Switching to Duloxetine From Selective Serotonin Reuptake Inhibitor Antidepressants: A Multicenter Trial Comparing 2 Switching Techniques

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Objective: To compare 2 methods of switching selective serotonin reuptake inhibitor (SSRI) nonresponders or partial responders to duloxetine.

Method: Adult outpatients with DSM-IV major depressive disorder, a Hamilton Rating Scale for Depression ($HAM\text{-}D_{17}$) total score of ≥ 15, and a Clinical Global Impressions-Severity of Illness score of ≥ 3 despite at least 6 weeks of SSRI treatment were randomly assigned to either abrupt discontinuation of SSRI immediately followed by initiation of duloxetine (direct switch [DS]; N = 183) or tapered discontinuation of SSRI over 2 weeks and simultaneous administration of duloxetine (start-taper switch [STS]; N = 185). Efficacy, safety, and tolerability outcomes associated with these 2 switch methods were compared following switch and after 10 weeks of duloxetine treatment. The study was conducted from August 2004 to March 2006.

Results: There was a significant improvement in depressive symptom severity in both switch groups as measured by mean change in $HAM\text{-}D_{17}$ total score ($p \leq .001$), but no difference between the switch groups (–10.23 DS vs. –10.49 STS). Criteria for noninferiority of the DS group to the STS group, which was the primary objective of the study, were met. Response rates (54.4% DS vs. 59.6% STS), remission rates (35.7% DS vs. 37.2% STS), and other secondary outcome measures were similar for both switch groups. Few patients discontinued the study due to adverse events (6.6% DS vs. 3.8% STS). Headache, dry mouth, and nausea were the most frequently reported adverse events in both switch groups.

Conclusions: Switch to duloxetine was associated with significant improvements in both emotional and painful physical symptoms of depression and was well tolerated and safe, regardless of which of the switch methods was used.

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Suboptimal response of patients with depression to antidepressant medication is a common clinical scenario. It has been estimated that only 50% to 60% of patients respond to their initial antidepressant monotherapy[1,2] and less than a third of patients achieve full remission of their depressive symptoms.[3,4] Aside from the burden that residual depressive symptoms place on patients, their families, and society as a whole, such symptoms also have prognostic implications, being associated with a significantly increased risk of relapse and suicide[5–7] as well as decreased quality of life and global functioning.[8] For this reason, the goal of therapy must be remission rather than just a degree of clinical response.[9]

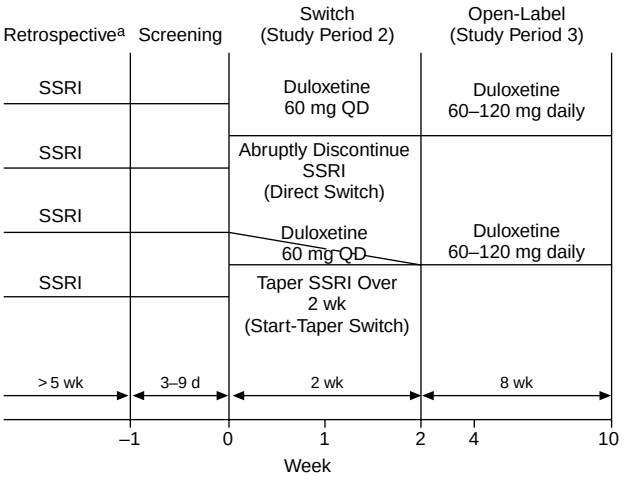
In general, patients presenting with an episode of depression are treated initially with antidepressant monotherapy, often selective serotonin reuptake inhibitors (SSRIs). In the event of suboptimal treatment response, a number of possible approaches can be employed. Aside from making all possible efforts to ensure that a patient has indeed been taking the prescribed drug (which may often not be the case), the simplest strategy is to initially maintain patients on their antidepressant medication at the starting dose, on the basis that some patients will, given more time, eventually respond.[10] A more common strategy is to increase the antidepressant dose. There is certainly a theoretical basis to support this strategy for some antidepressants for which there is a wide interindividual variation in plasma drug levels, such as duloxetine,[11] but interestingly, there are relatively few published data that unequivocally demonstrate the efficacy of

higher antidepressant doses when lower doses have failed.[12,13] Many of the published treatment guidelines nevertheless suggest dose increase as a first-line strategy for suboptimal response.[14] A further possible strategy following suboptimal response is to augment ongoing antidepressant therapy with 1 or more other agents. Augmentation is often reserved for cases in which other simpler strategies have failed. Lithium, certain antipsychotics, triiodothyronine, and buspirone are just some of the augmentation agents employed, and the evidence base to underpin augmentation with these and other agents ranges from strong to nonexistent.[15] Another commonly employed strategy, and the subject of this article, is to switch the patient to an alternative antidepressant, either within the same therapeutic class or within another therapeutic class.[16–18]

While there are a number of published studies and reviews (e.g., Nelson[19]) examining outcomes following within-class and cross-class antidepressant switch, it is perhaps surprising that despite switch being such a common clinical scenario, there are few published data to guide clinicians on the best method of switching from one antidepressant to another from a practical perspective. A number of treatment guidelines do make switching recommendations based on a combination of published data (where available) and good clinical practice.[20] A variety of switching methods can be employed, some of which have been studied in clinical trials. Possible switching methods include direct or immediate switch,[21–23] variable-duration downward titration of the drug to be discontinued followed by a drug-free "washout" period and then initiation of the new antidepressant,[24] cross-taper switch (gradual down-titration of the drug to be discontinued with simultaneous gradual up-titration of the new agent), and start-taper switch (gradual down-titration of the drug to be discontinued with simultaneous initiation of the new agent at the full starting dose). In some cases, the most appropriate switch method will clearly be dictated by the antidepressant being taken prior to the switch, or the antidepressant that is to be taken following the switch. For example, the combination of a monoamine oxidase inhibitor and a serotonergic antidepressant within another therapeutic class would expose the patient to a real risk of serotonin syndrome, so a substantial washout period between drugs is highly advisable in such circumstances.[25] For many drugs that have a more benign profile from the perspective of drug-drug interactions, however, the clinician is left with a need to minimize interruption of antidepressant treatment while having few published data upon which to make an evidence-based decision on how best to switch.

