked impairment; 10: extreme impairment. The level of global functioning was determined using the sum of the three domains.

Patients were considered to be in remission from their depressive symptoms if they had a QIDS-SR$_{16}$ total score ≤ 5 at any time during the study period. This cut-off point was chosen because it represents a similar symptom severity as a rating of ≤ 7 on the Hamilton Depression Rating Scale (17 items) scale.[35] Patients who had a rating of <3 on the three subscales of the SDS[36] and who also reported no days of reduced productivity in the previous week were considered in functional remission.

The EuroQoL-5 dimensions (EQ-5D) questionnaire was used to assess patients' Quality of Life (QoL). The EQ-5D is a self-rated, generic, QoL measure that includes five items (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each of which is scored on a scale from 1 (no problems) to 3 (extreme problems). The UK population utility score was used to calculate health utilities in all countries.[37] Additionally, the EQ-5D questionnaire also includes a EuroQoL visual analog scale (EQ-VAS) on which patients were asked to rate their overall health of that day on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state), thus providing an overall "health state" score.

Statistical analysis

Additional inclusion criteria were applied in this study. First, the present analysis includes only patients who initiated duloxetine, escitalopram, fluoxetine, paroxetine, or sertraline at baseline, given that other medications were prescribed to too few patients to produce robust results. We also required patients not to have missing data on the QIDS-SR$_{16}$ score at baseline and to have at least one assessable QIDS-SR$_{16}$ score during follow-up.

Patient characteristics at baseline and outcomes at each visit by treatment were described and compared using the chi-square test (for categorical variables) and the ANOVA test (for continuous variables).

As any observational study, patients receiving different treatments may have different baseline characteristics which may influence outcomes. In order to control for this possible selection bias, two strategies were employed. First, propensity scores were calculated using multinomial logistic regression models.[38,39] These propensity scores balance the different probabilities of treatment assignment. The covariates included in these models were country (countries with few patients were grouped), age, age at first episode, gender, independent living, living with a spouse/partner, educational attainment, employment level, number of depressive episodes in previous 24 months, MDD hospitalizations in previous 24 months, prior MDD treatments/therapies in previous 24 months, body mass index, having any significant preexisting comorbidities, a positive experience in his or her sexual relations in the last week, presence of PPS, and baseline CGI-S score.

Second, regression models were fitted to compare the outcomes of the different antidepressants. The covariates included in these models were age, gender, the baseline score of the outcome variable, and CGI-S when the outcomes are quality-of-life-related. Any variables that were significantly associated with the outcome (at $p < 0.1$) in univariate analyses were also included in the model.

Mixed effects modeling with repeated measures (MMRM) analysis was used to compare the levels of CGI-S and $QIDS\text{-}SR_{16}$ during follow-up between the treatment cohorts. Generalized estimating equation (GEE) regression models were fitted to compare response, remission, and recovery. Within-patient correlation was considered to have an unstructured covariance pattern. Observations were included while the initial medication was maintained.

Duloxetine was used as a reference category in all regression models. Since duloxetine has been shown to have relatively better results when compared with other antidepressants in the presence of PPS,[40] the analyses were repeated stratifying by PPS status.

The analyses were implemented using SAS 9.4. PROC MIXED for continuous response (MMRM analyses) and binomial response (PROC GENMOD) variables, respectively.

Results

Of the 1,246 patients included, 555 (44.5%) were taking duloxetine, 184 (14.8%) escitalopram, 153 (12.3%) fluoxetine, 190 (15.2%) paroxetine, and 164 (13.2%) sertraline. Of the 1,246 patients, 79.1% (n=985) were available at 24 weeks. Retention rates were very similar among treatment cohorts, with figures ranging from 76.8% (paroxetine) to 80.4% (fluoxetine).

