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Research paper

Comparison of effectiveness and side effects of selegiline transdermal system versus oral monoamine oxidase inhibitors and tricyclic antidepressants for treatment-resistant depression

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A B S T R A C T

Introduction: Several studies suggest that oral monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) may be more effective than serotonin reuptake inhibitors for treating treatment-resistant depression (TRD). Despite this advantage, they are now rarely prescribed due to concern over serious side effects. In contrast, selegiline transdermal system (STS) may present a safer alternative to oral MAOIs and TCAs; however, no studies have compared STS with other antidepressants.

Methods: Data from 117 patients who received STS, oral MAOIs, or TCAs for TRD were obtained from a university mood disorder clinic. Two linear regression models were created with severity and number of side effect categories endorsed as the dependent variable. Logistic regression models were created for each side effect category with presence of category as the dependent variable. In all models, antidepressant class was entered as the independent variable, with covariates.

Results: Although STS was less effective than oral MAOIs, it was significantly more effective than TCAs. STS treatment had significantly fewer side effect categories endorsed versus oral MAOIs and TCAs. Patients receiving STS were less likely to report gastrointestinal side effects versus TCAs and to endorse cardiovascular side effects versus oral MAOIs. In contrast, STS patients were more likely to report skin side effects versus oral MAOIs. There were no reported serious adverse events. Amongst the covariates, only the number of prior antidepressant trials predicted more side effect categories endorsed.

Conclusions: Although oral MAOI therapy has been eschewed by most clinicians, STS may be better tolerated than oral MAOIs and TCAs.

1. Introduction

In 2021, the National Institute of Mental Health (NIMH) estimated that 8.3 % of US adults experienced a major depressive episode in the past year, with 61.0 % receiving treatment (NIMH, 2021). Antidepressants are commonly prescribed to treat major depressive disorder (MDD) (Zhdanava et al., 2021), and have been shown to be effective for patients with more severe depression (NICE, 2011). However, many depressed patients fail to respond or remit during initial or subsequent antidepressant treatment (Pigott et al., 2023).

Patients who fail to respond or remit after two or more adequate antidepressant trials for MDD meet criteria for treatment-resistant depression (TRD) (Voineskos et al., 2020). Patients with TRD contribute a disproportionately high burden of illness compared to patients without TRD (Mrazek et al., 2014). For example, Mrazek et al. estimated that the national economic burden of TRD was around $29–48 billion annually. Furthermore, the largest treatment study to date in evaluating antidepressant effectiveness for outpatients with MDD, the *Sequenced Treatment Alternatives to Relieve Depression* (STAR*D) study, reported that 60 % of their patients failed to achieve remission even after a second, sequential course of antidepressant therapy (Pigott et al., 2023). Despite two more courses of antidepressant treatment for these patients, only an additional 2 % of STAR*D patients remitted.

Most patients who receive pharmacotherapy for MDD are now prescribed serotonin reuptake inhibitor(s) or serotonin-norepinephrine reuptake inhibitor(s) (Voineskos et al., 2020). Older pharmacologic classes of antidepressants (e.g., oral monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs)) are usually reserved for patients with more advanced-stage TRD compared to patients without TRD, due to concern over serious side effects. Several studies have shown that oral MAOIs and TCAs are effective in treating TRD (Amsterdam, 2006; Thase et al., 2002), with some studies reporting an advantage of MAOIs over TCAs (Kim et al., 2019; Thase et al., 1995). Despite this therapeutic advantage, clinicians continue to eschew oral MAOI and TCA therapy over concerns about dietary restrictions and possible hypertensive and other cardiovascular events.

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In this regard, first-generation MAOIs (e.g., phenelzine, tranylcypromine, isocarboxazid) are nonselective monoamine oxidase A and B enzyme inhibitors (Bied et al., 2015; Cristancho and Thase, 2016). MAO-A metabolizes norepinephrine, serotonin, and tyramine primarily in the gastrointestinal tract, whereas MAO-B metabolizes dopamine largely in the brain and blood platelets. Therefore, oral MAOIs can cause hypertensive events from ingestion of food and beverages high in tyramine content. In contrast, the selective MAO-B inhibitor, selegiline transdermal system (STS), was developed to not only maintain antidepressant effectiveness in reducing depressive symptoms, but also reduce the risk of tyramine-induced hypertension by bypassing the liver and gastrointestinal tract through the skin (Cristancho and Thase, 2016).

