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Research report

Predictors of relapse in patients with major depressive disorder in a 52-week, fixed dose, double blind, randomized trial of selegiline transdermal system (STS)

Saeheon Jang [a,b], Sungwon Jung [a,c], Chiun Pae [d], Kimberly Blanchard Portland[e], J Craig Nelson [f], Ashwin A. Patkar [a,*]

[a] Duke University Medical Center, Durham, NC, United States
[b] Bongseng Memorial Hospital, Republic of Korea
[c] Keimyung University, Republic of Korea
[d] Catholic University, Republic of Korea
[e] Mylan Specialty L.P., Basking Ridge, NJ, United States
[f] University of California, San Francisco, CA, United States

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ABSTRACT

Objective: We investigated patient and disease characteristics predictive of relapse of MDD during a 52-week placebo controlled trial of selegiline transdermal system (STS) to identify patient characteristics relevant for STS treatment.

Method: After 10 weeks of open-label stabilization with STS, 322 remitted patients with MDD were randomized to 52-weeks of double-blind treatment with STS (6 mg/24 h) or placebo (PLB). Relapse was defined as Hamilton Depression Rating Scale (HAMD-17) score of ≥ 14 and a CGI-S score of ≥ 3 with at least 2-point increase from the beginning of the double blind phase on 2 consecutive visits. Cox's proportional hazards regression was used to examine the effect of potential predictors (age, sex, age at onset of first MDD, early response pattern, number of previous antidepressant trials, severity of index episode, number of previous episodes, melancholic features, atypical features and anxious feature) on outcome. Exploratory analyses examined additional clinical variables (medical history, other psychiatric history, and individual items of HAM-D 28) on relapse.

Results: For all predictor variables analyzed, treatment Hazard Ratio (HR=0.48~0.54) was significantly in favor of STS (i.e., lower relapse risk than PLB). Age of onset was significantly predictive of relapse. Type, duration, and severity of depressive episodes, previous antidepressant trials, or demographic variables did not predict relapse. In additional exploratory analysis, eating disorder history and suicidal ideation were significant predictors of relapse after controlling for the effect of treatment in individual predictor analysis.

Conclusions: While age of onset, eating disorder history and suicidal ideation were significant predictors, the majority of clinical and demographic variables were not predictive of relapse. Given the post-hoc nature of analysis, the findings need confirmation from a prospective study. It appears that selegiline transdermal system was broadly effective in preventing relapse across different subtypes and symptoms clusters of MDD.

1. Introduction

Major depressive disorder (MDD) is a disease associated with a high relapse rate, even after seemingly effective pharmacological therapy. Relapse rates across studies range considerably but have been reported to be as high as 40% in some long-term MDD studies (McGrath et al., 2006). Understanding factors associated with relapse may enable better identification and monitoring of at-risk patients and thus lead to more effective long-term interventions. Predictors of MDD relapse identified in previous studies include both patient and disease characteristics, such as incomplete remission and residual symptomatology, chronicity, greater severity of MDD episodes, female gender, and age (McGrath et al., 2000; Katon et al., 2006; McGrath et al., 2006; Fava et al., 2009; Ten Doesschate et al., 2010). However, these findings have been somewhat inconsistent across studies and some are associated more or less with relapse from various types of pharmacological treatments.

* Corresponding author at: Duke University Medical Center, Durham, NC, United States. Tel.: +1 17325303363.
E-mail address: ashwin.patkar@duke.edu (A.A. Patkar).

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Monoamine oxidase inhibitors (MAOIs) were the first class of antidepressants and were considered the mainstay of depression treatment through the late 20th century due to the consistent antidepressant properties (Amsterdam and Shults, 2005). More recently, the utilization of MAOIs has been very limited, perhaps due to concerns regarding food and drug interactions. In fact, a recent analysis of antidepressant prescriptions indicated that MAOIs account for less than 0.3% of the entire antidepressant prescriptions in a given year. Treatment guidelines recommend utilizing MAOIs as 3rd to 5th line treatments for patients with MDD (Andersonet al., 2008; Lam et al., 2009; Suehs et al., 2009; American Psychiatric Association, 2010; Thase, 2012), although some recommend using MAOIs earlier for certain subgroups of patients such as those with atypical depression and some research indicates MAOIs may be particularly effective for those with atypical (Mcgrath et al., 2001; Thase, 2007) or treatment-resistant depression (Amsterdam and Shults, 2005; Nemeroff, 2007).