At baseline, there were no statistically significant differences in clinical severity, overall severity, and functioning among the treatment cohorts, as measured with the $QIDS\text{-}SR_{16}$, the CGI-S, or the SDS both in the overall sample and the Asian sample (Table 1). In the overall sample, there were differences in the presence of PPS, with patients starting duloxetine presenting those symptoms more frequently (58%) than patients receiving the other treatments (range 44%–47%). Those patients starting sertraline (36%) had a higher frequency of preexisting comorbidities (range 23%–26.8% in the other treatments).

Table 2 presents the outcomes of patients at 6 months by medication started at the baseline visit in the total sample. There were statistically significant differences in all outcomes. Mean $QIDS\text{-}SR_{16}$ scores at 24 weeks for patients who started duloxetine, escitalopram, fluoxetine, paroxetine, and sertraline were 1.97, 3.68, 3.76, 3.90, and 3.40, respectively. About 60% of the patients were in clinical remission at 24 weeks. The percentage of patients in clinical remission also varied depending on the medication started at baseline. These percentages were 65%, 55%, 55%, 52%, and 60%, for those patients who started duloxetine, escitalopram, fluoxetine, paroxetine, and sertraline at baseline, respectively. The percentage of patients achieving recovery was lower, with only 47% of the patients in recovery at 24 weeks. There were also differences among different treatment groups. The percentages of recovery were 55%, 41%, 43%, 35%, and 44% for duloxetine, escitalopram, fluoxetine, paroxetine, and sertraline, respectively.

Table 3 presents the results of the MMRM, which compares the rating of the outcome scales during follow-up adjusting for baseline differences and taking into account the probabilities of treatment initiation with a propensity score covariate. In the overall sample, patients who started duloxetine at baseline had a statistically significant lower rating on the $QIDS\text{-}SR_{16}$ depression severity score during follow-up. The greatest difference was between duloxetine and escitalopram (patients on escitalopram having a mean $QIDS\text{-}SR_{16}$ score 1.58 points higher than patients on duloxetine). The smallest difference was with sertraline (1.19 points). The results for the Asian sample were consistent with the overall results, except that there were no statistically significant differences between paroxetine and duloxetine. The analyses of the differences among cohorts in the CGI-S score during follow-up also showed statistically significant differences, favoring patients on duloxetine compared with the other

Table 1 Baseline patient characteristics by initial treatment

Baseline patient characteristics	Duloxetine	Escitalopram	Sertraline	Fluoxetine	Paroxetine	*p*-value
Overall sample						
Number (%)[a]	555 (44.5)	184 (14.8)	164 (13.2)	153 (12.3)	190 (15.2)	
Female, %	51.7	54.3	65.9	64.7	53.7	0.0031**
Age, years, mean (SD)	38.2 (10.2)	38.5 (10.8)	39.1 (10.3)	36.7 (10.4)	37.3 (11.2)	0.1539
Episode of MDD in the last 2 years, %	66.1	55.4	70.7	61.4	74.2	0.0013**
Preexisting comorbidities, %	23	26.4	36	24.3	26.8	0.0228*
Painful physical symptoms, %	58.4	47.3	47	44.4	44.4	0.0005***
CGI-S score, mean (SD)	4.5 (0.7)	4.6 (0.7)	4.5 (0.6)	4.5 (0.7)	4.6 (0.7)	0.3870
QIDS-SR$_{16}$ score, mean (SD)	14.2 (4.6)	14.5 (4.8)	14.2 (5)	13.9 (5.1)	14.8 (4.9)	0.6950
SDS total score, mean (SD)	17.4 (6.3)	18.2 (6.1)	17.4 (6.3)	16.4 (7.4)	18 (6.5)	0.2661
EQ-VAS, mean (SD)	43.4 (24.4)	39.1 (26.5)	43.6 (27.5)	40.8 (28.5)	47.3 (25.0)	0.0391**
EQ-5D utility score, mean (SD)	0.46 (0.32)	0.46 (0.32)	0.46 (0.34)	0.50 (0.32)	0.49 (0.35)	0.0807
Asian sample						
Number (%)[a]	382 (55.4)	92 (13.4)	54 (7.8)	61 (8.9)	100 (14.5)	
Female, %	46.9	50	53.7	52.5	38	0.2588
Age, years, mean (SD)	37.5 (9.8)	36.3 (9.4)	38.9 (9)	37.5 (10.8)	37.2 (11.3)	0.6217
Episode of MDD in the last 2 years, %	65.2	58.7	72.2	62.3	72	0.2739
Preexisting comorbidities, %	13.4	14.4	35.2	23.3	16	0.0009***
Painful physical symptoms, %	55.8	52.2	44.4	52.5	36.4	0.0115*
CGI-S score, mean (SD)	4.4 (0.6)	4.3 (0.5)	4.4 (0.5)	4.4 (0.6)	4.5 (0.7)	0.3144
QIDS-SR$_{16}$ score, mean (SD)	13.4 (4.5)	13.2 (4.7)	12.1 (5.1)	13.7 (4.1)	13.7 (4.5)	0.4445
SDS total score, mean (SD)	16.2 (6.1)	16.6 (6.1)	15.6 (5.8)	15.6 (6.8)	15.9 (6.3)	0.7211
EQ-VAS, mean (SD)	44.3 (23.6)	43.4 (23.7)	49.0 (28.2)	41.2 (25.8)	51.9 (22.3)	0.0107*
EQ-5D, mean (SD)	0.53 (0.30)	0.53 (0.31)	0.56 (0.31)	0.58 (0.28)	0.60 (0.31)	0.0025**