However, the prescription of STS remains low amongst clinicians due to the lack of published studies comparing the effectiveness and safety of STS to other antidepressants (Bied et al., 2015). Therefore, the current study aimed to compare the effectiveness and safety of STS treatment to oral MAOI and TCA treatments amongst patients with TRD. We hypothesized that STS would be superior to TCA treatment in patients with TRD and have a safer profile versus oral MAOIs and TCAs.

2. Methods

2.1. Subjects

Data were harvested from approximately 2500 clinical and research treatment charts of patients treated on the Depression Research Unit (DRU) at the University of Pennsylvania Medical Center between 1983 and 2015. At the time of initial patient contact, each subject underwent a detailed psychiatric history and semi-structured, diagnostic interview by JDA that was based upon the most current, available iteration of the Structured Clinical Interview for DSM (SCID) (Association, 2000).

In order to assess patients with treatment-resistant depression (TRD), we restricted inclusion criteria to patients with a treatment history of at least two prior adequate trials of an antidepressant (Voineskos et al., 2020). Other inclusion criteria for patients in our analyses were the following: a primary course of MAOI or TCA treatment; at least 18 years of age; a diagnosis of MDD; absence of psychosis, dementia, pregnancy, or an unstable medical condition (e.g., untreated hypertension diabetes mellitus, hepato-renal insufficiency, or malignancy); and no diagnosis of substance use disorder within the past three months.

The purpose and procedures of this study were reviewed and approved in accordance with the ethical standards of the Institutional Review Board (IRB) at the University of Pennsylvania. Informed consent by subject participants was waived by the IRB for this retrospective, chart review study.

2.2. Treatment

All pharmacotherapy administered on the DRU was conducted in accordance with the NIMH Treatment of Depression Collaborative Research Program (TDCRP) (Fawcett et al., 1987) and Good Clinical Practice Guidelines (Baber, 1994). This provided a 'real world' treatment approach to pharmacotherapy by not only allowing general medical oversight and advice-giving, but also minimizing the use of formalized, insight-oriented or behavioral forms of psychotherapy. All pharmacotherapy was individualized in accordance with relevant clinical and demographic variables (e.g., age, gender, number and type of prior antidepressant treatments, etc.) and administered at dose ranges and treatment durations considered to be clinically appropriate and adequate for each individual (Nierenberg et al., 1991). All oral MAOI-treated patients were administered a standardized low-tyramine diet and advised to avoid any serotonin-active medications (Shulman and Walker, 1999).

2.3. Outcome variables

Effectiveness was assessed using the Clinical Global Impressions-Severity (CGI-S) scale (Guy, 1976). Side effects were harvested from records of patient-reported and clinician-elicited safety profiles at each evaluation. The Patient-Rated Inventory of Side Effects (PRISE) (Rush et al., 2004) and the PRISE-Modified (PRISE-M) (Levy et al., 2021), assessments used to measure the frequency of side effects occurring in several organ/function domains, were used to categorize the side effect symptoms. Therefore, we classified side effects into the following systems: gastrointestinal; cardiovascular; skin; central nervous system (CNS); eye/ear; genital/urinary; sensory; sleep; sexual functioning; and other (agitation; anxiety; edema; weight gain; fatigue or drowsiness; muscle or joint ache; akathisia; and chocolate craving).

2.4. Statistical analyses

We tested for differences in effectiveness between STS versus oral MAOIs and TCAs by creating a linear regression model with CGI-S as the dependent variable, and antidepressant class (STS; oral MAOIs; TCAs) as a dummy coded independent variable. Gender, age, illness duration, episode duration, and number of prior antidepressant treatment trials were entered as demographic and clinical covariates. We also tested for differences in the number of side effect categories endorsed between STS versus oral MAOIs and TCAs by creating a similar linear regression model as noted above, except with the number of side effect categories endorsed as the dependent variable.

We assessed for differences in presence (or absence) of the side effect categories between STS versus oral MAOIs and TCAs by conducting logistic regression models with each side effect category as the dependent variable, and antidepressant class as a dummy coded independent variable. Gender, age, illness duration, episode duration, and number of prior antidepressant treatment trials were entered as demographic and clinical covariates. As there were 10 side effect categories, we intended to create 10 models; however, we only created 9 models because the STS condition did not have any patients who reported a side effect in the sexual functioning category. Because of the large number of post hoc tests, we only interpreted comparisons that met a Bonferroni-corrected α of $p < 0.0056$, which was calculated by dividing 0.05 by 9 (Bland and Altman, 1995). All analyses were conducted in R version 4.4.0 (Team, 2014).

