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Research paper

Relative effectiveness of tricyclic antidepressant versus monoamine oxidase inhibitor monotherapy for treatment-resistant depression

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A B S T R A C T

Objectives: Antidepressants may be less effective in treatment-resistant depression (TRD). In this exploratory study, we examined the widely held hypothesis that monoamine oxidase inhibitor (MAOI) therapy may be superior to tricyclic antidepressant (TCA) therapy for TRD. We also examined the influence of the number of prior treatment trials on TCA versus MAOI effectiveness in TRD.

Methods: Data were retrospectively extracted from approximately 2,500 treatment charts of patients with TRD who were attending a university mood disorder clinic between 1983 and 2015. Hierarchical linear modeling was used to examine the efficacy of drug class on outcome as well as the interaction between drug class and the number of prior antidepressant trials.

Results: 147 treatment outcome observations were made from 94 unipolar, depressed patients who either received TCA ($N = 47$) or MAOI ($N = 100$) monotherapy for TRD. For patients unresponsive to at least one prior trial, drug class significantly predicted end-of-treatment CGI/S scores, with TCAs showing worse (i.e., higher) end-of-treatment CGI/S scores relative to MAOI therapy ($b = 1.04$, $t = 4.98$, $p < 0.0001$). When examining the interaction between drug class and the number of prior antidepressant trials, the interaction effect was significant ($b = -0.50$, $t = -2.43$, $p = 0.02$); however, the advantage for MAOI versus TCA therapy decreases with more prior, failed, antidepressant trials.

Conclusion: Results suggest that MAOIs may be more effective than TCAs for early stage TRD. This difference in effectiveness between MAOIs and TCAs diminished as the number of prior treatment trials increased. However, the TCA sample size was limited and the analysis was retrospective with non-randomized conditions.

1. Introduction

When not adequately treated, major depressive disorder (MDD) accounts for more than 11% of the total, worldwide disease burden with potentially devastating consequences (Greden, 2001). Antidepressants have shown only modest overall efficacy for MDD and may be less effective for treatment-resistant depression (TRD). For example, results from the prospective, 'real world' *Sequenced Treatment Alternatives to Relieve Depression* (STAR*D) study suggested that repeated antidepressant treatment trials in non-remitting MDD subjects produced a cumulative remission rate of 67% (Rush et al., 2006). However, this appeared to be dependent upon the number of prior antidepressant trials that a subject received; in fact, the likelihood of remission decreased with each increase in antidepressant treatment trial (Amsterdam and Shults, 2005; Amsterdam et al., 2009; Fava et al., 2006; McGrath et al., 2006). Thus, antidepressants appeared to be less effective for patients with more advanced levels of TRD (Amsterdam and Shults, 2005; Amsterdam et al., 2009).

Although a universally accepted definition for staging TRD does not yet exist, some investigators have suggested that TRD be defined as non-response to initial antidepressant therapy; while others have suggested nonresponse to at least two antidepressant trials (Malhi et al., 2005; Souery et al., 1999). A systematic review identified five staging models for TRD, as reflected in the STAR*D study (Rush et al., 2006). Each stage increased by the number of prior antidepressant trials and was accompanied by a decrease in remission rates. For example, by treatment step 3 of the STAR*D study (i.e., non-response to at least 2 prior antidepressant trials), remission rates were only 12.3% for patients treated with mirtazapine and 19.8% in patients treated with nortriptyline (Fava et al., 2006). Finally, at STAR*D treatment step 4 (i.e., nonresponse to at least 3 prior antidepressant trials), remission rates were 13.7% for patients treated with combined mirtazapine plus venlafaxine, and only 6.9% for patients treated with tranylcypromine monotherapy (McGrath et al., 2006). Similar findings were observed in other studies of advanced stage TRD with tricyclic antidepressant (TCA) therapy (Nierenberg et al., 1994, **2003**) and with monoamine oxidase inhibitor (MAOI) therapy (Amsterdam and Shults, 2005).

Despite these low remission rates in TRD patients, there continues to be a widely held view in clinical psychopharmacology (with some evidence-based data to support it) that TCAs and especially MAOIs may be effective for patients with more advanced stage TRD who are unresponsive to prior antidepressant therapy (Amsterdam and Shults,

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2005; Fava, 2003; Nolen et al., 1988). Furthermore, a review of 20 studies of MAOI therapy for TRD found that more than 50% of TCA-resistant patients responded to MAOI therapy; although many of these studies were not well designed and underpowered (Thase et al., 1995). Nevertheless, despite endorsement of MAOI therapy for TRD by the American Psychiatric Association (Karasu et al., 2000) and the British Association for Psychopharmacology (Anderson et al., 2000), clinicians rarely prescribe MAOIs for TRD, and often treat TRD with unconventional and untested drug combinations of unknown effectiveness (Amsterdam and Shults, 2005; McGrath et al., 2006).