Notes: [a]These are percentages of patients in this treatment cohort compared with overall sample. Other percentages are proportion of individuals with that characteristic in the treatment cohort. *p<0.05; **p<0.01; ***p<0.001. Statistical comparisons are conducted across treatment cohorts.
Abbreviations: CGI-S, Clinical Global Impression-Severity; EQ-5D, Euro-QoL 5 dimensions; EQ-VAS, EuroQoL visual analog scale; MDD, major depressive disorder; QIDS-SR$_{16}$, 16-item Quick Inventory of Depressive Symptomatology Self-Report; SDS, Sheehan Disability Scale.

Table 2 Outcomes at 24 weeks by medication started at baseline, overall sample

Outcome scales	Duloxetine	Escitalopram	Fluoxetine	Paroxetine	Sertraline		*p*-value
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		
CGI-S	1.56 (0.88)	2.00 (1.17)	1.75 (0.94)	2.19 (1.05)	2.02 (1.08)		<0.0001
QIDS-SR$_{16}$	1.97 (2.82)	3.68 (3.34)	3.76 (3.41)	3.90 (3.33)	3.40 (3.33)		<0.0001
SDS	2.81 (4.38)	4.29 (5.46)	3.63 (4.60)	4.54 (4.60)	4.00 (4.75)		<0.0001
EQ-VAS	75.6 (34.0)	63.8 (37.0)	65.0 (35.4)	70.8 (32.2)	73.7 (27.7)		<0.0001
EQ-5D utility score	0.95 (0.11)	0.90 (0.15)	0.88 (0.17)	0.90 (0.16)	0.90 (0.15)		<0.0001
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	
Clinical remission							0.0002
No	54 (9.7)	29 (15.8)	33 (21.6)	36 (18.9)	26 (15.9)	178 (14.3)	
Yes	361 (65)	101 (54.9)	84 (54.9)	98 (51.6)	98 (59.8)	742 (59.6)	
Lost to follow-up	140 (25.2)	54 (29.3)	36 (23.5)	56 (29.5)	40 (24.4)	326 (26.2)	
Functional remission							<0.0001
No	104 (19)	54 (29.8)	44 (29.7)	64 (34.6)	49 (30.8)	315 (25.8)	
Yes	312 (57.1)	77 (42.5)	73 (49.3)	70 (37.8)	75 (47.2)	607 (49.8)	
Lost to follow-up	130 (23.8)	50 (27.6)	31 (20.9)	51 (27.6)	35 (22)	297 (24.4)	
Recovery							<0.0001
No	115 (21.1)	55 (30.4)	53 (35.8)	69 (37.3)	54 (34)	346 (28.4)	
Yes	300 (54.9)	74 (40.9)	63 (42.6)	65 (35.1)	70 (44)	572 (46.9)	
Lost to follow-up	131 (24)	52 (28.7)	32 (21.6)	51 (27.6)	35 (22)	301 (24.7)	

