CNS Spectrums (2014), **19**, 324–329. © Cambridge University Press 2013
doi:10.1017/S1092852913000655

ORIGINAL RESEARCH

Efficacy and safety of selegiline transdermal system (STS) for the atypical subtype of major depressive disorder: pooled analysis of 5 short-term, placebo-controlled trials

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Objective. The objective of the present study is to investigate the efficacy and safety of the selegiline transdermal system (STS) in major depressive disorder (MDD) with atypical features.

Methods. This was a post-hoc analysis of 5 short-term trials. The atypical subtype was defined as the presence of at least 1 item with a score of 2 or greater from items 22–26 on the 28-item Hamilton Depression Rating Scale (HAMD-28), and a maximum score of 1 point for items 6 (insomnia late), 12 (somatic symptoms, gastrointestinal), and 16 (loss of weight) to exclude vegetative features of melancholic depression. The mean changes of HAMD-28 total score from baseline to the endpoint (response rate defined as ≥50% reduction in HAMD-28 scores and remission rate defined as ≤10 HAMD-28 total score at the treatment endpoint) were compared between atypical and nonatypical groups.

Results. In this analysis, 352 subjects (STS = 168 vs placebo = 184) met the definition of atypical subtype at baseline. STS (n = 641) significantly decreased HAMD-28 total score compared with placebo (n = 648) from beginning to end of treatment (-10.7 ± 9.3 vs -9.4 ± 9.3; p = 0.014). STS showed comparable efficacy in patients with the atypical subtype compared with the nonatypical subtype for placebo-subtracted mean change in HAMD-28 total score (-2.11 ± 1.01 vs. -1.0 ± 0.60; p = 0.34), odds ratio (OR) for response (1.41 vs 1.23, p = 0.62), and OR for remission (1.77 vs 1.18, p = 0.22).

Conclusion. STS appears to be comparably efficacious and tolerable in atypical and nonatypical subtypes of MDD. Adequately powered, controlled, clinical trials are necessary to confirm our findings.

Received 15 July 2013; Accepted 16 August 2013; First published online 29 October 2013

Keywords: Atypical depression, efficacy, remission, response, selegiline transdermal system, tolerability.

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This study has been supported by funding from Mylan Specialty L.P. (formerly Dey Pharma, L.P.).

Some parts of this paper have been presented as a poster at the 25th Congress of the European College of Neuropsychopharmacology, Vienna, Austria, October 13–17, 2012.

Introduction

Atypical depression is one of the major subtypes of depression, and is characterized by reactive mood, appetite increase, hypersomnia, leaden paralysis, and interpersonal rejection sensitivity, although the core symptoms for atypical depression should be reconsidered in accordance with various definitions and concepts by different research groups and refined through accumulated

clinical research.[1,2] Interestingly, however, the Columbia University group (which focuses on mood reactivity) and the New South Wales University group (which focuses on anxiety symptoms and overlaps with hysteroid dysphoria) commonly consider atypical depression to be chronic, mild, nonendogenous (nonmelancholic), unipolar depression.[3] Patients with atypical depression are 2–3 times more likely to be female and often have a more chronic and complicated clinical course of depression.[1] In fact, according to the European epidemiological study, the rates of atypical depression in the general population, the prevalence rate was 4.5% for women and 1.2% for men.[4] In addition, the mean age of onset was earlier in patients with atypical depression than typical depression.[4–8]

The lifetime prevalence rate of atypical depression has not been well-studied and may vary among studies. In one previous study, approximately 17% of the patients having a diagnosis of major depressive disorder (MDD) showed a history of atypical depression.[9] Likewise, in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, approximately one-fifth of patients had a depression with atypical features, and women were 70% more likely to have atypical depression.[7]

Meanwhile, the hyperactivity of the hypothalamus--pituitary–adrenal (HPA) axis, which is associated with corticotropin-releasing hormone (CRH) hypersecretion and an impaired negative feedback, appears to be most consistently observed in depressed patients with melancholic features, while the reduced activity of the HPA axis and noradrenergic neurons was prominent in patients with atypical features.[10] Such findings (lower CRH and less impairment in noradrenergic system) were consistently found in a number of previous studies.[11,12] These findings are relevant to the study results that monoamine oxidase inhibitors (MAOIs) may be more efficacious for treating atypical depression than tricyclic antidepressants (TCAs), which have potent noradrenergic properties.[13,14]