Selegiline transdermal system (STS), an irreversible inhibitor of MAO-A and MAO-B, was developed to overcome some of the limitations of oral MAOIs, namely the food–drug interactions. The efficacy of STS for both acute and maintenance treatment for MDD was established in 3 short-term (6–8 week) (Bodkin and Amsterdam, 2002; Amsterdam, 2003; Feiger et al., 2006) and 1 long-term (52 week) (Amsterdam and Bodkin, 2006) relapse prevention trial. Transdermal delivery of selegiline, via STS, bypasses first pass metabolism. STS 6 mg/24 h is sparing of gastrointestinal MAO-A enzyme, the principal enzymatic barrier to ingested tyramine, and STS showed greater systemic delivery of selegiline (Mawhinney et al., 2003; Wecker et al., 2003) and a higher tyramine safety margin compared with oral MAOIs (Azzaro et al., 2006).

We performed a post-hoc analysis of a 52-week relapse prevention study of STS to: (1) investigate possible patient and disease characteristics predictive of relapse while controlling for treatment and (2) determine if any patient or disease characteristics predicted differential relapse rates between STS and placebo.

2. Methods

2.1. Study overview

This post-hoc analysis utilized data from a 52-week, double-blind, placebo-substitution, parallel group relapse prevention study with STS. The study design, protocol, assessments, and primary study results have been detailed elsewhere (Amsterdam and Bodkin, 2006).

2.2. Subjects

All subjects were outpatients, aged 18 yr and older, with the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) Axis I diagnosis of MDD and HAM-D 17 total score of ≥ 18. Females of childbearing potential could be enrolled if they had a negative serum pregnancy test at screening and agreed to use an acceptable form of birth control during the study. Before enrollment in the study, all patients gave written informed consent along with an explanation of possible side effects.

Subjects were excluded from the study if they previously participated in a STS clinical trial; had clinically significant abnormal laboratory or physical examination results; had a medical illness or malignancy; were currently receiving psychotherapy; had a clinically significant comorbid Axis I disorder or epilepsy; had electroconvulsive therapy (ECT) within the previous 90 days; had a serious risk of suicide; had a lack of response or hypersensitivity to a MAOI; had a positive urine screening for drugs of abuse and a history of substance abuse within 6 months; or had an allergy involving dermal manifestations.

Subjects meeting inclusion criteria were enrolled into a 10-week, open-label phase with 6 mg/24 h of STS. Patients were considered to have responded (stabilized) to STS treatment if they demonstrated HAM-D 17 score of less than or equal to 10 at either study week 8 or 9 and again at study week 10. Responders to STS therapy underwent random assignment, either to continue taking 6 mg/24 h of STS or to take placebo, for 52 weeks or until relapse. Those patients who did not meet the criteria for response to STS therapy at the end of the open-label phase did not enter the randomized phase of the trial and were treated as clinically warranted.

2.3. Outcome measures

HAM-D 28 (a HAM-D 17 score was also extracted from HAM-D 28), Montgomery-Åsberg Depression Rating Scale (MADRS), Clinical Global Impression Severity of Illness and Improvement (CGI-S and CGI-I, respectively) were conducted at baseline and at each study visit. Concomitant medications and adverse events were assessed at every visit.

Relapse was defined a priori as subjects who had HAM-D 17 score of 14 or more, and CGI-S score of 3 or more (with at least a 2-point increase from double-blind baseline), and meeting protocol defined DSM-IV criteria for MDD. For this analysis, we defined early response as $\geq 50\%$ reduction in HAM-D 17 within 2 weeks of beginning of open-label phase; severe depression as HAM-D 17 total score ≥ 28; chronic type as ≥ 2 yr duration of a current or most recent episode; melancholic subtype as ≥ 12 subtotal score of items 1, 2, 7, 8, 10 and 13 of HAM-D 28; atypical subtype as presence of at least 1 item with a score of ≥ 2 or on items 22–26 on the 28-item Hamilton Depression Rating Scale (HAMD-28), and a maximum score of one point for items 6 (insomnia late), 12 (somatic symptoms, gastrointestinal), and 16 (loss of weight) to exclude vegetative features of melancholic depression; anxious depression as a HAMD-28 anxiety/somatization factor (item 10–12, 13, 15 and 17) score ≥ 7 (Tollefson and Holman, 1993); residual symptoms as items with a score of ≥ 1 at end point of open-label phase. Degree of treatment resistance was stratified into two groups: no previous antidepressant failures, ≥ 1 antidepressant failures), and depression severity into three groups: mild as a score of HAM-D $17 > 7$ and < 20, moderate as ≥ 20 and < 28, and severe as ≥ 28. We used multiplier 10 for age of onset of MDD in calculation of hazard ratio.