3. Results

Table 1 presents the demographic and clinical characteristics of the 117 patients in our sample. Of the 117 patients, 33 received STS treatment; 53 received oral MAOI treatment; and 31 received TCA treatment. Table 2 provides the type of treatment, maximum daily dose, and duration of treatment trial. All 33 patients in the STS treatment condition received a maximum dose of 6 mg daily.

3.1. Effectiveness

Patients who received STS treatment had significantly higher (i.e., worse) CGI-S scores versus oral MAOI treatments ($b = -0.62$, $t = -2.14$, $p = 0.035$). However, patients who received STS treatment had significantly lower (i.e., better) CGI-S scores versus patients who received TCA treatments ($b = 0.81$, $t = 2.46$, $p = 0.016$). No other demographic or clinical covariates were significant. See Fig. 1.

3.2. Side effect categories

Patients prescribed STS reported fewer categories of side effects versus oral MAOI treatments ($b = 0.84$, $t = 2.03$, $p = 0.047$) and TCA treatments ($b = 1.19$, $t = 2.54$, $p = 0.013$). Only the number of prior antidepressant treatment trials was significant amongst the covariates

Table 1
Demographic and clinical characteristics by treatment group.

Variable	STS ($n = 33$)	Oral MAOIs ($n = 53$)	TCAs ($n = 31$)	All subjects ($n = 117$)	p-value
Age (years), mean ± SD	41.2 ± 11.8	42.7 ± 13.3	45.6 ± 17.1	43.0 ± 14.0	0.445
Female, %	54.5 %	66.0 %	45.2 %	57.3 %	0.164
Duration of illness (years), mean ± SD	19.5 ± 12.3	16.9 ± 10.7	13.5 ± 12.0	16.8 ± 11.6	0.118
Duration of current depressive episode (years), mean ± SD	4.4 ± 5.2	6.0 ± 6.5	3.7 ± 4.5	4.9 ± 5.7	0.168
Number of prior antidepressant trials, mean ± SD	4.5 ± 2.9	6.7 ± 4.5	5.3 ± 4.7	5.7 ± 4.2	0.052

p-values were estimated using ANOVA and χ^2 tests for continuous and categorical variables, respectively.

Table 2
Type of treatment, maximum daily dose, and duration of treatment trial.

Antidepressant treatment	Subjects (n)	Daily dosage (mg)	Duration of trial (weeks)
Selegiline Transdermal System	33	6 ± 0	15.2 ± 11.8
MAOIs			
Tranylcypromine	21	69 ± 41	90.2 ± 227.8
Phenelzine	18	64 ± 19	35.1 ± 44.4
Isocarboxazid	14	49 ± 25	25.2 ± 23.6
TCAs			
Desipramine	20	258 ± 82	12.2 ± 8.5
Doxepin	4	206 ± 153	18.0 ± 8.5
Imipramine	3	283 ± 104	12.7 ± 10.8
Chlorimipramine	2	225 ± 106	30.0 ± 36.8
Protriptyline	2	32 ± 32	12.0 ± 11.3

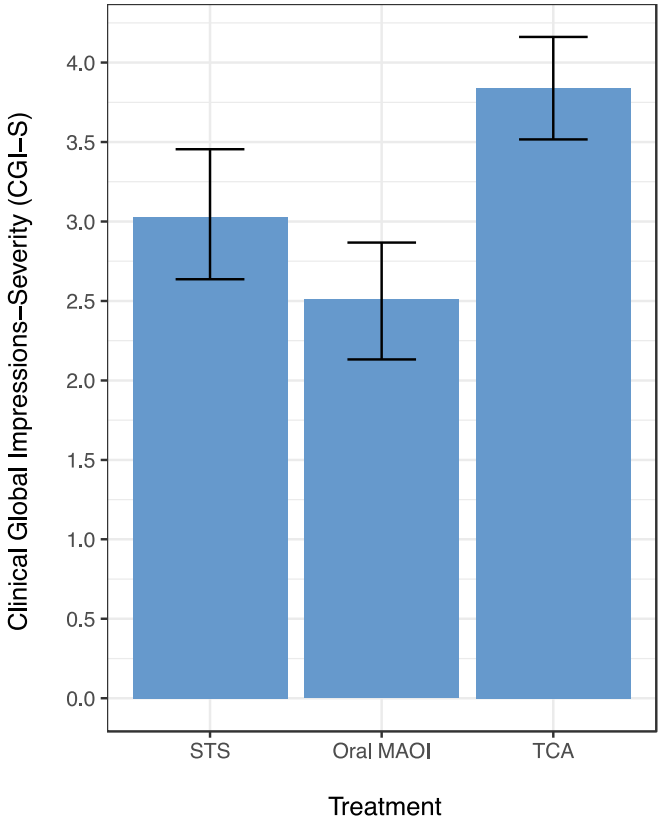

Fig. 1. Mean antidepressant effectiveness (CGI-S).