Transdermal administration of selegiline permits inhibition of MAO-A and MAO-B enzymes in the brain while preserving the activity of MAO-A in the gastrointestinal system, thereby reducing the risk of possible interactions with tyramine-rich foods.[15] In fact, a number of newer formulations of antidepressants with improved safety and tolerability profiles with different drug delivery technologies have been introduced in the current market.[16–19]

The U.S. Food and Drug Administration (FDA) approved the selegiline transdermal system (STS) for the treatment of MDD in February 2006, and it has now become the first skin (transdermal) patch indicated for MDD.[16,17] In clinical trials with STS, it has been shown to be efficacious and safe in patients with MDD; there were no reports of hypertensive crisis associated with STS, and 6 of the 7 clinical trials were conducted without dietary modifications at any dose.[18] A meta-analysis of all 5 short-term trials evaluating treatment effects of STS for patients with MDD has been previously reported.[20] According to the results, STS demonstrated significant treatment effects on core depression symptoms (HAM-D Bech 6 items: depressed mood, guilt, work and activities, retardation, psychic anxiety, general somatic symptoms), reverse vegetative symptoms (oversleeping, overeating), motor retardation, suicide, and genital symptoms (libido).[20] Significant STS treatment effects were also noted for each Montgomery–Åsberg Depression Rating Scale (MADRS) item except for reduced sleep and appetite. The most prominent MADRS effects were improvement in sadness, lassitude, and poor concentration.

In this analysis, we conducted a post-hoc, pooled data analysis of 5 short-term, randomized, double-blind, placebo-controlled trials with STS (4 8-week studies: 3 fixed-dose trials with 6 mg/24 h and 1 flexible dose trial with 6, 9, and 12 mg/24 h, and 1 6-week trial: fixed dose 6 mg/24 h), to evaluate the efficacy and safety of STS for the subgroups of patients with atypical features.

Method

Study design

Data were pooled from 5 placebo-controlled studies that were conducted at multiple sites within the United States (STS n = 641; placebo n = 648).[20–23] All trials were conducted in accordance with the Declaration of Helsinki and received appropriate approval by the institutional review board or independent ethics committee. Details of the original study methods have been described previously. Briefly, in such trials, patients applied the STS patch, which delivered 3 mg/24 h (10 cm^2), 6 mg/24 h (20 cm^2), 9 mg/24 h (30 cm^2), or 12 mg/24 h (40 cm^2). In the 5 randomized, double-blind, placebo-controlled clinical trials (RCTs), patients applied STS patches containing either drug or an identical-appearing placebo patch. Three placebo-controlled efficacy trials compared fixed-dose STS 6 mg/24 h versus placebo, 1 efficacy trial compared 2 fixed doses (STS 3 mg/24 h and 6 mg/24 h) versus placebo, and 1 efficacy trial employed flexible-dose titration comparing STS administered within a dose range of 6 mg/24 h to 12 mg/24 h versus placebo.

Patients

Men and women, 18–65 years of age, were eligible for enrollment in a trial (≥18 years for Feiger et al's study).[20] Patients were required to meet *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) criteria for MDD, single episode or recurrent, moderate to severe, and have a baseline HAM-D17 score

≥20. Except for the first study,[21] patients were not advised to follow a tyramine-restricted diet.

Atypical features subgroups

In accordance with published literature,[24] atypical subtype was defined as presence of at least 1 item with a score of 2 or greater from items 22–26 on the 28-item Hamilton Depression Rating Scale (HAMD-28), and a maximum score of 1 point for items 6 (insomnia late), 12 (somatic symptoms, gastrointestinal), and 16 (loss of weight) to exclude vegetative features of melancholic depression. Response was defined as ≥50% reduction in HAMD-28 scores, and remission was defined as ≤10 HAMD-28 score at the last visit of the trials.

Assessments

Efficacy scales included the HAMD-28 and the MADRS. The Bech 6-item subscale, comprising HAMD items (1) depressed mood, (2) guilt, (7) work and activities, (8) retardation, (10) psychic anxiety, and (13) somatic general, was used as an outcome measure for core depression symptoms. Safety and tolerability were evaluated by monitoring of adverse events (AEs).