Note: Statistical comparisons are conducted across treatment cohorts.
Abbreviations: CGI-S, Clinical Global Impression-Severity; EQ-5D, Euro-QoL 5 dimensions; EQ-VAS, EuroQoL visual analog scale; QIDS-SR$_{16}$, 16-item Quick Inventory of Depressive Symptomatology Self-Report; SDS, Sheehan Disability Scale.

Table 3 Estimated adjusted effect of initial treatment on QIDS-SR$_{16}$, CGI-S, and SDS (MMRM model)

Outcome scales	Overall sample	Asian sample
	Coefficient (95% CI)	Coefficient (95% CI)
QIDS-SR$_{16}$		
Escitalopram versus duloxetine	1.58 (1.03 to 2.12)***	1.20 (0.51 to 1.90)**
Fluoxetine versus duloxetine	1.48 (0.90 to 2.06)***	1.55 (0.75 to 2.35)**
Paroxetine versus duloxetine	1.53 (1.00 to 2.07)***	0.61 (−0.06 to 1.29)
Sertraline versus duloxetine	1.19 (0.61 to 1.78)***	1.83 (0.88 to 2.78)**
CGI-S		
Escitalopram versus duloxetine	0.40 (0.25 to 0.56)***	0.22 (0.03 to 0.41)*
Fluoxetine versus duloxetine	0.22 (0.05 to 0.38)*	0.26 (0.04 to 0.49)*
Paroxetine versus duloxetine	0.38 (0.23 to 0.54)***	0.23 (0.05 to 0.42)*
Sertraline versus duloxetine	0.32 (0.16 to 0.49)**	0.53 (0.26 to 0.79)**
SDS		
Escitalopram versus duloxetine	1.43 (0.59 to 2.26)**	0.45 (−0.45 to 1.36)
Fluoxetine versus duloxetine	1.46 (0.58 to 2.34)*	1.47 (0.36 to 2.59)*
Paroxetine versus duloxetine	1.70 (0.89 to 2.52)***	0.39 (−0.51 to 1.29)
Sertraline versus duloxetine	1.37 (0.48 to 2.26)*	2.29 (1.11 to 3.47)**
EQ-VAS		
Escitalopram versus duloxetine	−6.49 (−10.28 to −2.70)**	−3.62 (−8.32 to 1.07)
Fluoxetine versus duloxetine	−2.03 (−6.19 to 2.12)	−4.37 (−10.22 to 1.48)
Paroxetine versus duloxetine	−5.56 (−9.29 to −1.83)*	−2.88 (−7.52 to 1.77)
Sertraline versus duloxetine	−4.58 (−8.67 to −0.50)*	−8.53 (−14.78 to −2.28)*
EQ-5D utility score		
Escitalopram versus duloxetine	−0.05 (−0.07 to −0.03)***	−0.035 (−0.063 to −0.007)*
Fluoxetine versus duloxetine	−0.07 (−0.09 to −0.04)***	−0.067 (−0.099 to −0.035)***
Paroxetine versus duloxetine	−0.04 (−0.06 to −0.02)**	−0.014 (−0.041 to 0.014)
Sertraline versus duloxetine	−0.04 (−0.06 to −0.01)*	−0.040 (−0.079 to −0.001)*