2.4. Statistical methods

All analyses were done on the modified intent-to-treat (m-ITT) population for double-blind phase of the study. Patients who received study drug and also had at least one post-baseline HAM-D assessment were included in the m-ITT populations. T-tests and Chi-squares were used to compare the demography and baseline characteristic for analyzed sample and assess the association of socio-demographic and clinical characteristics with relapse of MDD. Kaplan–Meier (K–M) survival analysis was used to assess the time to relapse with statistical significance determined by the log-rank test. Cox proportional hazards models were employed to identify predictors of relapse. We considered potential predictors as age, sex, age at onset of MDD, early response pattern, presence of melancholic subtype, presence of atypical subtype, presence of anxious subtype, history of antidepressants treatment failure, chronicity, depression severity (based on baseline HAM-D 17 total scores of open-label phase) and residual symptoms. In the first step for identifying potential predictors, individual hazard model included treatment and one of potential predictors. In second step for assessing consistency of the treatment effect, individual hazard model included treatment, individual predictor and treatment-by-predictor interaction. This was done only

for categorical predictors, for the convenience of interpretation. To categorize some continuous variables, we used the median or a clinically relevant value. For categorical predictors, we performed a hazard model in the total sample and in each subsample of predictors to see the difference of treatment effect in case with significance in the treatment-predictor interaction.

Additional exploratory models were tested to detect possible predictors using the following variables: medical history, other psychiatric history with exception of MDD and individual items of HAM-D 28 at the beginning of 10-week open label. The analytic processes were same as in the analysis of potential predictors.

Final hazard model which included treatment and all other significant predictors in previous analysis was tested to determine final predictors using multivariate Cox proportional hazards regression with a backward elimination procedure. All reported statistical tests used 0.05 two-tailed significance levels.

3. Results

3.1. Patient demographics and disposition

Of the 675 patients who began open-label treatment, 366 patients completed the open-label phase, and 322 were subsequently randomized to double-blind STS 6 mg/24 h treatment ($n=159$) or placebo ($n=163$). The completion rates were 35.2% ($n=56$) and 30.7% ($n=50$) respectively ($p=0.408$). Almost all patient demographic and clinical characteristics were similar across treatment groups (Table 1).

3.2. Relapse of MDD and time to relapse of MDD

Significantly fewer STS patients (16.8%) relapsed compared to placebo (30.7%) at study week 52 ($p=0.004$). The time to relapse was significantly longer in the STS group compared with placebo ($p=0.0048$) (Fig. 1).

3.3. Hazard models for identifying potential predictors (Table 2 and Fig. 2)

For all predictor variables in total sample analysis, treatment HR was significantly in favor of STS (i.e., lower relapse risk than PLB). After controlling for the effect of treatment, age (years, multiplier 10 in calculation) at onset of 1st MDD predicted significantly relapse of MDD (HR=0.84, $p=0.034$). The risk of relapse decreased by 16.3% for every 10 yr increased in the age of onset. Other potential predictors were significant in individual predictor analyses. The findings are summarized in Table 2 and Fig. 2.

3.4. Hazard models for identifying possible predictors of relapse

For all predictor variables in total sample analysis, treatment HR was significantly in favor of STS (i.e., lower relapse risk than PLB) as in hazard models for potential predictors.

1. Medical history: Among 14 medical illness categories based on organ systems, no variables were significant in individual predictor analyses after controlling for the effect of treatment. Head–eye–ear–nose–throat (HEENT) illness history showed significant treatment-by-predictor interaction ($p=0.042$). For positive history of HEENT illness, STS (15.0%) had benefit to PLB (43.0%) but not for negative history of HEENT illness (27.0% and 32.1% respectively).
2. Other psychiatric history: Among 8 other psychiatric history variables with the exception of MDD, eating disorder (ED) history (80.0% vs. 23.1%) was predictive of higher relapse (HR=4.67, 95% CI=1.70–12.87, $p<0.01$) after controlling for the effect of treatment.

Table 1
Demographic and clinical data of randomized groups.

		STS group ($n=159$)	PLB group ($n=163$)	P-value
Female (%)		65.0	71.1	
Race (%)	Caucasian	82.4	82.2	
	Hispanic	8.2	8.6	
	Black	5.0	5.5	
	Asian	0.6	1.2	
	Other	3.8	2.5	
Marital status (%)	Single	30.2	27.6	
	Married	39.0	36.8	
	Separated	3.1	5.5	
	Divorced	26.4	25.8	
	Widowed	1.3	4.3	
Age (mean ± SD)		42.7 ± 12.4	44.4 ± 11.3	
MDE specifier (%)	Recurrent	62.9	62.6	
	Chronic[a]	39.0	34.4	
	Atypical[b]	20.8	19.0	
	Melancholic[c]	61.0	54.6	
	Anxious[d]	59.1	55.8	
AD Tx failures (%)	No previous AD	57.0	59.5	
	≥1AD failures	43.0	40.5	
Relapse of MDD (%)		16.8	30.7	0.004**
EARLY STS Responder (%)[e]		20.1	14.7	
		Mean(SD)	Mean(SD)	
Onset age (years)		34.2 (14.3)	34.4 (14.6)	
HAM-D28 total[f]		30.7 (5.3)	30.1 (5.4)	
HAM-D17 total[f]		23.2 (3.9)	23.1 (3.5)	
MADRS[f]		29.9 (5.9)	29.6 (5.7)	
CGI-S[f]		4.6 (0.7)	4.6 (0.7)	