In the current exploratory study, we tested the widely held hypothesis that MAOI therapy is superior to TCA therapy for TRD patients. We also assessed whether the effectiveness of TCA or MAOI therapy may be adversely affected by the number of prior antidepressant trials. To test the latter hypothesis, we examined the interaction between the type of antidepressant treatment condition and the number of prior antidepressant trials.

2. Methods

2.1. Subjects

The data for this retrospective, chart review study were harvested from approximately 2,500 clinical and research treatment charts of patients treated at the Depression Research Unit (DRU) of the University of Pennsylvania Medical Center between 1983 and 2015. Charts were retrospectively examined in alphabetical order using family name, starting from A to Z; with subjects included in the database being ≥18 years old, having a history of TRD who were either partially or non-responsive to at least one prior, adequate antidepressant treatment trial and who also received at least one adequate treatment trial with a TCA and/or a MAOI at any time during the life-time course of their affective illness.

At the time of initial 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) format for either DSM-III, DSM-III-R, or DSM-IV-TR (DSM-III, 1980; DSM-III-R, 1987; DSM-IV-TR, 1994). All subjects were at least 18 years old and met DSM-III, DSM-III-R, or DSM-IV-TR criteria for unipolar major depressive disorder, which was validated by the most currently available iteration of the SCID format (First, 2005). Subjects had a minimum Clinical Global Impressions/Severity (CGI/S) scale score ≥ 4 (i.e., at least moderately depressed) (Busner and Targum, 2007). Subjects with other, non-affective DSM Axis I or II disorders were not excluded from the database, provided that the concurrent, non-affective disorders did not constitute the primary psychiatric diagnosis. This procedure provided for more 'real world' cohorts of patients with TRD.

Exclusion criteria for incorporation into the database were: subjects younger than 18 years old, current DSM Axis I primary diagnosis other than unipolar major depressive episode, mania, psychosis, substance use disorder within the preceding 3 months, dementia, pregnancy, breast feeding, or an unstable medical condition (e.g., untreated hypertension diabetes mellitus, hepato-renal insufficiency, or malignancy). [*Note* – Subjects who received adequate antidepressant therapy on more than one occasion with no response or who received antidepressant therapy for another depressive episode were recorded in the database as separate treatment observation entries, but with the same subject identification code. Consequently, we applied repeated measures methodology using hierarchical linear modeling in order to control for multiple observations from these subjects (Gelman and Hill, 2006), as described in the *Statistical methods* section.]

2.2. Procedures

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 university IRB for this retrospective, chart review study; and all data identification and database storage conformed with Good Clinical Practice guidelines for human research (Baber, 1994), with oversight by the local Office of Human Research.

Best estimates of the number of prior major depressive episodes since onset of illness were ascertained at the initial clinic intake from each subject via a detailed, semi-structured clinical interview (First, 2005) and by a detailed examination of each subsequent narrative chart entry. Similarly, best estimates of prior adequate antidepressant and other psychotropic drug therapy during prior and current depressive episodes were determined at the time of initial subject intake via the SCID format and available medical and pharmacy records. Adequacy of all subsequent antidepressant and adjunctive antidepressant treatment trials was established by review of each narrative chart entry using an adaptation of the Harvard Antidepressant Treatment History of the SCID (Nierenberg and Amsterdam, 1990; Nierenberg et al., 1991a). Treatment trials of unverified adequacy were excluded, while trials of borderline adequacy were individually examined by the investigators for a consensus determination. Efficacy was retrospectively assessed via review of chart narrative entries using the Clinical Global Impressions/Severity (CGI/S) and Clinical Global Impressions/Change (CGI/C) scales (Guy, 1976). However, for the present analysis, the primary outcome variable was end-of-treatment CGI/S score.