Duloxetine is a dual reuptake inhibitor of serotonin and norepinephrine (SNRI) that has been approved for the treatment of major depressive disorder (MDD) and the management of diabetic peripheral neuropathic pain in the United States and other geographies, including Europe. As previously stated, despite the fact that switch from one antidepressant to another is a common clinical scenario, there are few actual data to guide clinicians on the relative merits of different switching techniques. The objective of this study was to compare the efficacy, safety, and tolerability outcomes associated with 2 different methods of switching SSRI nonresponders or partial responders to duloxetine.

Figure 1. Study Design



[a]Patients taking any SSRI (at any licensed dose) at study entry.
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

METHOD

Study Design

Our study was a multicenter, open-label, randomized trial conducted in 4 European countries (Spain, France, Italy, and the United Kingdom). The study was conducted at 33 centers, and all investigators were psychiatrists. The investigators at each site were responsible for efficacy ratings and for the safety of patients. All the investigators received study-specific training from the sponsor. Key aspects of the study design are shown in Figure 1. The study included 4 study periods.

Study period 1 was a 3- to 9-day screening phase designed to determine whether patients met all of the inclusion criteria and none of the exclusion criteria. All patients were SSRI nonresponders or partial responders, and they continued to take their SSRI during the screening phase. Study period 2 was the switch period, in which eligible patients were randomly assigned to switch to duloxetine via either direct switch (DS) or start-taper switch (STS) methods. Patients assigned to the DS treatment group had their SSRI antidepressant abruptly discontinued on the day of randomization, and duloxetine was then initiated at a dose of 60 mg/day on the following day. Patients assigned to the STS treatment group had their SSRI antidepressant tapered down over a 2-week period, while simultaneously

initiating duloxetine at a dose of 60 mg/day, resulting in a 2-week overlap between SSRI and duloxetine treatment. Due to the enormous number of possible SSRI and dose permutations at study entry, study investigators were instructed to use their clinical judgment to devise an appropriate 2-week SSRI down-titration regimen for patients in the STS group. Guidance was provided to investigators within the study protocol, stating that the SSRI dose should be reduced to approximately half the entry dose after 1 week of the SSRI taper and to zero after 2 weeks. Study period 3 was an 8-week open-label treatment phase during which the duloxetine dose could be increased from 60 to 90 mg/day, and thereafter to a maximum of 120 mg/day at the discretion of the investigator and on the basis of clinical need. Study period 4 was an optional 2- to 3-week taper phase during which patients completing the study or discontinuing the study after at least 2 weeks of duloxetine treatment could, if the investigator wished, be gradually tapered off study drug. Patients taking duloxetine at a dose of 60 mg/day at taper phase entry received 30 mg/day of duloxetine for a week and then no study drug for the following week. Patients taking duloxetine at a dose of 90 or 120 mg/day at taper phase entry received 60 mg/day of duloxetine for a week, followed by 30 mg/day for a week, and then no study drug for a further week.

The duration of the enrollment of patients into the study was 16 months, and the study was conducted from August 2004 to March 2006. The study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by ethics review boards covering each site. All patients provided written informed consent prior to undertaking any study procedure. This study was sponsored by Eli Lilly and Company (clinical trial registration identifier NCT00191932).

Patients

Study participants were male and female outpatients of ≥ 18 years of age who, in the opinion of the investigators, met diagnostic criteria for MDD as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV).[26] At baseline, all patients also were required to have a Hamilton Rating Scale for Depression ($HAM\text{-}D_{17}$)[27,28] total score of ≥ 15 and a Clinical Global Impressions-Severity of Illness scale (CGI-S)[29] score of ≥ 3, and had to be taking an SSRI antidepressant at a dose licensed for the treatment of depression, with a total duration of treatment with that SSRI of no less than 6 weeks. Reasons for study exclusion included the following: current primary Axis I diagnosis other than MDD, including but not limited to dysthymia; previous diagnosis of bipolar disorder, schizophrenia, or other psychotic disorder; lack of response of the current episode of depression to an SNRI at a clinically appropriate dose for a minimum of 4 weeks; serious medical illness or clinically significant laboratory abnormalities; and use of an excluded concomitant medication. Patients were not allowed to take other antidepressants during the study. They were also not permitted to take certain other centrally acting medications such as antipsychotics, antimanic agents, and antimigraine drugs. Benzodiazepines and hypnotics were permitted based upon the investigator's opinion of need.

Efficacy Measures

Primary. The primary objective of the study was to test the hypothesis that antidepressant efficacy following abrupt discontinuation of an SSRI antidepressant and simultaneous initiation of duloxetine at a dose of 60 to 120 mg daily (direct switch) is noninferior to antidepressant efficacy following tapered discontinuation of an SSRI antidepressant and simultaneous administration of duloxetine at a dose of 60 to 120 mg daily (start-taper switch), as measured by mean change from baseline to endpoint on the $HAM\text{-}D_{17}$[27,28] total score, during 10 weeks of treatment in outpatients with MDD who had not responded adequately to antidepressant treatment for their current episode of depression.