AD Tx: antidepressant treatment, AEs: adverse events, HAM-D: Hamilton depression rating scale, MADRS: Montgomery-Åsberg Depression Rating Scale, MDD: major depressive disorder, MDE: major depressive episode, PLB: placebo, STS: selegiline transdermal system.
*$p<0.05$, **$p<0.01$.
[a] Duration of episode >2 yr.
[b] A score of 2 in at least one of the items 22–26 of the Hamilton-Depression-Rating-Scale (HAM-D) 28 and a maximum score of one point for items 6 (insomnia late), 12 (somatic symptoms, gastrointestinal), and 16 (loss of weight) to exclude vegetative features of melancholic depression.
[c] Bech HAMD 6-item score (items 1, 2, 7, 8, 10 and 13) ≥12.
[d] A HAMD-28 anxiety/somatization factor (item 10–12, 13, 15 and 17) score ≥7.
[e] HAM-D28 score decrease ≥50% within 2 weeks after treatment.
[f] Baseline.

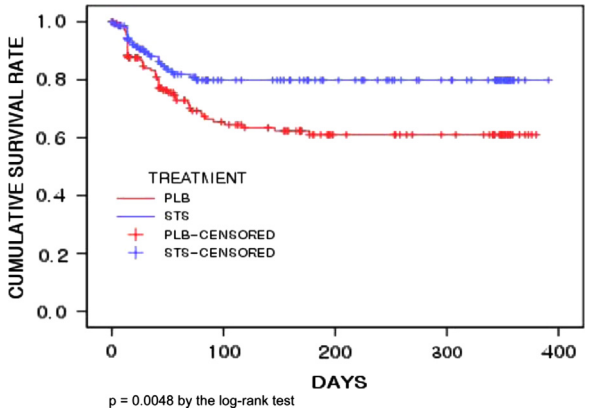

Fig. 1. Time to MDD relapse with STS and PLB. $p=0.0048$ by the log-rank test

Table 2
Cox proportional regression analysis of all variables for assessing predictors of relapse of MDD.

Variable	Variable hazard ratio[a]	Treatment-by-variable p-value[b]
Sex=female	0.790	0.658
Age (years) ≥45	1.160	0.662
Age (10 yr) at first MDD episode	0.837	0.034*
Early response	0.925	0.555
Melancholic subtype	1.004	0.310
Atypical subtype	1.000	0.294
Anxious subtype	1.006	0.984
AD Tx failures (≥1 AD failures)	1.076	0.620
Severe type (≥28 HAM-D 17 total)	0.957	0.073
Residual symptoms based on HAM-D 28 at the end of 10-week open-label phase	0.255~1.452	0.088~0.987
Medical History	0.085~1.520	0.042~0.966
Psychiatric History	1.213~4.762	0.767~0.973
Depressive symptoms based on HAM-D 28 (Cont.) at the beginning of 10-week open-label phase	0.778~1.398	/

HAM-D: Hamilton depression rating scale, K-M: Kaplan-Meier, MDD: major depressive disorder, PLB: placebo, STS: selegiline transdermal system,
♦ Age (years) at first MDD episode category: <20, 20≤ and <40, and 40 ≤.
♦ Medical History category: HEENT, endocrinal, musculoskeletal, hematologic, pulmonary, cardiovascular, gastro/hepatic, allergic, dermatologic, urologic/renal, immunological, neurological, reproductive illnesses were included as variables in analyzing.
♦ Other psychiatry history category: suicidal attempt, panic disorder, substance abuse, PTSD and eating disorders were included as variables in analyzing.
"Cont." indicates that the continuous form of the predictor variable is used.
"/" Indicates it is impossible to calculate figures.
**$p<0.01$ by Cox proportional regression.

[a] Variable hazard ratios were reported from model with treatment and predictor. Variable hazard ratios based on 2 categories are for the second category vs. the first category.
[b] From model with treatment, predictor, and interaction.
* $p<0.05$.