Statistical analyses

The primary efficacy outcome, the mean change from baseline to the endpoint in HAMD-28 total score, was evaluated using the last-observation-carried-forward data set, by analysis of covariance (ANCOVA), with treatment and study as main effects and baseline HAMD-28 total score as covariate.

Treatment comparisons of response and remission rates were evaluated by a Cochran–Mantel–Haenszel Test, controlling for study. Odds ratios (ORs) for the differences in HAMD-28 response and remission between atypical and nonatypical groups at the endpoint were calculated using a logistic regression model controlling for study and treatment.

All statistical tests were interpreted at the 5% significance level. All analyses were conducted using SAS 9 (SAS Institute, Cary, NC, USA).

Results

Whole sample

The sample comprised 1289 patients with both a baseline and post-baseline HAM-D28 rating. For the MADRS, 1288 patients had both a baseline and post-baseline rating for items 5–10 and 1287 patients for items 1–4. The mean age across the 5 trials was 42 ± 11.3 years, with the majority being women (62%) and white (85%); 64% had recurrent depression, and mean HAMD-28 and MADRS scores at baseline were 29 and 28, respectively. STS (n = 641) significantly decreased HAMD-28 total score compared with placebo (n = 648) from beginning to end of treatment (–10.7 ± 9.3 vs. –9.4 ± 9.3; p = 0.014).

Subjects with or without atypical features

Three hundred fifty-two subjects (STS = 168 vs placebo = 184) met the definition of atypical subtype at baseline. Baseline characteristics for the pooled subgroups are shown in Table 1. There were no significant differences in demographic characteristics between the atypical and nonatypical groups, with the exception of the baseline HAMD-28 and HAMD-17 total scores. The baseline HAMD-28 was significantly higher in the atypical subgroup than in the nonatypical subgroup, while baseline HAMD-17 total score was significantly higher in the nonatypical subgroup than in the atypical subgroup.

STS showed comparable efficacy in patients with the atypical subtype compared with the nonatypical subtype for placebo-subtracted mean change in HAMD-28 total score (–2.11 ± 1.01 vs –1.0 ± 0.60; p = 0.34), OR for response (1.41 vs 1.23; p = 0.62), and OR for remission (1.77 vs 1.18; p = 0.22), respectively (Figures 1 and 2).

Completion rates were comparable across subgroups. Overall discontinuation rates were not significantly different between the atypical and nonatypical subtypes within the STS group (29% vs 23%). The rates of AEs leading to study discontinuation and noncompliance were also similar. For patients receiving STS, the rates of the 3 most frequently reported AEs were comparable between the atypical and nonatypical subtypes: application site reactions (ASRs, 26% vs 27%), headache (18% vs 17%), and insomnia (14% for both).

Discussion

The results of this analysis of pooled data from 5 randomized, double-blind, placebo-controlled, clinical trials of STS propose that STS may be effective and relatively well-tolerated in MDD patients with atypical features.

In our sub-analysis, STS significantly decreased HAMD-28 total score compared with placebo from beginning to end of treatment. In addition, STS showed comparable efficacy in patients with the atypical subtype compared with the nonatypical subtype for placebo-subtracted mean change in HAMD-28 total score as well as OR comparisons for response and remission, respectively. Hence, our results are in line with and in support of both findings from individual RCTs and the recent meta-analysis including all 5 RCTs of STS that demonstrated the treatment effects of STS on overall depressive symptoms and individual atypical depression

TABLE 1. Baseline demographics and HAMD scores for subjects receiving STS by depression subtype

	Atypical (n = 168) (25%)	Nonatypical (n = 498) (75%)	p-value
Sex—Female (%)	68	60	0.086
Age (mean ± SD)	40.3 ± 11.5	41.9 ± 11.5	0.11
HAMD-28 total score (mean ± SD)	30.7 ± 4.5	28.8 ± 4.2	<0.001
HAMD-17 total score (mean ± SD)	22.2 ± 2.6	23.4 ± 2.8	<0.001

HAMD, Hamilton Depression Rating Scale; SD, standard deviation.