The $HAM\text{-}D_{17}$ was used to assess the severity of depressive symptoms during the course of the study. The $HAM\text{-}D_{17}$ total score ranges from 0 (not at all depressed) to 52 (most severely depressed).

Secondary. Secondary outcome measures included response rates (defined as the proportion of patients with a ≥ 50% reduction in $HAM\text{-}D_{17}$ total score from baseline to endpoint) and remission rates (defined as the proportion of patients achieving a $HAM\text{-}D_{17}$ total score of ≤ 7 at endpoint). Global benefit-risk assessment was included as a composite measure of benefit (defined as remission at endpoint) and risk (defined by 4 categories: no spontaneous treatment-emergent adverse events (TEAEs), mild or moderate TEAEs, severe TEAEs, and discontinuation with a reason of self-reported AE).[30] The CGI-S,[29] a physician-rated scale for the assessment of severity of illness (rated on a scale of 1 [normal, not at all ill] to 7 [among the most extremely ill patients]), and the Patient's Global Impressions of Improvement Scale,[29] a patient-rated instrument that measures the improvement of the patient's symptoms (rated on a scale of 1 [very much improved] via 4 [no change] to 7 [very much worse]), were also included. Visual Analog Scales (VAS) for Pain were used to assess the experience of overall pain, headache, back pain, shoulder pain, pain interference with daily activities, and proportion of the day with pain.[31] The EuroQol Questionnaire (EQ-5D)[32] (health state value and VAS for patient's health state today) and the Symptom Questionnaire-Somatic Subscale (SQ-SS)[33] were used to assess health outcomes, quality of life, and somatic symptoms. The 36-item Short Form Health Survey also was used to assess the patient's general quality of life.[34] A single-item VAS for Patient Satisfaction With Medication (0–100 mm; 0 = very dissatisfied, 100 = very satisfied)

was used to assess patients' subjective experience of switching to duloxetine.

Safety and Tolerability Measures

Safety and tolerability were assessed via the collection of spontaneously reported TEAEs during the study. Adverse events and vital signs (including blood pressure and heart rate) were collected at study baseline and at each study visit. Study site personnel were required to report any serious adverse events as well as all discontinuations due to adverse events. Urinalysis was conducted at baseline, and blood draws for laboratory tests including blood chemistry and hematology occurred at baseline and at endpoint.

Statistical Analyses

The primary outcome of the study was change between baseline and the 10-week endpoint (last-observation-carried-forward [LOCF] analysis) in the HAM-D_{17} score, and the sample size for the study was planned based upon this variable. Approximately 360 patients were to be randomly assigned to either the direct switch or the start-taper switch treatment group in a 1:1 ratio. With 180 patients per arm, and assuming that the direct switch group would have a slightly better response than the start-taper switch treatment group (by 0.5 points), it was anticipated that there would be 79% power to demonstrate the noninferiority of the direct switch compared with the start-taper switch using a 1-sided 90% confidence interval for the difference between the group mean changes, a common standard deviation of 7 points, and an equivalence limit ("delta") of 1.15 points and allowing for up to 10% of patients discontinuing the study without providing postbaseline efficacy data. The choice of delta was made using data from earlier duloxetine studies that indicated an overall mean difference in HAM-D_{17} total score improvement between duloxetine and placebo of about 2.3 points. Therefore, 1.15 points represents half of the advantage of duloxetine over placebo, which is in accordance with the commonly accepted standard that delta should be between one third and one half of the advantage of the active comparator over placebo.

An intent-to-treat principle was applied in all efficacy and safety analyses, meaning that all randomly assigned patients were included in the analyses in the groups to which they were assigned by random allocation even if they did not follow the protocol.

Change between baseline and the 10-week endpoint in the HAM-D_{17} score was analyzed using an analysis of covariance (ANCOVA) model including treatment group, baseline HAM-D_{17} total, and country, and the upper bound of the 90% 1-sided confidence interval for the difference in mean change between the DS and STS groups was compared to the prespecified value of 1.15 for the noninferiority test. For the secondary continuous efficacy variables, the same methodology was used, but 2-sided 95% confidence intervals were reported. Additionally, a mixed-effects model repeated measures analysis was performed using all observations collected over the study period.

Response and remission rates on the HAM-D_{17} were compared between the treatment groups using Cochran-Mantel-Haenszel tests controlling for country. In all comparisons in which baseline and endpoint were used, baseline refers to the last nonmissing observation at or before the randomization visit and endpoint to the last nonmissing observation during the 10-week treatment period.

Fisher exact test was used to compare the groups with respect to safety variables such as adverse events and discontinuation rates. For efficacy and safety analyses, treatment-group differences with a 2-sided significance level of $\leq .05$ were deemed to be statistically significant.

The results of 2 subgroup analyses are also reported here. The patients were grouped into those who received a low dose of SSRI before entering the study and those who received a high dose. Patients who received trazodone were omitted from this analysis. The second subgroup analysis divided the patients into those who had received the SSRI for less than 26 weeks and those who had received it for 26 weeks or longer. The effect of each subgroup on changes in HAM-D_{17} and VAS for Pain over the study period was investigated by including terms for the subgroup and for the subgroup-by-treatment interaction in the ANCOVA model described above.