2.3. Treatment

For the current analysis, only subjects with a primary diagnosis of unipolar major depressive disorder were included. 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 whereby general medical oversight and advice-giving were permitted, while the use of formalized, insight-oriented or behavioral forms of psychotherapy were minimized. All pharmacotherapy was individualized in accordance with relevant clinical and demographic factors (e.g., age, gender, concurrent medical disorders, number of prior treatments, etc.) and administered at dose ranges and treatment durations considered to be clinically appropriate and adequate for each individual (Nierenberg et al., 1991b) (see Tables 1 and 2). When clinically warranted, plasma TCA concentrations were obtained to assure appropriate TCA dosage in patients who were slow or rapid drug metabolizers (Schatzberg et al., 1986). All MAOI-treated patients were administered a standardized low-tyramine diet (Shulman and Walker, 1999) and advised to avoid any serotonin-active medications.

2.4. Statistical methods

Analyses were conducted using *R* 3.4.0 (Team, 2014). Subjects with

Table 1
MAOI type, mean maximum daily dose, and duration of treatment trials.

MAOI type	Subjects (n)	Daily dose (mg)[a]	Duration of trial (weeks)[a]
Isocarboxazid	26	51.2 ± 23.6	34.6 ± 59.4
Phenelzine	24	63.9 ± 19.3	32.9 ± 42.1
Selegiline (Oral Route)	6	47.5 ± 27.2	21.6 ± 7.3
Tranylcypromine	44	64.0 ± 38.5	60.1 ± 161.8

[a] Statistics are reported as mean ± standard deviation.

Table 2
TCA type, mean maximum daily dose, and duration of treatment trials.

TCA type	Subjects (n)	Daily dosage (mg)[a]	Duration of trial (weeks)[a]
Clomipramine	7	214.3 ± 95.6	15.4 ± 22.8
Desipramine	27	261.1 ± 71.2	12.8 ± 7.5
Doxepin	6	195.8 ± 120.8	18.0 ± 8.5
Imipramine	5	300.0 ± 93.5	37.5 ± 50.4
Protriptyline	2	17.5 ± 10.6	20 ± 0

[a] Statistics are reported as mean ± standard deviation.

missing data from both outcome and independent variables were excluded from analyses. Initial analyses summarized baseline demographic and clinical variables. Outlier values ≥ 3 standard deviations (SD) above the mean were winsorized. All baseline predictors were then mean-centered and standardized using the preProcess() function from the *R* package caret (Kuhn, 2015) to protect against potential errors in statistical inference (Kraemer and Blasey, 2004). The primary outcome variable was end-of-treatment CGI/S score. In order to control for individual subject differences, we used hierarchical linear modeling that allowed for random intercept of subject, via the package lme4 (Bates et al., 2014).

For the primary effectiveness comparison, we modeled CGI/S scores as predicted by the type of antidepressant received (i.e., TCA versus MAOI), while including the following covariates: age, gender, illness length, episode duration, and number of prior adequate antidepressant trials. To determine whether the number of prior trials moderated the effectiveness of the type of antidepressant received, we modeled CGI/S scores by the interaction between type of antidepressant and number of prior treatment trials (with age, gender, illness length and, episode duration included as covariates). Two-sided tests of hypotheses and a $p < 0.05$ value were used to determine statistical significance.

3. Results

3.1. Baseline clinical & demographic features

A total of 147 treatment outcome observations were made from 94 unipolar, depressed subjects who received either adequate TCA ($N = 47$) or MAOI ($N = 100$) monotherapy. Of these entries, 53 subjects received two or more adequate TCA and/or MAOI therapy on two or more separate occasions over the course of their affective illness. Of the 147 observations, 8 subjects had one prior antidepressant trial, 18 subjects had two prior trials, 17 subjects had three prior trials, and 104 subjects had four or more prior antidepressant trials.

Of the subjects prescribed an MAOI, 44% received tranylcypromine, 26% received isocarboxazid, 24% received phenelzine, and 6% received oral selegiline. Of the subjects prescribed a TCA, 57% received desipramine, 15% received clomipramine, 13% received doxepin, 11% received imipramine, and 4% received protriptyline.

Table 3 displays the comparative clinical and demographic data for the TCA and MAOI treatment conditions. There were a greater number of prior antidepressant treatment trials for the MAOI group ($p = 0.03$) and a longer current episode duration for the MAOI group ($p = 0.04$). Tables 1 and 2 display the average maximum dose and duration of treatment trial for each type of TCA or MAOI administered.

3.2. Relative effectiveness of TCA versus MAOI monotherapy

For subjects unresponsive to ≥ 1 prior, adequate antidepressant trial, the treatment condition significantly predicted end-of-treatment CGI/S scores, with TCA therapy showing higher (i.e., worse) end-of-treatment CGI/S score ratings relative to those of MAOI therapy ($b = 1.04$, $t = 4.98$, $p < 0.0001$). There was no statistically significant effect of other pre-treatment covariates on outcome.