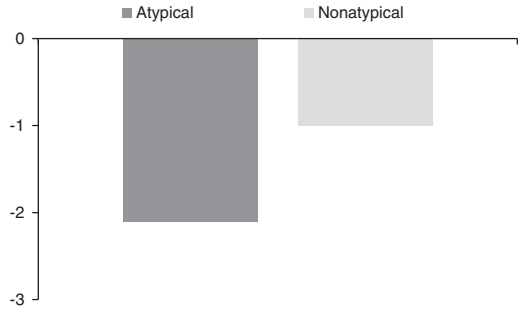

FIGURE 1. Placebo-subtracted mean change in HAMD-28 total score (–2.11 ± 1.01 vs –1.0 ± 0.60, p = 0.34) in atypical versus nonatypical subtypes treated with STS. Abbreviations: HAMD, Hamilton Depression Rating Scale; STS, selegiline transdermal system.

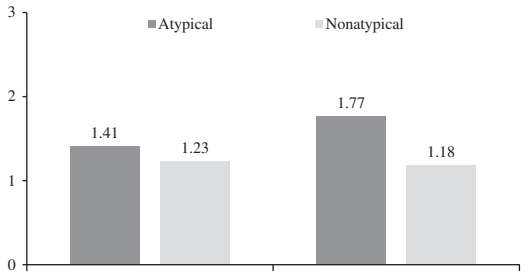

FIGURE 2. Odds ratios for response and remission in atypical versus nonatypical subtypes treated with STS. Abbreviations: STS, selegiline transdermal system.

symptoms captured by the HAMD-28 rating scales.[20–23] In addition, the results are also in line with the results from a post-hoc analysis of the 10-week, open-label phase of a relapse prevention trial of STS[25]; in the study, the change from baseline to last visit in HAMD-28 total score was comparable between atypical (N = 189) and nonatypical (N = 456) groups (-17.4 vs -16.8).[25] The atypical group also appeared to have a numerically higher remission rate than the nonatypical group (65.6% vs 58.1%), although the difference was not statistically significant.[25]

Previous studies have suggested that patients with atypical features may be less responsive to antidepressant treatment than those without atypical features, which was also confirmed in the recent findings from the STAR*D trial.[2,26] According to the sub-analysis for patients with atypical features of STAR*D trial (level 1 data finding),[27] patients with atypical features were found to show more positive family history of suicide, longer current episode, earlier onset age of MDD (< 18 years), comorbid psychiatric disorders (eg, panic disorder, social phobia, drug abuse, etc), and anxious features or chronic depression. These findings are also consistently found in previous studies.[2] In addition, in the sub-analysis for patients with atypical features of STAR*D trial,[27] patients with atypical features were also significantly less likely to reach remission as assessed by HAMD-17 (23.5% vs 28.4%, respectively) and the 16-item Quick Inventory of Depressive Symptomatology–Self-Rated (QIDS-SR16) (28.6% vs. 33.8%, respectively) than those without. Also, the remission occurred significantly later in participants with atypical features than for those without atypical features. In fact, patients without atypical features were more likely to remit between weeks 2 and 6, while more patients with atypical features remitted at week 10 and after week 12, indicating a need for more continuous treatment and careful observation to exactly evaluate whether the treatment is successful for patients with atypical features, compared with those without atypical features.[27] Such poor antidepressant treatment effects were not also improved in the next treatment, level 2 of the STAR*D trial (switch to different antidepressant such as bupropion sustained-release, venlafaxine extended-release, or sertraline; or augmentation with bupropion or buspirone).[28]

Hence, our sub-analysis data may suggest that STS may be another viable treatment option for patients with atypical features, since STS showed comparable efficacy regardless of presence or absence of atypical features in terms of overall improvement in depressive symptoms, response, and remission based on our sub-analysis.