Note: *$p<0.05$; **$p<0.001$; ***$p<0.0001$.
Abbreviations: CGI-S, Clinical Global Impression-Severity; EQ-5D, Euro-QoL 5 dimensions; EQ-VAS, EuroQoL visual analog scale; MMRM, mixed effects modeling with repeated measures; QIDS-SR$_{16}$, 16-item Quick Inventory of Depressive Symptomatology Self-Report; SDS, Sheehan Disability Scale.

treatment cohorts. For the Asian sample, the differences were also statistically significant in all cases. Compared with patients receiving duloxetine, the other treatment cohorts have a higher rating on the SDS during follow-up in the overall sample, indicating that these patients had higher disability and lower functioning. In the case of the Asian sample, the statistically significant differences were with fluoxetine and sertraline, with higher functioning in the patients being treated with duloxetine. The analysis of QoL also showed that patients who started treatment with duloxetine had a greater QoL at endpoint than patients starting other treatments.

Table 4 presents the results of the GEE logistic model comparing the frequency of presenting clinical remission, functional remission, and recovery during follow-up, adjusting for baseline differences and probabilities of treatment initiation. In the overall sample, patients starting duloxetine had a higher probability of clinical and functional remission and recovery than patients being treated with other antidepressants. The odds ratios ranged from 0.38 to 0.50, indicating that the probability of remission or recovery of the patients being treated with duloxetine was approximately

twice the probability of achieving remission and recovery in the other cohorts. The results in the Asian sample were consistent, although they showed larger variability with some comparisons not reaching statistical significance.

Figure 1 presents the course of the QIDS-SR$_{16}$, the CGI-S score, and the SDS over follow-up by treatment cohort stratified by the presence of PPS at baseline. Differences between duloxetine and other treatment cohorts were mostly present in patients with PPS at baseline.

Discussion

This post-hoc analysis of data from a 6-month, prospective, observational study conducted mostly in Asia and Mexico shows that although duloxetine, escitalopram, sertraline, fluoxetine, and paroxetine improve the clinical status and functioning of patients in treatment for MDD, the effect of duloxetine is likely greater than that of the SSRIs. In terms of recovery, which includes both clinical and functional remissions, 55% of the patients on duloxetine recovered at 6 months, while the percentage for the other treatments ranged from 35% to 47%. The differences were statistically

Table 4 Estimated adjusted effect of initial treatment on clinical remission, functional remission, and recovery (GEE logistic model)[a]

Treatment outcome	Overall sample	Asian sample
	Odds ratio (95% CI)	Odds ratio (95% CI)
Clinical remission		
Escitalopram versus duloxetine	0.46 (0.33 to 0.64)***	0.63 (0.39 to 1.02)
Fluoxetine versus duloxetine	0.42 (0.29 to 0.61)***	0.37 (0.20 to 0.70)**
Paroxetine versus duloxetine	0.40 (0.29 to 0.56)***	0.56 (0.36 to 0.89)*
Sertraline versus duloxetine	0.50 (0.35 to 0.71)**	0.34 (0.17 to 0.67)**
Functional remission		
Escitalopram versus duloxetine	0.48 (0.34 to 0.67)***	0.59 (0.37 to 0.93)*
Fluoxetine versus duloxetine	0.46 (0.32 to 0.67)***	0.49 (0.25 to 0.95)*
Paroxetine versus duloxetine	0.43 (0.31 to 0.60)***	0.65 (0.39 to 1.07)
Sertraline versus duloxetine	0.49 (0.35 to 0.70)***	0.33 (0.17 to 0.62)**
Recovery		
Escitalopram versus duloxetine	0.42 (0.30 to 0.60)***	0.61 (0.37 to 1)*
Fluoxetine versus duloxetine	0.38 (0.26 to 0.55)***	0.27 (0.13 to 0.56)**
Paroxetine versus duloxetine	0.45 (0.32 to 0.64)***	0.70 (0.40 to 1.21)
Sertraline versus duloxetine	0.46 (0.33 to 0.65)***	0.39 (0.18 to 0.82)*

Notes: [a]GEE logistic regression model adjusted for baseline covariates. *$p<0.05$; **$p<0.01$; ***$p<0.001$.
Abbreviation: GEE, generalized estimating equation.

significant in all cases, even after adjusting for baseline differences among the treatment cohorts and different probabilities of treatment initiation. Previous analyses from this study which compared duloxetine with the pooled SSRI group showed consistent results.[41–43] These differences between duloxetine and the SSRIs seem to be mostly driven by patients with PPS at study entry. This is the first study comparing the recovery rates for all these antidepressants.