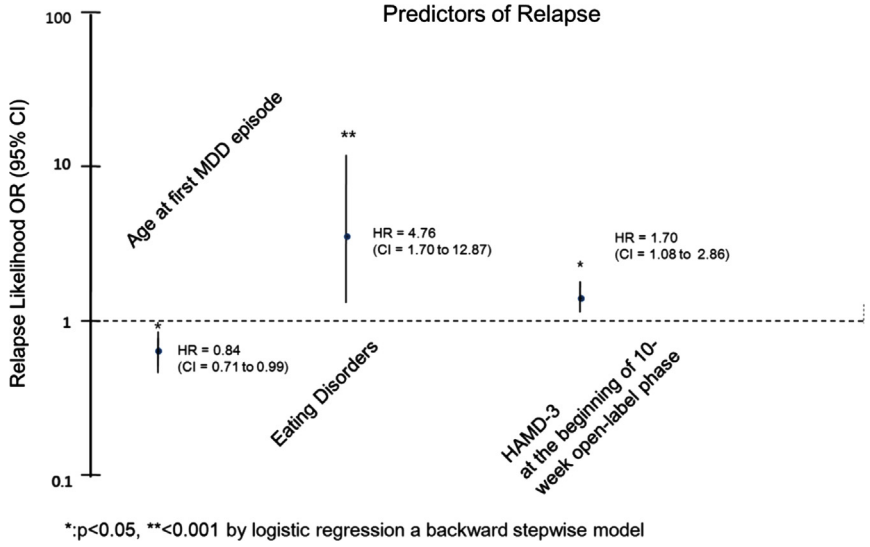

Fig. 2. Summary of Cox proportional regression analysis of significant variables in variable hazard ratio.

3. HAM-D 28 individual items at the beginning of the open label phase: suicidal ideation (HR=1.70, 95% CI=1.08–2.86 $p<0.05$) was predictive of relapse after controlling for the effect of treatment.

3.5. Final hazard model for predictor of relapse

The final predictors which were retained after accounting for all other significant predictor were ED illness history (HR=3.41, 95% CI=1.19–9.80, $p=0.022$) and suicidal ideation (HR=1.33, 95% CI=1.02–1.73, $p=0.037$). The treatment effect was also significant in this model indicating the relapse prevention efficacy for STS (HR=0.48, 95% CI=0.30–0.79, $p=0.003$).

4. Discussion

In this post-hoc analysis, we evaluated several potential demographic and clinical predictors which have been implicated in relapse of MDD. There were two important findings. First, we found age at onset of 1st MDD, eating disorders (ED) and suicidal ideation predicted higher relapse rate. Second, we confirmed the previous findings of lower overall relapse rate with STS compared to placebo.

Several studies have examined the role of age at onset of MDD as a potential predictor of relapse and found conflicting results. Consistent with our findings, few studies have reported that earlier age of onset of MDD is associated with higher risk of relapse (O'Leary and Lee, 1996; Klein et al., 1999; Gilman et al.,

2003), while others studies have found no association (Kovacs et al., 2003; Birmaher et al., 2004). Sample heterogeneity and number could be possible explanations for the discrepant findings.

Suicidal ideations during index episode are of clinical and research concern. Traditionally, clinical trials have excluded subjects with suicide risk, and therefore limited the study of their influence on the clinical course of illness. Notwithstanding these limitations, suicide attempts or suicidal ideation during the index episode have been found to predict relapse in MDD (Lewinsohn et al., 1994; Barkow et al., 2003).

While comorbid psychopathology such as dysthymia (Warner et al., 1992; Barkow et al., 2003), anxiety disorders (Wilhelm et al., 1999) and substance use disorders (Coryell et al., 1991; Alpert et al., 1994; Barkow et al., 2003) have been found to increase relapse risk in MDD, few studies have examined the role of comorbid eating disorders and the findings have not been consistent. Eating disorders have high rates (range between 50% and 75%) of comorbidity with MDD (American Psychiatric Association, 2006) and comorbid MDD and ED have been associated with adverse ED outcomes (Lowe et al., 2001; Berkman et al., 2007). Conversely, higher baseline depressive severity in ED patients has been found to be associated with higher likelihood of MDD relapse (Mischoulon et al., 2011).