Our sub-analysis showed that STS is a safe and relatively well-tolerated medication for patients with MDD regardless of the presence or absence of atypical features. Overall discontinuation rates were comparable between the atypical and nonatypical subtypes within the STS group. The rates of AEs leading to study discontinuation and noncompliance were also similar. For patients receiving STS, rates of the 3 most frequently reported AEs were comparable between the

atypical and nonatypical subtypes. Such findings are comparable with those reported in individual RCTs,[21–23] a postmarket surveillance study,[19] and a placebo-controlled, 52-week relapse prevention study.[29] In the relapse prevention study,[29] significantly fewer STS patients experienced relapse of MDD episode (16.8%) compared with placebo (30.7%). In addition, the safety profile of STS was also similar to placebo with the exception of ASRs; likewise placebo treatment group, hypertensive crisis were not also reported in STS treatment group, despite the lack of requirement for dietary tyramine restrictions. These findings are also consistent with results of a post-hoc analysis of the 10-week, open-label phase of a relapse prevention trial of STS.[25]

Interestingly, according to a sub-analysis of the STAR*D trial,[27] participants with atypical features had significantly more antidepressant side-effect intensity (atypical vs. nonatypical, none to trivial intensity: 38% vs. 44.4%; moderate to severe: 62% vs. 55.6%) and burden (atypical vs. nonatypical, none to mild impairment: 56.6% vs. 62.5%; moderate to unable to function: 43.3% vs. 37.8%) than those without atypical features, although the number of serious AEs or psychiatric serious AEs, or in treatment intolerance, were not significantly different between the 2 subgroups. However, the prescribing information for STS specifies that due to the potential for serotonin syndrome, which is potentially life-threatening, STS should not be used with antidepressants that have serotonergic properties. After stopping treatment with any antidepressant, approximately 1 week (5 weeks for fluoxetine) should elapse before starting therapy with STS. At least 2 weeks should elapse after stopping STS before starting any antidepressants because it takes 2 weeks to regenerate enough MAO enzyme in the brain to catabolize monoamines.[16,17,19,30]

The present study has clear limitations since it is a post-hoc analysis. Multiplicity of analysis has been known to result in an increased risk of type I error, permitting a conclusion of statistically significant differences when none truly exist. It also jeopardizes randomization of the original study. The sample size was relatively small to be generalized into clinical practice. However, under our statistical parameters and after adjusting with covariates, the power of the sample to detect a medium to large effect size (Cohen's *d*) was estimated to be at least 0.6875, which corresponds to a difference of 1.1 in the placebo-subtracted mean changes in HAMD-28 total score between those with and without atypical features. In this post-hoc analysis, the compliance factor that can affect the treatment outcomes was not considered. This limitation should be also considered in the interpretation of the present study. Finally, according to a recent study, it was found that mixed-effect model repeated measure (MMRM) analysis appeared to be a superior approach in controlling type I error rates and minimizing biases, as compared to last observation carried forward (LOCF) ANCOVA analysis, from a sensitivity analysis of 48 clinical trial datasets obtained from 25 New Drug Applications (NDA) submissions of neurological and psychiatric drug products to the FDA.[31]

Conclusion

In this pooled analysis, STS appears to be comparably efficacious and tolerable in atypical and nonatypical subtypes of MDD. Therefore, these findings propose that STS may be considered 1 of viable treatment options for the treatment of patients with atypical depression in clinical practice. Adequately powered, randomized, placebo-controlled, clinical trials are necessary to confirm these findings in the future.

Disclosures

Dr. Patkar is a consultant for and/or on the advisory boards of Bristol-Myers Squibb, Mylan Specialty L.P., GlaxoSmithKline, Pfizer, and Reckitt Benckiser; has received honoraria and is on the speaker's bureaus of Bristol-Myers Squibb, GlaxoSmithKline, Mylan Specialty L.P., and Reckitt Benckiser; and has received research support from AstraZeneca, Bristol-Myers Squibb, Forest, GlaxoSmithKline, Janssen, McNeil Consumer and Mylan Specialty L.P., the National Institutes of Health, Organon, Jazz Pharmaceuticals, and Pfizer. Drs. Pae, Jang, and Jung have no conflicts of interest. Dr. Nelson has served as an advisor or consultant for Avanir, Bristol-Myers Squibb, Cenestra Health, Corcept, Mylan Specialty L.P., Eli Lilly, Forest, Labopharm, Lundbeck, Medtronic, Merck, Otsuka, Pfizer, and Sunovion; received lecture honoraria from Eli Lilly Global, Lundbeck, Otsuka Asia, and Merck Asia; received research support from NIMH and HRSA; and owns stock in Atossa. Dr. Portland is an employee of Mylan Specialty L.P., and may hold stock and/or stock options in Mylan.

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