These results add to the current debate on the relative effectiveness of SSRIs versus SNRIs. A Cochrane review analyzing the efficacy of duloxetine in patients with depression conducted some years ago concluded that duloxetine did not seem to provide a significant advantage in efficacy over other antidepressive agents for the acute-phase treatment of major depression.[11] However, there has been recent evidence that supports a relative advantage of duloxetine versus other antidepressants. A reanalysis of data from seven clinical trials that studied the effects of duloxetine, SSRIs, and placebo which included more than 1,800 patients found that while both duloxetine and SSRIs were significantly better than placebo in patients who were placebo-non remitters, only duloxetine was significantly different from placebo in placebo-remitters.[44] Even more recently, Chekroud et al[45] revaluated the efficacy of antidepressant treatments using data from several clinical trials, including the STAR*D and the CO-MED trials (The ClinicalTrials.gov Identifier for these clinical trials are NCT00021528 and NCT00590863, respectively). They analyzed the efficacy of antidepressants on empirically defined groups of symptoms, namely core emotional symptoms, sleep and atypical symptoms, and found that high-dose duloxetine outperformed escitalopram in treating core emotional symptoms.

Differences between SSRIs and SNRIs, particularly duloxetine, seem to be driven by a greater effectiveness of SNRIs in patients with PPS or higher clinical severity. Thase et al[46] found that, despite comparable overall effectiveness of duloxetine and two SSRIs (fluoxetine and paroxetine) in patients with depression, when the analyses were restricted to patients with moderate-to-severe depression, duloxetine-treated patients experienced a higher remission rate than those treated with the two SSRIs. Kuga et al,[54] using data from an observational study conducted in Japan, analyzed the effectiveness of five antidepressants, duloxetine and four SSRIs (escitalopram, sertraline, paroxetine, and fluvoxamine). They found that treatment with duloxetine was superior to SSRIs on most outcome measures in patients with higher PPS at baseline and in patients with more severe baseline depression. Additionally, a 12-week pragmatic randomized clinical trial comparing the effectiveness of duloxetine versus genetic SSRIs found that improvement at 12 weeks in pain symptoms was greater in patients being treated with duloxetine than with SSRIs.[47] Mancini et al[55] reported that the greater improvement in functioning in patients treated with duloxetine versus placebo is mediated by its effects on emotional and painful physical symptoms.