The published literature regarding predictors of relapse in depression has implicated several other clinical variables; however the findings also have not been very consistent. Residual depressive symptoms (Fava et al., 2009; Nierenberg et al., 2010; Yang et al., 2010), and early response to treatment (Quitkin et al., 1984; Stewart et al., 1998; Mulder et al., 2006; Ciudad et al., 2012) have been among the more consistent predictors reported in trials. However, our study did not show predictive value of these variables for relapse of MDD. Differences in clinical population may be one explanation for the discrepant findings. Over half the sample had no history of previous antidepressant treatment, and subjects with comorbid Axis I disorders were excluded, yielding a sample which was different than the patient population seen in clinical practice or tertiary care settings. The overall relapse rates in the present study were low compared to other trials (STS = 16.8%, placebo = 30.7%). For example, in a similarly designed 52-week placebo controlled trial with fluoxetine, the relapse rates at the end of the continuation phase (6 months after randomization) were 35.2% for the fluoxetine group and 61.8% for the placebo group; after 1 yr, they were 45.9% for the fluoxetine group and 72.0% for the placebo group. Chronicity, symptom severity, a neurovegetative symptom pattern, and female gender were all associated with a significantly greater risk of relapse, with no difference observed between fluoxetine and placebo (McGrathand et al., 2006).

In this post-hoc analysis we did not observe a preferential effect of STS on atypical depression (HR = 0.83, $p = 0.73$) compared to non-atypical depression (HR = 0.45, $p = 0.004$). A meta-analysis of RCT in atypical depression (Henkel et al., 2006) found an effect size of 0.45 for a comparison of MAOIs vs. placebo, an effect size of 0.27 for MAOIs vs. tricyclic antidepressants and available data are insufficient for a direct comparison between MAOIs and selective serotonin reuptake inhibitors. Almost all the studies were conducted with oral, irreversible MAOIs and the authors mentioned the need for prospective studies testing more recently developed antidepressants with an improved safety profile.

The strengths of the trial were a large sample size, well defined criteria for relapse, a fixed dose strategy that minimized placebo responses related to expectations of dose increases, and systematic evaluation of subject compliance. The principal limitation of our study is that this was a post-hoc analysis of a relapse prevention trial that was not designed to examine predictors of relapse. Inherent in such post-hoc analyses is the paucity of clinical information on subjects. For example, information about level of treatment resistance, and family history was not fully available. The sequenced treatment alternatives to relieve depression (STAR*D) trial showed that remission rates decline with successive treatment failures indicating the adverse impact of treatment resistance (Rush et al., 2006). In the STAR*D trial, a comparison of tranylcypromine with extended release venlafaxine + mirtazapine group in patients who had failed to remit or could not tolerate three previous antidepressant trials found modest remission rates for both the tranylcypromine group (6.9%) and the extended-release venlafaxine plus mirtazapine group (13.7%) that were not significantly different (McGrath et al., 2006). Finally, the effect of comorbid Axis I disorders could not be examined because subjects with significant comorbid psychiatric disorders were excluded from the trial. Finally blood levels of selegiline were not obtained that may have provided additional information.

The clinical implications are as follows: First, continuation and maintenance treatment with STS at 6 mg/24 h dose which has no dietary restrictions in patients whose major depression has responded appears to be effective across a range of severity, symptom pattern, and chronicity. Second, irrespective of subtypes of major depression, patients benefit from maintenance treatment with STS. However it appears that those with younger age at onset of MDD and history of eating disorders or suicidal ideations may be at a higher risk of relapse. Whether this population required higher doses of STS, additional psychotherapy or alternative medications, need be studied further.

In conclusion, the majority of the clinical or demographic variables that were studied were not predictive of relapse. Although younger age at onset of MDD, history of eating disorders and suicidal ideation predicted relapse, given the post-hoc nature of analysis, the findings need confirmation from a prospective study. It appears that selegiline transdermal system was broadly effective in major depression across different subtypes and symptom clusters in preventing relapse compared to placebo.

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Conflict of interest

Dr. Portland is an employee of Mylan Specialty L.P. and may hold stock and/or stock options in Mylan. Dr. Jang has received grant/support from Janssen, Lundbeck and Otsuka; has served as a speaker for Janssen, Sanofi-Aventis, AstraZeneca, GlaxoSmithkline and Eli Lilly. Dr. Jung has nothing to disclose. Dr. Jae has received grant support from Janssen; has served as a speaker for Eli Lilly, GlaxoSmithkline, Pfizer, Janssen, Otsuka, AstraZeneca and Sanofi-Aventis. Dr. Pae has received research grants from GlaxoSmithKline Korea, GlaxoSmithKline, AstraZeneca Korea, Janssen Pharmaceuticals Korea, Eli Lilly Korea, KHIDI, Otsuka Korea, Wyeth Korea, Ministry of Health and Welfare, Korea Research Foundation, and Korean Institute of Science and Technology Evaluation and Planning; has received honoraria from and is on the speakers bureaus of GlaxoSmithKline Korea, Pfizer Korea, Lundbeck Korea, Sandoz Korea, AstraZeneca Korea, Jeil Pharmaceuticals, Eisai Korea, Janssen Korea, Eli Lilly Korea, and Otsuka Korea; and has stock holdings in Dongwha Pharmaceuticals. 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, Merck Asia; received research support from NIMH and HRSA; and owns stock in Atossa.Dr. Patkar is a consultant for and/or on the advisory boards of Bristol-Myers Squibb, GlaxoSmithKline, Mylan Specialty L.P., 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.