RESULTS

Demographics and Clinical Characteristics

Thirty-one patients were excluded from the study at the screening stage, with the most common reason being a failure to meet protocol entry criteria. A total of 368 outpatients were randomly assigned to either DS (N = 183) or STS (N = 185) treatment groups. The baseline demographics and clinical characteristics of patients were not significantly different between the 2 switch groups (Table 1). Most patients were female, were white, and had experienced previous episodes of depression. Mean baseline depressive symptoms and overall disease severity, as measured by the HAM-D_{17} and CGI-S rating scales, respectively, considerably exceeded the thresholds for study entry, and patients also had significant levels of pain at baseline as evidenced by mean scores of greater than 30 mm on all 6 VAS pain scales.

Information regarding the SSRIs being taken by patients at study entry is shown in Table 2. In summary, more patients were taking paroxetine than any other SSRI at study entry, followed by (in descending order of frequency) citalopram, fluoxetine, sertraline, and escitalopram. Only 4 fluvoxamine-treated patients were included

Table 1. Baseline Demographics and Psychiatric Characteristics of All Patients Randomly Assigned to Treatment

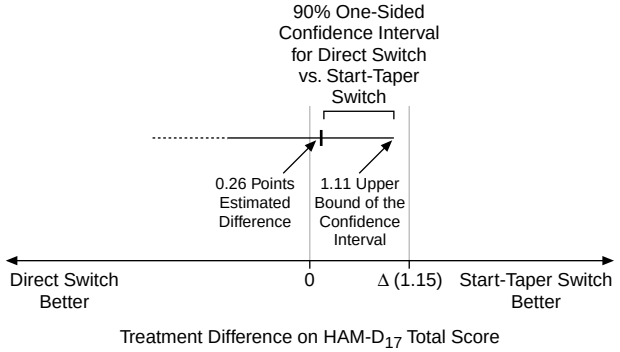
Characteristic	Direct Switch (N = 183)	Start-Taper Switch (N = 185)
Gender, female, N (%)	141 (77.0)	142 (76.8)
Origin, white, N (%)	183 (100)	183 (98.9)
Age, mean (SD), y	49.5 (12.5)	48.6 (13.1)
Patients with previous MDD episode, N (%)[a]	142 (78.5)	131 (71.2)
Duration of current MDD episode, wk		
Mean (SD)	26.4 (23.8)	38.0 (55.0)
Median	20.0	23.5
HAM-D_{17} total score, mean (SD)	21.3 (3.6)	21.5 (3.9)
CGI-S score, mean (SD)	4.2 (0.7)	4.2 (0.7)
VAS for Pain, mean (SD), mm		
Overall pain	45.4 (29.6)	45.9 (29.9)
Headache	38.6 (31.8)	36.5 (32.2)
Back pain	41.2 (33.3)	40.1 (33.0)
Shoulder pain	37.5 (33.0)	37.0 (34.2)
Interference with daily activities	45.8 (32.2)	46.5 (32.7)
Time in pain while awake	48.0 (32.3)	49.4 (32.6)

[a]Data are missing for 2 patients in the direct switch group and 1 patient in the start-taper switch group
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D_{17} = 17-item Hamilton Rating Scale for Depression, MDD = major depressive disorder, VAS = Visual Analog Scale.

Table 2. Characteristics of Selective Serotonin Reuptake Inhibitor (SSRI) Use at Baseline Including Dose and Duration of Treatment

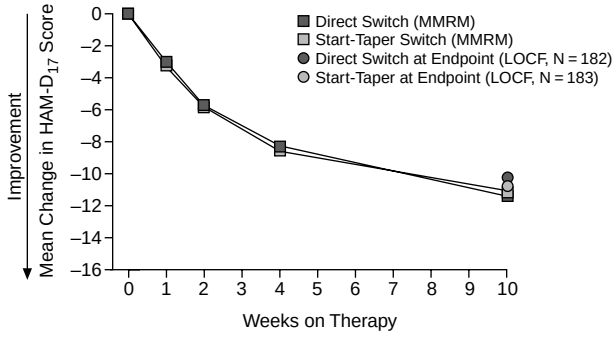
	Direct Switch			Start-Taper Switch		
SSRI	N (%)	Mean Dose (mg)	Median Duration (wk)	N (%)	Mean Dose (mg)	Median Duration (wk)
Citalopram	34 (18.6)	31.2	18.1	41 (22.2)	28.4	20.7
Escitalopram	25 (13.7)	15.6	18.1	24 (13.0)	15.8	22.9
Fluoxetine	40 (21.9)	26.3	30.1	30 (16.2)	25.0	37.6
Fluvoxamine	3 (1.6)	116.7	28.1	1 (0.5)	100.0	85.1
Paroxetine	48 (26.2)	28.1	38.7	52 (28.1)	27.1	21.4
Sertraline	32 (17.5)	96.1	46.6	36 (19.5)	94.4	28.4
Overall	…	…	24.1	…	…	23.4

Figure 2. Noninferiority of Direct Switch as Compared With Start-Taper Switch in the Primary Efficacy Measure[a]



[a]Change from baseline to endpoint in HAM-D_{17} total score: direct switch, –10.23; start-taper switch, –10.49.
Abbreviation: HAM-D_{17} = 17-item Hamilton Rating Scale for Depression.