3.3. Interaction between treatment condition and number of prior treatment trials

We modeled CGI/S scores as predicted by the interaction between antidepressant condition and the number of prior treatment trials. The main effect of antidepressant drug class significantly predicted end-of-treatment CGI/S scores; patients receiving TCAs had higher (i.e., worse) end-of-treatment CGI/S scores versus MAOIs ($b = 0.99$, $t = 4.80$, $p < 0.0001$). The main effect of number of prior treatments on CGI/S scores was not significant ($b = 0.06$, $t = 0.46$, $p = 0.65$). However, the interaction between the type of antidepressant and number of prior treatments was significant ($b = -0.50$, $t = -2.43$, $p = 0.02$). No other covariates were significant.

Fig. 1 shows the interaction effect between the treatment condition and the number of prior antidepressant trials, and suggests that MAOIs are more effective than TCAs for subjects who have fewer prior antidepressant trials. However, the difference in efficacy between MAOIs and TCAs diminishes as the number of prior treatment trials increases.

4. Discussion

The current study found that MAOI therapy was generally more effective than TCA therapy for subjects with TRD. In contrast to the findings of Amsterdam and Shults (2005), we did not find that the main effect of the number of prior antidepressant trials had a significant impact on outcome and, therefore, could not conclude that MDD patients with more advanced TRD (i.e., more prior antidepressant treatment trials) had a poorer outcome. However, the interaction between the type of antidepressant and the number of prior treatment trials was significant, indicating that while MAOIs were generally more effective than TCAs for early stage TRD, the added benefit from MAOIs decreased for subjects with a history of more prior antidepressant exposure. Considering that prior studies showed a significant negative relationship between the number of prior antidepressant trials and likelihood of

Table 3
Baseline characteristics for subjects receiving TCA or MAOI monotherapy.

Characteristic	All subjects ($N = 147$)	TCA ($N = 47$)	MAOI ($N = 100$)	*P* value
Demographics				
Age	42.9 ± 14.9	43.2 ± 16.8	42.8 ± 14.1	0.89
Female	53.7%			
(79/147)	44.7%			
(21/47)	58.0% (58/100)	0.13		
Clinical features				
Number of prior antidepressant trials	7.0 ± 5.0	5.7 ± 4.8	7.6 ± 5.1	0.03*
Illness duration (years)	15.2 ± 10.2	13.5 ± 10.1	15.9 ± 10.3	0.19
Episode duration (years)	6.3 ± 6.1	4.9 ± 5.4	7.0 ± 6.4	0.04*

Statistics reported are in percentages (n/N) for categorical variables and mean ± SD (n) for continuous variables. *P* values reported are based on χ^2 test for categorical variables and ANOVA test for continuous variables.
* $p < 0.05$, ** $p < 0.01$

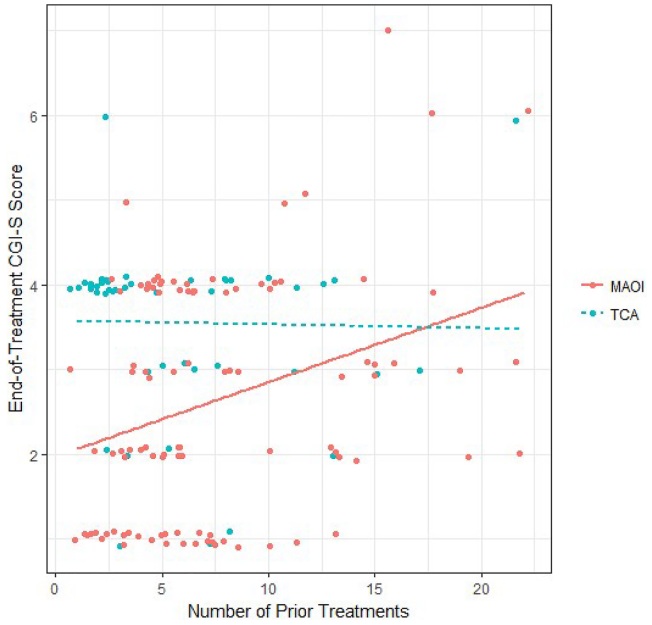

Fig. 1. Interaction between prior antidepressant trials and type of antidepressant received.

response (Rush et al., 2006), we were surprised to find that the main effect of the number of prior antidepressant trials in the current study was not significant for TCAs. This could have resulted from the smaller sample size of the TCA condition and/or that subjects who received TCA monotherapy in the current study had a lower number of prior antidepressant trials (versus the MAOI condition; $p = 0.03$). This difference may have reduced the necessary power to detect this main effect for subjects receiving TCA monotherapy.