($b = 0.08$, $t = 2.05$, $p = 0.044$). See Fig. 2.

Table 3 presents the number of patients who endorsed each side effect category for the three treatment groups. Patients receiving STS had a lower likelihood of reporting gastrointestinal side effects versus

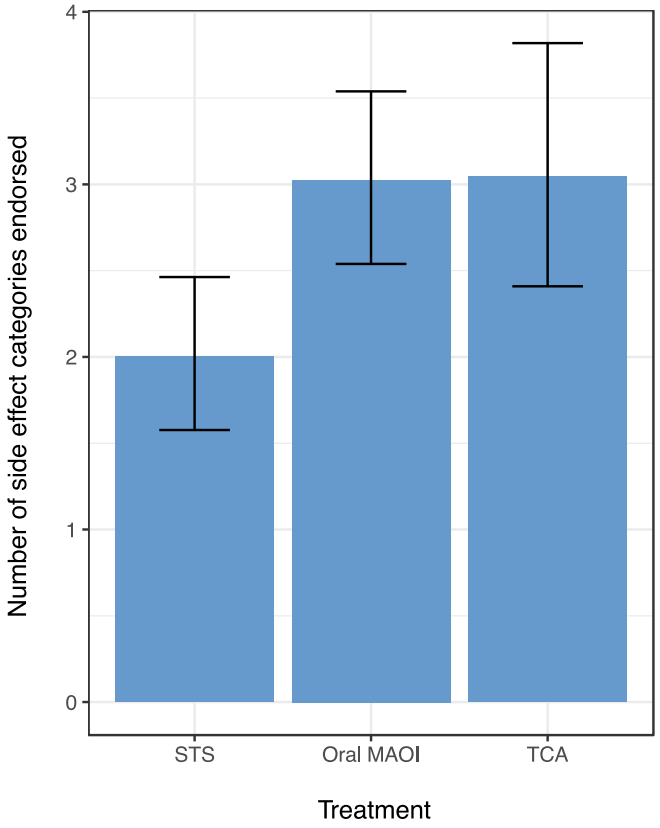

Fig. 2. Mean number of side effect categories endorsed.

patients receiving TCA treatment ($OR = 15.88$, $z = 3.23$, $p = 0.001$) and a lower likelihood of endorsing cardiovascular side effects versus patients receiving oral MAOI treatment ($OR = 10.65$, $z = 2.83$, $p = 0.005$). However, patients receiving oral MAOIs had a lower likelihood of reporting skin side effects than patients receiving STS ($OR = 0.03$, $z = -3.83$, $p < 0.001$). There were no reported serious adverse events across the three treatment conditions (e.g., hypertensive event, serotonin syndrome).

4. Discussion

We are unaware of any previously published studies that compared the effectiveness and tolerability of STS with oral MAOIs or other antidepressants for patients with TRD. Using retrospective data from patients who received STS, oral MAOI, or TCA treatment for TRD, we found that patients reported fewer side effect categories during STS treatment compared to oral MAOIs and TCAs. While oral MAOIs exhibited greater antidepressant effectiveness versus STS, the latter therapy still demonstrated significant superiority versus TCA therapy.

While there have been no direct comparisons between STS and other

Table 3
Number of patients endorsing side effect category across treatment groups, and the logistic regression for probability of endorsing side effect category (controlling for covariates).

Side effect category	STS (n = 33)	Oral MAOIs (n = 53)	TCAs (n = 31)	Logistic regression: MAOI vs STS			Logistic regression: TCA vs STS		
				OR	*z*	*p*	*OR*	*z*	*p*
Gastrointestinal	10 (30.3 %)	23 (43.4 %)	19 (61.3 %)	3.02	1.86	0.062	15.88	3.23	0.001*
Cardiovascular	2 (6.1 %)	20 (37.7 %)	6 (19.4 %)	10.65	2.83	0.005*	5.66	1.90	0.058
Skin	16 (48.5 %)	4 (7.5 %)	5 (16.1 %)	0.03	−3.83	<0.001*	0.14	−2.50	0.012
CNS	7 (21.2 %)	16 (30.2 %)	10 (32.3 %)	1.53	0.70	0.482	1.89	0.96	0.338
Eye/ear	2 (6.1 %)	3 (5.7 %)	0 (0.0 %)	0.93	−0.07	0.941	–	–	–
Genital/urinary	1 (3.0 %)	5 (9.4 %)	4 (12.9 %)	2.76	0.83	0.409	3.84	1.07	0.283
Sensory	1 (3.0 %)	2 (3.8 %)	6 (19.4 %)	1.38	0.22	0.823	33.71	2.46	0.014
Sleep	5 (15.2 %)	18 (34.0 %)	3 (9.7 %)	3.03	1.73	0.085	0.75	−0.34	0.735
Sexual functioning	0 (0.0 %)	5 (9.4 %)	3 (9.7 %)	–	–	–	–	–	–
Other	8 (24.2 %)	22 (41.5 %)	11 (35.5 %)	2.60	1.61	0.108	2.80	1.51	0.131