Figure 3. Time Course of Improvement in Mean Change of HAM-D_{17} Total Score for Both Switch Groups[a]



[a]No statistically significant difference between treatment groups at any time (repeated-measures analysis of variance).
Abbreviations: HAM-D_{17} = 17-item Hamilton Rating Scale for Depression, LOCF = last observation carried forward, MMRM = mixed-effects model repeated measures.

in the study, and 2 trazodone patients were enrolled. Median duration of SSRI treatment prior to study entry was considerably longer than the 6-week minimum specified in the study protocol (24.1 weeks in the DS group and 23.4 weeks in the STS group), and SSRI dose at study entry varied across the respective dose ranges. Patients with a longer duration of SSRI treatment at study entry (≥ 26 weeks) tended to be slightly older, be female, and have at least 1 previous episode of depression. Patients taking a higher SSRI dose at the time of study entry also tended to be older and had a longer duration of SSRI treatment at study entry.

Patient Disposition

Of those patients randomly assigned, a total of 154 (84.2%) patients in the DS group and 160 (86.5%) patients in the STS group completed the study. The most frequently reported reasons for discontinuation were patient decision (7.1% DS vs. 5.9% STS; p = .678) and adverse event (6.6% DS vs. 3.8% STS; p = .248). There were no significant differences between the 2 switch groups in the proportions of patients who discontinued overall or for any particular reason.

Dosing

At study endpoint, 42.4% and 41.7% of patients in the DS and STS groups, respectively, were still taking duloxetine at the starting dose of 60 mg/day; 45.9% and 37.7% of patients in the DS and STS groups were taking a 90-mg/day dose; and 11.6% and 20.6% of patients in the DS and STS groups were receiving the maximum allowed dose of 120 mg/day.

Table 3. Outcomes of All Secondary Efficacy Measures[a]

Variable	Direct Switch: Baseline Score, Mean (SD)	Direct Switch: Adjusted Mean Change to Endpoint	Direct Switch: p Value[a]	Start-Taper Switch: Baseline Score, Mean (SD)	Start-Taper Switch: Adjusted Mean Change to Endpoint	Start-Taper Switch: p Value[b]
EQ-5D HSV	0.33 (0.34)	0.20	< .001	0.32 (0.33)	0.19	< .001
EQ-5D VAS score	42.1 (19.2)	15.7	< .001	41.2 (19.5)	14.9	< .001
SQ-SS	10.2 (4.1)	–2.26	< .001	10.3 (4.1)	–2.35	< .001
SF-36						
Mental component summary	19.7 (9.9)	14.09	< .001	19.6 (10.0)	14.18	< .001
Physical component summary	41.8 (11.6)	1.90	.006	40.8 (10.2)	2.82	< .001
VAS for Pain						
Overall	45.4 (29.6)	–9.02	< .001	45.9 (29.9)	–7.90	< .001
Headache	38.6 (31.8)	–10.59	< .001	36.5 (32.2)	–7.10	< .001
Back pain	41.2 (33.3)	–7.46	< .001	40.1 (33.0)	–8.54	< .001
Shoulder	37.5 (33.0)	–6.44	.002	37.0 (34.2)	–5.93	.004
Interference	45.8 (32.2)	–13.21	< .001	46.5 (32.7)	–10.25	< .001
Time in pain when awake	48.0 (32.3)	–11.89	< .001	49.4 (32.6)	–10.60	< .001
CGI-S	4.2 (0.7)	–1.56	< .001	4.2 (0.7)	–1.60	< .001
Response, N (%)	Value at Endpoint			Value at Endpoint		
No	83 (45.6)			74 (40.4)		
Yes	99 (54.4)			109 (59.6)		
Remission, N (%)						
No	117 (64.3)			115 (62.8)		
Yes	65 (35.7)			68 (37.2)		
Patient Satisfaction With Medication VAS score, mean	61.8			63.1		
PGI-I score, mean	2.77			2.83		

[a]Response and remission data are missing for 1 patient in the direct switch group and 2 patients in the start-taper switch group who had no postbaseline HAM-D data. Similarly, the Ns vary slightly across the results in this table due to missing data.
[b]Significant within-group differences. Not significantly different between the 2 switch groups.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, EQ-5D = EuroQOL Questionnaire, HSV = health state value, PGI-I = Patient's Global Impressions of Improvement, SF-36 = 36-item Short Form Health Survey, SQ-SS = Symptom Questionnaire-Somatic Subscale, VAS = Visual Analog Scale.

Efficacy

The DS group met the a priori–defined criteria for noninferiority to STS group (Figure 2). As measured by baseline-to-endpoint change in the HAM-D_{17} total score, both DS (–10.23 [95% CI = –11.26 to –9.20; $p \leq .001$]) and STS (–10.49 [95% CI = –11.52 to –9.45; $p \leq .001$]) groups improved significantly from baseline, but there was no significant difference between switch groups.

Analysis of mean change in HAM-D_{17} total score from baseline, as a function of time, is shown in Figure 3. There was no difference between switch groups at any measured time point, notably at week 1 and week 2 during the switching period.

The results of other secondary efficacy, health outcome, and patient satisfaction analyses are shown in Table 3. A significant within-group improvement was seen for all secondary efficacy measures regardless of switch method, and no significant differences were seen between DS and STS groups on any efficacy measure. Notable outcomes include response rates of 54.4% (DS group) versus 59.6% (STS group) and remission rates of 35.7% (DS group) versus 37.2% (STS group) at study endpoint. Pain also improved significantly as measured by all 6 VAS pain scales, although once again no significant differences were seen between the 2 switch groups.