Strengths

This study has found advantages of duloxetine not only in improving the mood symptoms but also in improving patient functioning. Previous studies have also found a greater
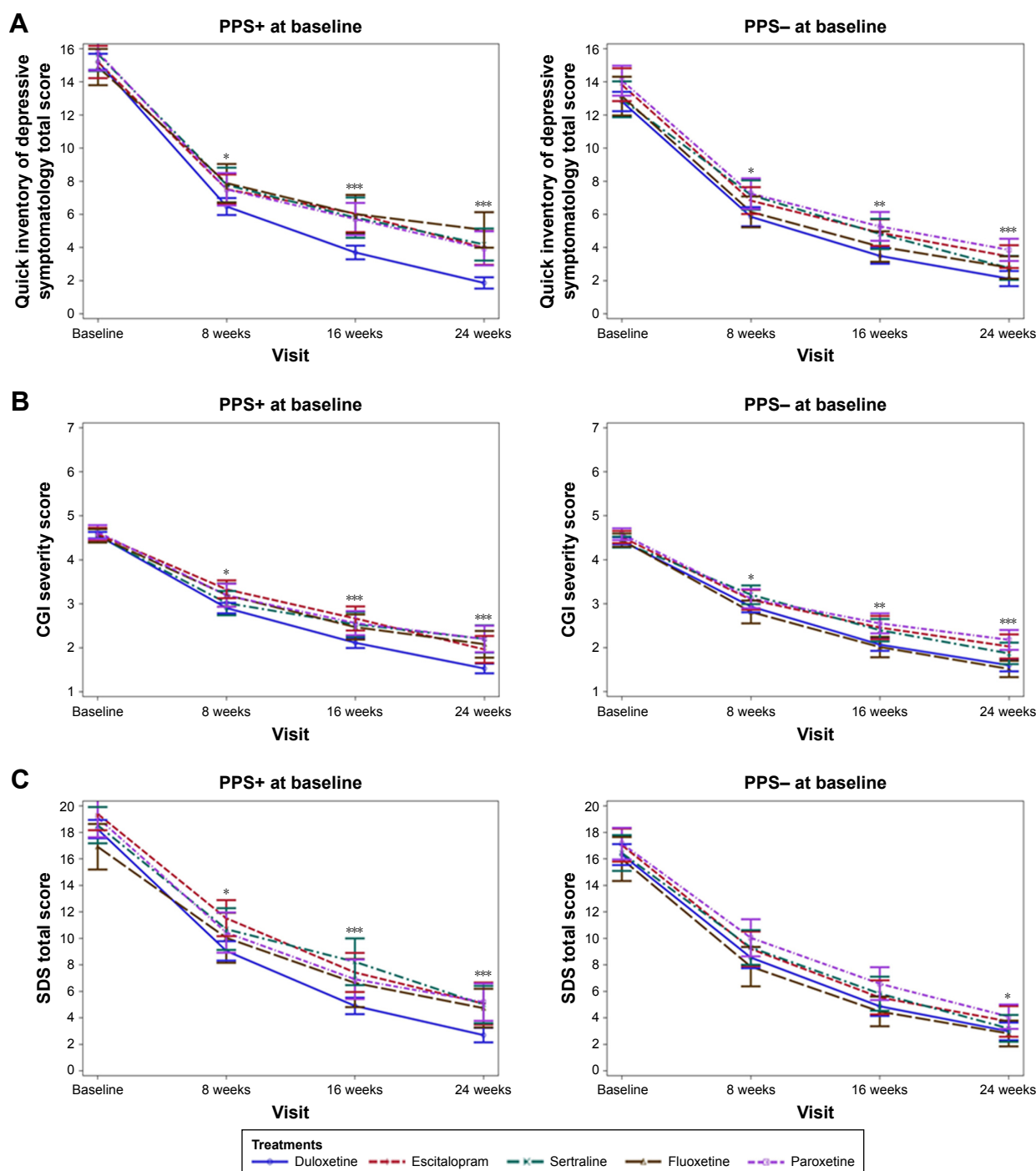
Figure 1 Change in (**A**) QIDS-SR$_{16}$, (**B**) CGI-S, and (**C**) SDS over follow-up by treatment and PPS status at baseline.
Notes: *$p<0.05$; **$p<0.001$; ***$p<0.0001$. Statistical comparisons are conducted across treatment cohorts.
Abbreviations: CGI-S, Clinical Global Impression-Severity; PPS, painful physical symptoms; QIDS-SR$_{16}$, 16-item Quick Inventory of Depressive Symptomatology Self-Report; SDS, Sheehan Disability Scale.

improvement in functioning in patients taking duloxetine. For example, the 12-week pragmatic randomized clinical trial comparing the effectiveness of duloxetine versus genetic SSRIs described above reported that significantly greater benefit for duloxetine compared with SSRIs was demonstrated on measures of functioning.[47] In a single-arm,

open-label study analyzing the effects of switching to duloxetine, Sheehan et al[48] found relevant improvement in functioning. Furthermore, to evaluate the effects of duloxetine on functioning in general MDD patients, two clinical trials with similar protocols and comparable patient populations were analyzed.[49] Duloxetine was superior compared with

placebo in improving functioning in one trial but not in the other one, although it narrowly missed statistical significance in the latter (p=0.051).