* Significant at the Bonferroni-corrected α of $p < 0.0056$.

antidepressants, Rossano et al. (2023) conducted a systematic review and meta-analysis to assess the efficacy and tolerability of oral and transdermal selegiline formulation for several mental health disorders; they concluded that the oral formulation of selegiline had better efficacy for treating depression than STS. Our results in the current analysis showed a similar finding: that STS was less effective than oral MAOIs in patients with TRD.

In the present study, all patients in the STS treatment condition received a standardized dosage of 6 mg daily, which is the lowest of the available STS dosages (i.e., 6 mg/day, 9 mg/day, and 12 mg/day) (Bied et al., 2015). Therefore, patients in our current study may have experienced a larger therapeutic effect – perhaps even to a similar level as the oral MAOIs – at higher doses of STS. However, there also may have been decreased tolerability. While a tyramine-restricted diet is not necessary for STS at a dose of 6 mg daily, the U.S. Food and Drug Administration recommends a low-tyramine diet with the administration of higher daily STS doses due to limited safety data (Asnis and Henderson, 2014).

STS was developed to reduce the risk of tyramine-induced hypertensive events by bypassing the liver and intestine via direct transdermal absorption (Cristancho and Thase, 2016). While the current study found that STS resulted in a lower likelihood of reporting gastrointestinal side effects versus TCA therapy and cardiovascular side effects versus oral MAOI treatment, we also observed that STS was associated with a higher likelihood of reported skin side effects versus oral MAOI treatment. The current findings are consistent with Bodkin and Amsterdam's (2002) and Amsterdam's (2003), in which they concluded that skin reactions at the patch site occurred more frequently in the STS than placebo condition.

Interestingly, the number of prior antidepressant treatment trials predicted a higher number of side effect categories endorsed. This may reflect the phenomenon of sensitization to antidepressants, in which patients who were treated with more prior antidepressant trials demonstrated an increased risk of side effects (Amsterdam and Kim, 2019; Fava, 2020; Fava and Offidani, 2011).

4.1. Limitations

Several caveats should be considered when interpreting our results. For example, the current analysis was retrospective in nature with data harvested from clinic charts of subjects treated with either TCA or MAOI therapy for TRD, the sample size for each of the treatment conditions was relatively small, and the measurements for effectiveness and side effects endorsed were not standardized. In addition, the dose and duration of the TCA and oral MAOI therapy were not standardized, but rather administered in a dose escalation fashion based largely upon 'real world' clinical response and tolerability. All outcome ratings were performed in a retrospective fashion via a chart review undertaken by only one treating clinician (JDA) at multiple time points; therefore, the primary outcome measure used for this analysis was the CGI—S. It also is possible that the longer oral MAOI (versus TCA and STS) treatment duration in the current study may have contributed to its greater effectiveness, and that this observation was an artifact of longer treatment duration. Furthermore, while we were able to comment on the number of side effect categories endorsed, and the likelihood of patients reporting those categories, we did not have data informing patients' subjective experience of the burden, intensity, or frequency of these side effects (Kim and Xu, 2024; Wisniewski et al., 2006).

4.2. Future directions

Future studies should be conducted to compare the relative efficacy and tolerability of STS versus other antidepressants through a randomized controlled trial with larger sample sizes. A future study should attempt to establish a dose-response relationship of STS for both effectiveness and tolerability. It would be interesting if a future study examined the extent to which a tyramine-restricted diet is required at higher doses of STS treatment (Cristancho and Thase, 2016; Robinson and Amsterdam, 2008).

In conclusion, the current analysis suggests that STS treatment may be a reasonable alternative to oral MAOIs and TCAs for the treatment of TRD, with a more favorable side effect profile.

CRediT authorship contribution statement

Thomas T. Kim: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Colin Xu:** Writing – review & editing, Methodology, Formal analysis. **Jay D. Amsterdam:** Writing – review & editing, Investigation, Conceptualization.

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Declaration of competing interest

None.

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