Effect of Exclusion of Fluoxetine-Treated Patients on Efficacy

Fluoxetine has the longest plasma half-life of all the SSRIs, and its major metabolite norfluoxetine has an even longer half-life than its parent.[35] Even when abruptly discontinued, fluoxetine effectively self-tapers, and for this reason the primary (noninferiority of DS vs. STS) and HAM-D_{17} mean change from baseline analyses were run again with fluoxetine-treated patients (N = 70) excluded in order to ascertain whether outcomes would be different. In the event, DS remained noninferior to STS, and mean change from baseline to endpoint on the HAM-D_{17} total score was once again not significantly different between DS and STS treatment groups.

Safety and Tolerability

No deaths were reported during the study. A total of 5 patients reported at least 1 serious adverse event (3 patients [1.6%] in the DS group and 2 patients [1.1%] in the STS group). Serious adverse events included 2 suicide attempts, both of which occurred in DS patients, although not within 2 weeks of the switch.

The switch groups were also compared with respect to the assessment of global benefit-risk, which revealed

Table 4. Treatment-Emergent Adverse Events Reported With ≥ 3% Incidence in the Direct Switch (N = 183) and Start-Taper Switch (N = 185) Groups in Study Periods 2 and 3[a]

Event	Direct Switch, N (%)	Start-Taper Switch, N (%)
≥ 1 Treatment-emergent adverse event	100 (54.6)	93 (50.3)
Headache	24 (13.1)	18 (9.7)
Dry mouth	19 (10.4)	22 (11.9)
Nausea	15 (8.2)	15 (8.1)
Constipation	13 (7.1)	15 (8.1)
Insomnia	13 (7.1)	15 (8.1)
Hyperhidrosis	10 (5.5)	12 (6.5)
Somnolence	8 (4.4)	13 (7.0)
Libido decreased	6 (3.3)	2 (1.1)
Diarrhea	5 (2.7)	7 (3.8)
Dizziness	4 (2.2)	9 (4.9)
Abdominal pain upper	3 (1.6)	9 (4.9)
Weight increased	2 (1.1)	6 (3.2)

[a]No significant differences between the 2 switch groups.

no significant differences (p = .626) between DS and STS groups by this method of risk-benefit assessment.

Very few patients in either switch group discontinued the study due to an adverse event (12 patients [6.6%] in the DS group and 7 patients [3.8%] in the STS group). Nausea (3 patients overall), constipation (2 patients overall), and suicide attempt (2 patients overall) were the adverse events most frequently reported as being the reason for study discontinuation, and there were no significant differences between the DS and STS groups in the adverse event discontinuation rate overall, or the rate of study discontinuation due to any particular adverse event. Adverse event discontinuations were also compared between the switch groups after 2 weeks of treatment. Five patients in the DS group and 4 patients in the STS group discontinued the study within the first 2 weeks of the study.

Treatment-emergent adverse events with an incidence ≥ 3% in either switch group are shown in Table 4. Approximately half the patients in both switch groups reported no adverse event at all during the study. Headache was the most frequently reported adverse event in the DS group (13.1%, compared with 9.7% in the STS group), and dry mouth was most frequently reported by patients in the STS group (11.9%, compared with 10.4% in the DS group). Nausea, constipation, and insomnia were the next most frequently reported events. No adverse event was reported significantly more frequently by one switch group compared with the other. Treatment-emergent adverse event rates were also compared after 2 weeks of treatment. Sixty-nine (37.7%) patients in the DS group and 72 (38.9%) patients in the STS group reported at least 1 TEAE within 2 weeks of starting the study.

Changes in vital signs (heart rate, systolic blood pressure, diastolic blood pressure), laboratory tests, and weight were not significantly different between the 2 switch groups, and associated mean change values were not considered to be clinically significant.

Optional Taper Phase

As previously described, patients completing the study, or discontinuing the study after at least 2 weeks of duloxetine treatment, were permitted to enter an optional 2- to 3-week taper phase. A total of 39 DS and 40 STS patients entered the taper phase at the discretion of the investigator. One serious adverse event (major depression) was reported by 1 patient during the taper phase, and 3 patients discontinued the taper phase due to an adverse event. One or more discontinuation-emergent adverse events (DEAEs) were reported by 15.4% of patients in the DS treatment group versus 17.5% of patients in the STS group (p > .999). Vertigo, insomnia, and dizziness were the only DEAEs reported by more than 3% of patients during the taper phase, with vertigo (4 patients [10.3%] in the DS group vs. no patients in the STS group) being the most frequently reported.

Effect of SSRI Dose on Efficacy and Safety/Tolerability

To assess whether the dose of SSRI being taken at study entry influenced efficacy and safety/tolerability outcomes following switch, the study sample was split into "low" and "high" dose groups, and outcomes were compared for these groups. A low dose of SSRI was defined as the licensed starting dose of SSRI (citalopram 20 mg/day, escitalopram 10 mg/day, fluoxetine 20 mg/day, fluvoxamine 100 mg/day, paroxetine 20 mg/day, and sertraline 50 mg/day) or below, while a high dose was defined as all doses above the licensed starting dose. There was a trend toward greater improvement in HAM-D_{17} outcomes in patients who entered the study taking a high dose of SSRI, but no consistent effect of dose on pain as measured by VAS. From the perspective of safety and tolerability, more high-dose than low-dose patients reported an SAE, although due to the low number of events reported (only 5 patients reported at least 1 SAE), the significance of this finding is unclear. Patients taking a high dose of SSRI at study entry reported more TEAEs (55.6% reported at least 1 TEAE) compared with those taking a low dose of SSRI (49.5%), a difference that appears to have been predominantly driven by increased reporting of TEAEs in the DS group.