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References

Alpert, J.E., Maddocks, A., et al., 1994. Childhood psychopathology retrospectively assessed among adults with early onset major depression. Journal of Affective Disorders 31 (3), 165–171.

American Psychiatric Association, 2006. Treatment of patients with eating disorders, third ed.American Journal of Psychiatry, 163. American Psychiatric Association, Washington, D.C., pp. 4–54.

American Psychiatric Association, 2010. Practice guideline for the treatment of patients with major depressive disorder. American Psychiatric Association, Washington, D.C..

Amsterdam, J.D., 2003. A double-blind, placebo-controlled trial of the safety and efficacy of selegiline transdermal system without dietary restrictions in patients with major depressive disorder. Journal of Clinical Psychiatry 64 (2), 208–214.

Amsterdam, J.D., Bodkin, J.A., 2006. Selegiline transdermal system in the prevention of relapse of major depressive disorder: a 52-week, double-blind, placebo-substitution, parallel-group clinical trial. Journal of Clinical Psychopharmacology **26** (6), 579–586.

Amsterdam, J.D., Shults, J., 2005. MAOI efficacy and safety in advanced stage treatment-resistant depression—a retrospective study. Journal of Affective Disorders **89** (1–3), 183–188.

Anderson, I.M., Ferrier, I.N., et al., 2008. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2000 British Association for Psychopharmacology guidelines. Journal of Psychopharmacology 22 (4), 343–396.

Azzaro, A.J., Vandenberg, C.M., et al., 2006. Tyramine pressor sensitivity during treatment with the selegiline transdermal system 6 mg/24 h in healthy subjects. Journal of Clinical Pharmacology 46 (8), 933–944.

Barkow, K., Maier, W., et al., 2003. Risk factors for depression at 12-month follow-up in adult primary health care patients with major depression: an international prospective study. Journal of Affective Disorders 76 (1–3), 157–169.

Berkman, N.D., Lohr, K.N., et al., 2007. Outcomes of eating disorders: a systematic review of the literature. International Journal of Eating Disorders 40 (4), 293–309.

Birmaher, B., Williamson, D.E., et al., 2004. Clinical presentation and course of depression in youth: does onset in childhood differ from onset in adolescence? Journal of the American Academy of Child and Adolescent Psychiatry 43 (1), 63–70.

Bodkin, J.A., Amsterdam, J.D., 2002. Transdermal selegiline in major depression: a double-blind, placebo-controlled, parallel-group study in outpatients. American Journal of Psychiatry 159 (11), 1869–1875.

Ciudad, A., Alvarez, E., et al., 2012. Early response and remission as predictors of a good outcome of a major depressive episode at 12-month follow-up: a prospective, longitudinal, observational study. Journal of Clinical Psychiatry 73 (2), 185–191.

Coryell, W., Endicott, J., et al., 1991. Predictors of relapse into major depressive disorder in a nonclinical population. American Journal of Psychiatry 148 (10), 1353–1358.

Fava, M., Wiltse, C., et al., 2009. Predictors of relapse in a study of duloxetine treatment in patients with major depressive disorder. Journal of Affective Disorders 113 (3), 263–271.

Feiger, A.D., Rickels, K., et al., 2006. Selegiline transdermal system for the treatment of major depressive disorder: an 8-week, double-blind, placebo-controlled, flexible-dose titration trial. Journal of Clinical Psychiatry 67 (9), 1354–1361.

Gilman, S.E., Kawachi, I., et al., 2003. Socio-economic status, family disruption and residential stability in childhood: relation to onset, recurrence and remission of major depression. Psychological Medicine 33 (8), 1341–1355.

Henkel, V., Mergl, R., et al., 2006. Treatment of depression with atypical features: a meta-analytic approach. Psychiatry Research 141 (1), 89–101.

Katon, W.J., Fan, M.Y., et al., 2006. Depressive symptom deterioration in a large primary care-based elderly cohort. American Journal of Geriatric Psychiatry 14 (3), 246–254.

Klein, D.N., Schatzberg, A.F., et al., 1999. Age of onset in chronic major depression: relation to demographic and clinical variables, family history, and treatment response. Journal of Affective Disorders 55 (2–3), 149–157.

Kovacs, M., Obrosky, D.S., et al., 2003. Developmental changes in the phenomenology of depression in girls compared to boys from childhood onward. Journal of Affective Disorders 74 (1), 33–48.