Several expert reports have suggested that TCA and MAOI therapy may be effective for TRD (Amsterdam, 2006; Amsterdam and Shults, 2005; Anderson et al., 2000; Lesse, 1978; Nolen, 1989; Thase et al., 1995). Despite concerns over cardiovascular and dietary restrictions associated with MAOI therapy (Blackwell et al., 1967; Sjoqvist, 1965), there has support for MAOI use for TRD (Amsterdam, 2006; Kennedy, 1997; McGrath et al., 2006; Thase et al., 1995). One early evidence-based review of TRD suggested that MAOI therapy may be more effective than TCA therapy in non-endogenous MDD (White and Simpson, 1981), and this observation was confirmed in more than 400 subjects undergoing double blind, placebo-controlled TCA versus MAOI therapy (Liebowitz et al., 1988; McGrath et al., 1993). In these studies, phenelzine, an MAOI, was found to be superior to imipramine, a TCA, and placebo. From these results and other studies of MAOIs (Himmelhoch et al., 1991; Thase et al., 1992a; Thase et al., 1992b), the *International Expert Panel on Refractory Depression* recommended that adequate treatment of advanced stage TRD should always include the use of MAOI therapy (Souery et al., 1999).

In addition, a review of 20 studies of TCA and MAOI therapy of TRD found that more than 50% of TCA non-responders benefitted from MAOI therapy (Thase et al., 1995). Other studies have also shown efficacy of MAOI therapy in TCA-resistant depression. For example, a study of high dose tranylcypromine in TCA-resistant subjects found a 72% response rate and a 50% remission rate in subjects unresponsive to an average of seven prior antidepressant treatment trials (Amsterdam, 1991). In another study, Himmelhoch et al. found tranylcypromine to be superior to imipramine monotherapy in a double-blind study (Himmelhoch et al., 1991); while a follow up, cross-over study in treatment non-responders found a 75% response rate to tranylcypromine in imipramine-resistant subjects, and only a 25% response rate with imipramine in tranylcypromine non-responders (Thase et al., 1992a,b).

Several caveats should be considered in the interpretation of the current data. For example, the current analysis was retrospective in nature with data harvested from clinic charts of subjects treated with either TCA and/or MAOI therapy for TRD. As a result, information on the adequacy of prior AD trials was necessarily limited to the treatment administered at the time and based primarily upon the judgment of the treating clinician on dosage and duration of therapy. While plasma TCA levels were often obtained to determine the adequacy of TCA dosing in individuals suspected of being rapid pharmacokinetic metabolizers of TCA therapy, they were not routinely obtained in every subject not suspected of being a rapid TCA metabolizer. Moreover, some subjects may have had a partial response to one or more prior antidepressant treatments in the current depressive episode, and this factor may have affected the outcome of TCA or MAOI therapy. The dose and duration of the TCA and MAOI therapy was 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 the treating clinician. It is possible that the shorter TCA (versus MAOI) treatment duration in the current study may have contributed to the greater MAOI response rate, and that this observation was an artifact of longer treatment duration or a regression toward the mean.

Finally, the sample size of the two treatment cohorts was limited with 147 treatment observations derived from 94 subjects administered either TCA or MAOI monotherapy. Also, the current study only compared TCA with MAOI monotherapy, and did not compare TCA or MAOI outcome to that of other antidepressant drug classes.

In summary, MAOIs appear to be efficacious for subjects with early-stage TRD compared to TCAs; however, this advantage seems to decrease with an increase in number of prior antidepressant trials. Future research should attempt to replicate this phenomenon and examine, with a larger sample, whether TCA therapy exhibits a similar decrease in effectiveness as MAOI therapy.

Conflict of interest

Mr. Thomas Kim is not a member of any pharmaceutical industry-sponsored advisory board or speaker's bureau, and has no financial interest in any pharmaceutical or medical device company. Mr. Colin Xu is not a member of any pharmaceutical industry-sponsored advisory board or speaker's bureau, and has no financial interest in any pharmaceutical or medical device company. Dr. Amsterdam is not a member of any pharmaceutical industry-sponsored advisory board or speaker's bureau, and has no financial interest in any pharmaceutical or medical device company.

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