Effect of Duration of SSRI Treatment on Efficacy and Safety/Tolerability

To assess whether the duration of SSRI treatment prior to study entry influenced efficacy and safety/tolerability outcomes following switch, the study sample was split into groups with a "short" and "long" duration of treatment, and outcomes were compared for these groups. A 26-week cutoff was chosen to delineate the short and long

treatment duration groups. There was a trend toward greater improvement in patients with a short duration of treatment compared with a longer duration of treatment at study entry as measured by change from baseline on the HAM-D_{17} total score and HAM-D_{17} subscales. This difference reached statistical significance for the HAM-D_{17} sleep subscale ($p = .017$). Patients with a shorter duration of SSRI treatment also had lower baseline scores on the VAS for Pain, and exhibited a greater reduction from baseline in VAS pain scores that reached statistical significance for overall pain ($p = .024$), pain interference ($p = .008$), and pain while awake ($p = .012$). There was no consistent effect of duration of SSRI treatment on SAE or TEAE reporting rates.

DISCUSSION

The current study is, to our knowledge, the first to compare outcomes associated with 2 different methods of switching antidepressant nonresponders or partial responders from one antidepressant to another.

Before the results were in hand, a case could have been made for association of superior efficacy and/or tolerability outcomes with either of the switch methods under study. In the case of the DS group, for instance, it might have been hypothesized that the abrupt discontinuation of the SSRI would result in an excess of DEAEs compared with the STS group and hence a greater rate of early study discontinuations due to adverse events. This higher rate of early discontinuation could consequently have impacted efficacy outcomes, due to the LOCF statistical methodology employed. On the other hand, the 2-week overlap of SSRI and duloxetine treatment in the STS group might have been associated with a greater adverse event burden compared with that of the DS group, leading to more discontinuations due to adverse events and hence poorer efficacy outcomes, again due to the use of LOCF methodology. In fact, both methods of switch were associated with similar efficacy, low discontinuation rates due to adverse events, and low TEAE rates overall, with no significant efficacy or tolerability differences seen between the switch groups.

Interestingly, both the adverse event discontinuation rates and the TEAE rates seen with duloxetine in this study (regardless of switch method used) were lower than those previously reported in published duloxetine studies (e.g., Detke et al.[36,37]), suggesting that patients switching to duloxetine from SSRIs might tolerate duloxetine better than patients not already receiving an SSRI at the time of duloxetine initiation. This hypothesis is consistent with data from Wohlreich et al.,[38] who conducted a study in which outcomes associated with initiation of duloxetine treatment were compared for untreated patients with MDD versus patients who were taking low to medium doses of SSRIs or venlafaxine and were abruptly switched to duloxetine. Study discontinuations due to adverse events in the Wohlreich study were significantly lower in switch patients (6.1%) compared with previously untreated patients initiating duloxetine (16.1%), and data from our study together with Wohlreich et al.[38] suggest that prior use of an antidepressant seems to act as a "buffer" against adverse events associated with subsequent initiation of a different antidepressant (duloxetine in this case).

Further support for this hypothesis comes from a comparison of the adverse events seen in the current study with the published adverse event profile for duloxetine. Nausea, predominantly a serotonergic adverse event, is consistently reported as the most frequent adverse event in duloxetine studies with a rate of approximately 20%.[39] In our study, however, the nausea rate across the 2 switch groups was much lower at approximately 8%, and other than headache, the other most frequently reported TEAEs (dry mouth, constipation, insomnia, and hyperhidrosis) are all norepinephrine (NE)-associated adverse events. This finding not only provides tangible clinical evidence of the effects of duloxetine on NE at clinically relevant doses, but also demonstrates that prior use of an SSRI appears to buffer serotonergic side effects but not NE-related events, so NE-related events appear much more prominently in the overall mix of TEAEs seen in our study.

The study met its a priori–specified primary outcome, namely the demonstration of noninferiority of the DS method of switching SSRI-treated patients to duloxetine, compared with STS. This is potentially useful information for clinicians planning on switching SSRI nonresponders or partial responders to duloxetine, as a DS method does not require clinicians to devise a potentially complex patient-specific regimen of SSRI down-titration to accompany initiation of duloxetine, something that might be confusing and difficult to correctly adhere to for the patient.

While the lack of a control group limits conclusions that can be drawn about overall efficacy following switch, mean HAM-D_{17} total scores fell on average by more than 50% from baseline after 10 weeks of treatment regardless of the method of switch employed and despite the relatively hard-to-treat nature of the study population. Efficacy outcomes from the current study compare favorably with results from Level 2 of the Sequenced Treatment Alternatives to Relieve Depression (STAR-D) study,[40] where switch of citalopram nonremitters (or those who could not tolerate citalopram) to bupropion sustained release, sertraline, and venlafaxine extended release yielded remission rates of 21.3%, 17.6%, and 24.8%, respectively, after up to 14 weeks of treatment, compared with remission rates of 35.7% (DS) and 37.2% (STS) after 10 weeks of duloxetine treatment in the current study. It is unclear why SSRI nonresponders or partial responders who were switched to duloxetine in the current study

should have fared better than the citalopram patients switched to other antidepressants in the STAR-D study, and specifically whether this difference in outcomes is related to duloxetine's efficacy in this patient population or merely a result of differences in the patient populations studied or the study designs. The longer duration of treatment in STAR-D (14 vs. 10 weeks) and the inclusion of patients who did not tolerate previous treatment in STAR-D (rather than all patients being nonresponders or partial responders, as was the case in the current duloxetine study) would, however, seem to disadvantage duloxetine in a comparison between these 2 switching studies. Further suitably designed studies are therefore required to elucidate whether a real difference favoring switch to duloxetine versus other agents exists.