Lam, R.W., Kennedy, S.H., et al., 2009. Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. III. Pharmacotherapy. Journal of Affective Disorders 117 (Suppl. 1), S26–43.

Lewinsohn, P.M., Zeiss, A.M., 1989. Probability of relapse after recovery from an episode of depression. Journal of Abnormal Psychology 9898 (2), 107–116.

Lowe, B., Zipfel, S., et al., 2001. Long-term outcome of anorexia nervosa in a prospective 21-year follow-up study. Psychological Medicine 31 (5), 881–890.

Mawhinney, M., Cole, D., et al., 2003. Daily transdermal administration of selegiline to guinea-pigs preferentially inhibits monoamine oxidase activity in brain when compared with intestinal and hepatic tissues. Journal of Pharmacy and Pharmacology 55 (1), 27–34.

McGrath, P.J., Stewart, J.W., et al., 2000. Predictors of relapse during fluoxetine continuation or maintenance treatment of major depression. Journal of Clinical Psychiatry 61 (7), 518–524.

Mcgrath, P.J., Stewart, J.W., et al., 2001. The use of monoamine oxidase inhibitors for treating atypical depression. Psychiatric Annals 31, 371–375.

McGrath, P.J., Stewart, J.W., et al., 2006. Predictors of relapse in a prospective study of fluoxetine treatment of major depression. American Journal of Psychiatry 163 (9), 1542–1548.

Mischoulon, D., Eddy, K.T., et al., 2011. Depression and eating disorders: treatment and course. Journal of Affective Disorders 130 (3), 470–477.

Mulder, R.T., Joyce, P.R., et al., 2006. Six months of treatment for depression: outcome and predictors of the course of illness. American Journal of Psychiatry 163 (1), 95–100.

Nemeroff, C.B., 2007. Prevalence and management of treatment-resistant depression. Journal of Clinical Psychiatry 68 (Suppl. 8), 17–25.

Nierenberg, A.A., Husain, M.M., et al., 2010. Residual symptoms after remission of major depressive disorder with citalopram and risk of relapse: a STAR*D report. Psychological Medicine 40 (1), 41–50.

O'Leary, D.A., Lee, A.S., 1996. Seven year prognosis in depression. Mortality and readmission risk in the Nottingham ECT cohort. British Journal of Psychiatry 169 (4), 423–429.

Quitkin, F.M., Rabkin, J.G., et al., 1984. Identification of true drug response to antidepressants. Use of pattern analysis. Archives of General Psychiatry 41 (8), 782–786.

Rush, A.J., Trivedi M.H., et al. 2006. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. American Journal of Pychiatry 163(11) 1905–1917.

Stewart, J.W., Quitkin, F.M., et al., 1998. Use of pattern analysis to predict differential relapse of remitted patients with major depression during 1 year of treatment with fluoxetine or placebo. Archives of General Psychiatry 55 (4), 334–343.

Suehs, B.T., Argo, T.R., et al., 2009. Texas Medication Algorithm Project Procedural Manual: Major Depressive Disorder Algorithms. Texas Department of State Health Services, Austin, TX.

Ten Doesschate, M.C., Bockting, C.L., et al., 2010. Prediction of recurrence in recurrent depression: a 5.5-year prospective study. Journal of Clinical Psychiatry 71 (8), 984–991.

Thase, M.E., 2007. Recognition and diagnosis of atypical depression. Journal of Clinical Psychiatry 68 (Suppl. 8), 11–16.

Thase, M.E., 2012. The role of monoamine oxidase inhibitors in depression treatment guidelines. Journal of Clinical Psychiatry 73 (Suppl. 1), 10–16.

Tollefson, G.D., Holman, S.L., 1993. Analysis of the Hamilton Depression Rating Scale factors from a double-blind, placebo-controlled trial of fluoxetine in geriatric major depression. International Clinical Psychopharmacology 8 (4), 253–259.

Warner, V., Weissman, M.M., et al., 1992. The course of major depression in the offspring of depressed parents. Incidence, recurrence, and recovery. Archives of General Psychiatry 49 (10), 795–801.

Wecker, L., James, S., et al., 2003. Transdermal selegiline: targeted effects on monoamine oxidases in the brain. Biological Psychiatry 54 (10), 1099–1104.

Wilhelm, K., Parker, G., et al., 1999. Psychological predictors of single and recurrent major depressive episodes. Journal of Affective Disorders 54 (1–2), 139–147.

Yang, H., Chuzi, S., et al., 2010. Type of residual symptom and risk of relapse during the continuation/maintenance phase treatment of major depressive disorder with the selective serotonin reuptake inhibitor fluoxetine. European Archives of Psychiatry and Clinical Neuroscience 260 (2), 145–150.