QoL informs on the patients' evaluation of their health status.[50,51] Treatments that improve QoL produce improvements in subjective patient well-being. Accordingly, QoL is increasingly being considered as a relevant outcome measure as it evaluates the patient perspective.[52] Our results indicate that the relative advantages in improvement of mood and functioning symptoms of duloxetine versus each of the SSRIs translate into improvements in patient's self-perceived health status.

As the data from Asian countries are scarce, we repeated the analyses with the cohort of patients coming from Asian countries. The results were highly consistent, despite showing greater variability in the estimates, probably due to the smaller sample size.

Limitations

These results should be interpreted in the context of the following study limitations. First, due to the observational design of this study, our findings do not imply causal relationships. Although we employed statistical modeling techniques to limit potential sources of bias between treatment groups at study entry and the different probabilities of receiving each of the treatments, the statistical techniques used may not completely eliminate the impact of imbalances between treatment groups. Second, the primary objective of this observational study was to assess the frequency of TESD in the treatment of MDD. Sexual dysfunction has been reported to be two to three times more prevalent in patients with depression compared with the general population.[53] Our study included only those patients who were sexually active without sexual dysfunction at baseline, and thus our findings may not be immediately generalizable to patients with MDD as a whole. Future research is warranted to determine whether these findings can be replicated in MDD patients not meeting our inclusion/exclusion criteria. Finally, although more than one thousand patients from Asia were included in this observational study, they may not be representative of patients with MDD in the region as a whole.

Conclusion

Patients treated with duloxetine achieved better clinical outcomes in terms of depression severity and greater functioning during a 6-month follow-up than patients being treated with escitalopram, sertraline, fluoxetine, and paroxetine. Similar results were obtained for the overall sample and for the subgroup of patients from Asian countries. The superiority of duloxetine over SSRIs on QoL outcomes appeared to be more pronounced in patients with PPS than in patients without such symptoms at baseline. However, our study included only those patients who were sexually active without sexual dysfunction at baseline, and therefore these findings may not be immediately generalizable to patients with MDD as a whole.

Acknowledgment

Disclosure

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Supplementary materials
The list of Ethical Review Board (ERB) for the B1J-MC-B019 observational study

AUSTRIA

Ethikkommission für das Bundesland Salzburg

CHINA

ERB of First Medical College of Haerbin University
ERB of People Hospital of Wuhan University
ERB of Second Hospital of Soochow University
ERB of Shandong Mental Health Center
ERB of Sixth University of Beijing University
ERB of Shanghai Mental Health Center
ERB of Guangzhou First People Hospital
ERB of Beijing Anding Hospital of Capital Medical University

HONG KONG

Institutional Review Board of the University of Hong Kong/ Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB)

ISRAEL

Shalvata Hospital ERB
Sheba M.C. ERB
Rambam M.C. ERB
Abarbanel Hospital ERB
Soroka M.C. ERB

MALAYSIA

Medical Ethics Committee, Universiti Malaya Medical Centre

MEXICO

Mexico Centre for Clinical Research S.A. de C.V.

PHILIPPINES

Makati Medical Institutional Review Board, Makati, Luzon
The Medical City Institutional Review Board, Ortigas Avenue, Pasig City, Metro Manila
St Luke's Institutional Ethics Review Committee, Quezon City, Luzon

SAUDI ARABIA

Medicare Specialist Clinics, Riyadh

SINGAPORE

NHG Domain Specific Review Board

TAIWAN

Join Institutional review board, Taipei
National Taiwan University Hospital (NTUH) Research Ethics Committee (REC), Taipei
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THAILAND

Srithanya Hospital, Nonthaburi

UNITED ARAB EMIRATES

Psychiatry Hospital Abu Dhabi, Abu Dhabi