Two suicide attempts occurred in the DS group versus none in the STS group, 1 in a patient switching from citalopram and 1 in a patient switching from fluoxetine. Both patients fully recovered following the attempts. While suicide-related behaviors might be expected in this population of patients with predominantly recurrent depression of moderate severity despite a period of SSRI treatment, both events occurred in the DS group, which raises the question of whether the switch methodology played a part or whether the distribution of events was driven by chance. The timing of events (reported at 21 and 62 days postswitch, respectively) would tend to suggest that the events were not related to the switching method, but the occurrence of these 2 events clearly reinforces the risks faced by depressed patients and the need for particularly close monitoring early in treatment and around the time of a switch in treatment.

When the study protocol was being developed, there was a desire for both scientific and ethical reasons to define inclusion criteria so as to ensure that the populations being studied were robustly nonresponsive to their prescribed SSRI prior to switch. This was achieved by (1) requiring that patients entering the trial met DSM-IV criteria for MDD, (2) requiring that patients met at least a certain a priori–defined level of MDD symptom severity (namely a HAM-D_{17} total score of 15 or more), and (3) requiring that all patients had been treated with their SSRI at a licensed therapeutic dose for at least 6 weeks prior to switching. In practice, the symptom severity of patients entering the study (a HAM-D_{17} total score of approximately 21.5 at baseline, compared with the required threshold of 15 or more) and the median duration of SSRI treatment prior to switch (approximately 24 weeks, compared with the required duration of at least 6 weeks) more than met the defined criteria, and in the opinion of the authors confirm that the population was indeed "fit for purpose." SSRI doses at study entry varied across the relevant dose ranges, and that in fact the majority of escitalopram- and sertraline-treated patients were taking doses in excess of the starting dose at study entry (i.e., most patients were up-titrated in the search for an adequate response rather than being quickly switched from the starting dose of SSRI) further reinforces that view.

In summary, efficacy, safety, and tolerability outcomes following switch of SSRI nonresponders or partial responders to duloxetine were similar regardless of whether a DS or STS method was employed. Prestudy predictions that DS might be associated with an excess of DEAEs and hence poorer safety and tolerability outcomes overall were not borne out in practice, and in fact, switch appears to have been well tolerated regardless of the switch group to which patients were assigned. Efficacy outcomes were robust, particularly when one bears in mind the population under study, and compare favorably to outcomes seen in Level 2 of the STAR-D study following switch of SSRI-treated patients to other antidepressants.

Once a clinician has made the decision to switch a patient from one antidepressant to another, the most appropriate switching method will be a matter of clinical judgment and depend on a number of factors (particularly the antidepressant that the patient is taking and the chosen replacement). This study suggests that a direct-switch method of switching SSRI nonresponders or partial responders to duloxetine is associated with comparable efficacy and safety/tolerability outcomes to a start-taper switch method.

Limitations

As previously described, due to the large number of possible SSRI and dose permutations for patients entering the study, it was necessary for study investigators to use their clinical judgment to devise an appropriate 2-week down-titration regimen for patients in the STS group. While general guidance was provided to investigators within the study protocol to the effect that the SSRI dose should be reduced to approximately half the entry dose after 1 week of the taper, the taper was nevertheless not rigidly standardized. Furthermore, again as a result of the large number of possible SSRI/dose permutations and the need for investigators to therefore use clinical judgment on a patient-by-patient basis in order to effect the taper in the STS group, it was not feasible to blind the study, so biases inherent in open-label studies (for instance, observer expectation bias, where knowledge of the intervention received might influence data recording[41]) could have been a factor in the observed outcomes. A further limitation is that the lack of a control group in addition to the switch groups limits the conclusions that can be drawn about the efficacy and tolerability of duloxetine following switch. Finally, inclusion of fluoxetine-treated patients in the study could theoretically have confounded the results due to the long half-life of fluoxetine and its major metabolite norfluoxetine (which effectively provides its own taper). In practice, however, as described in the Results section, the result of the primary

analysis was markedly similar regardless of whether fluoxetine-treated patients were included or excluded in the analysis, so inclusion of fluoxetine-treated patients did not in fact appear to impact the primary endpoint.

Drug names: bupropion (Wellbutrin and others), buspirone (BuSpar and others), citalopram (Celexa and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), lithium (Eskalith, Lithobid, and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).

Author contributions: The authors accept full responsibility for the conduct of this study, had full access to all data from this study, and participated in the decision to publish the data. **Dr. Perahia** was the physician responsible for overseeing the conduct of this study. He was involved in all aspects of data review and interpretation. He has also been involved in the planning and presentation of all data disclosures from this study, including writing and reviewing this manuscript. **Ms. Quail** was the statistician responsible for planning the data analyses and was also involved in the planning of study data disclosures and review of this manuscript. **Dr. Desaiah** worked with Dr. Perahia to draft the manuscript and assisted in data interpretation. **Dr. Corruble** was a key investigator in the study and was involved in data review and interpretation, including the development of this manuscript. **Dr. Fava** has been a consultant to Eli Lilly and Co. in the development of previous duloxetine studies (including switching studies). He was involved in the review and interpretation of data from this study and also participated in the planning of this manuscript and review of successive drafts.

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