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Predictors of Response to Monoamine Oxidase Inhibitors: do they Exist?

Jonathan R. T. Davidson[1], Earl L. Giller[2], Sidney Zisook[3], and Michael J. Helms[4]

[1]Duke University Medical Center, P.O.Box 3812, Durham, NC 27710, USA
[2]University of Connecticut, School of Medicine, Department of Psychiatry, 263 Farmington Avenue, Farmington, CT 06032, USA
[3]University of California at San Diego, 3427 4th Avenue, San Diego, CA 92103, USA
[4]Biometry and Medicine Informations Division, C & F Medicine, Duke University Medical Center, P.O.Box 2914, Durham, NC 27710, USA

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Summary. Multiple regression analysis was conducted on potential response predictors in a double-blind study of monoamine oxidase inhibitors (MAOI) and placebo treatment in 130 depressed outpatients. Positive main effects were found for sex (female), lack of prior hospitalization, presence of precipitating events. A negative main effect was found for concurrent physical illness. Treatment × predictor effects were found for distinct quality and non-reactivity. Non-reactivity was associated with positive outcome in both study groups, but the effect was significantly enhanced in the treatment group. Distinct quality demonstrated a more complex effect, its presence being associated with decreased improvement in the treatment group and greater improvement in the control group. No atypical depressive symptoms predicted MAOI response, and we were unable to characterize a specifically responsive MAOI syndrome.

Key words: MAO inhibitors – Response – Predictors

Introduction

There is a substantial literature on predictors of response to MAO inhibitor drugs, much of which has already been reviewed by ourselves and others (Davidson et al. 1988; Zisook et al. 1985; Quitkin et al. 1979; Pare 1985; Joyce and Paykel 1989). For the most part, such studies have failed to take into account those factors which might be associated with spontaneous remission. To do so, it is necessary to utilize a placebo or untreated control group. The above mentioned reviews discuss predictor studies which vary considerably in design, adequacy of drug dose and duration of treatment. Often these studies have examined a wide variety of variables without taking advantage of multivariate statistical techniques that are best suited to complex data. On the other hand, it has to be acknowledged that multivariate techniques can identify opportunistic relationships resulting from chance associations.

Three reports have examined predictors of MAOI outcome in contrast to those of a tricyclic and/or placebo by means of multiple regression techniques (Kay et al. 1973; Bhat et al. 1984; Mountjoy et al. 1977). In the first report, Kay et al. examined predictors of response to amitriptyline and phenelzine. Although drug doses would be considered inadequate by present day standards, a number of interesting findings were noted nonetheless. Poor response to both drugs was associated with ideas of reference, whereas good response to both drugs was associated with extraversion. Blaming others predicted a good response to phenelzine and poor response to amitriptyline. High neuroticism, subjective retardation, pyknic habitus and neurotic personality were all associated with poor response to phenelzine. Good response to amitriptyline was predicted by depersonalization, mood reactivity, diurnal variation (mood worse p.m.), lack of irritability.

In the second study, Bhat et al. (1973) applied multiple regression techniques to data from a trial of phenelzine, amitriptyline and placebo. Poor response to phenelzine was predicted by insomnia, anorexia, impaired work and interests and by self-pity. In the amitriptyline group, worse outcome was associated with retardation, and, in contrast to the report by Kay et al. (1973), with mood reactivity. Poor outcome with placebo was associated with impaired work and interests, and good outcome was associated with somatic anxiety. This study thus differed in several ways from the report of Kay and associates, and provided no real support for the notion of "MAOI specific" predictors.

Mountjoy et al. (1977) performed a series of separate multiple regression analysis in which symptoms, premorbid personality items and biochemical measures were the independent variables and improvement was the dependent variable. All patients in the Mountjoy report had completed 4 weeks' treatment with a combination of phenelzine, diazepam and nitrazepam, or with a combi-

Offprint requests to: Dr. J. Davidson

nation of placebo, diazepam and nitrazepam. As with the other two studies, few predictors emerged. The authors did find, however, that fear of telephoning in public was positively associated with good outcome for phenelzine, and episodic tension was associated with poor outcome for phenelzine. Situational phobias, dizzy attacks and fear of leaving the house all came close to significance as predictors of positive outcome for phenelzine. Total anxiety score on the Newcastle Diagnostic Index (Gurney et al. 1972) was predictive of overall response for the combined phenelzine and placebo groups, being almost significant as a predictor for phenelzine and placebo separately. Extraversion correlated with poor outcome for placebo. Neither personality nor biochemical measures were associated with outcome. The use of benzodiazepines in all patients complicates interpretation of these results.

Following the above review, we present a study which examined possible predictors of response to the hydrazine MAO inhibitor, isocarboxazid, and to placebo, in a double-blind trial. As will be described in further detail, we employed a stepdown linear regression technique. In particular, we wished to substantiate whether or not specific MAOI response predictors might occur, using groups of variables from our data base that have been associated with outcome in previous studies, as reviewed above.

Method

A full report of this study, its design and outcome have been presented previously (Davidson et al. 1988). One hundred and seventy-four patients with RDC major, minor or intermittent depression (Spitzer et al. 1978) entered this 6-week treatment trial. One hundred and thirty completed the minimum required 3 weeks and form the subject of our report. Isocarboxazid was significantly more effective than placebo in the total group. Among subgroups, the drug was effective in endogenous depression/melancholia, non-endogenous depression/non-melancholia, BPRS (Overall 1974) based anxious and hostile depressions, and RDC (Spitzer et al. 1978) major depression. Drug was equivalent to placebo in BPRS retarded and agitated-excited subtypes, and in RDC minor depression. Mean drug doses were 48.3 mg/day at week 3, and 49.3 mg/day at week 6, and they were associated with high levels of MAO inhibition, indicating that the dose was probably adequate.

Outcome Measures and Predictor Variables

A variety of outcome measures were used in the efficacy study, of which the 24-item Hamilton Depression Scale (HDS) (Hamilton 1967) and 5-point physician-rated Clinical Global Improvement (CGI) have been selected as the dependent variables in this report. The five anchor points on the CGI are as follows:

1 = very much improved,
2 = much improved,
3 = minimally improved,
4 = no change,
5 = worse.

All are rated with reference to baseline. The final observed HDS and CGI scores are taken as the outcome measures.

Seven different predictor categories were assessed in the first stage of this analysis. The items which proved significant in each category were then combined together and analyzed as possible predictors in a combined model as the second stage of analysis. Items in the seven categories were:

(1) Demographics – Age and sex of the patient.
(2) Duration of Illness – Duration of depression (months).
(3) Historical – First episode before age 40 years, frequent alcohol use, no previous psychiatric hospitalization, severe discord at home in childhood.
(4) Stressors – Concurrent physical illness, precipitating factors, marital problems.
(5) Brief Psychiatric Rating Scale – BPRS type of depression (anxious, hostile, agitated/excited, retarded depressions).
(6) Traditional Symptom Predictors – This category consists of selected symptoms from the database which have been traditionally associated with either good or poor response to MAOI drugs. These are phobic symptoms, distinct quality of mood, non-reactivity to environment, increased appetite, blame projection, self-pity, pervasive loss of interest.
(7) Severity and Endogenicity – Measures of severity comprise total baseline HDS and BPRS scores and RDC major/minor depression. Endogenicity is measured by total Newcastle Scale (Carney et al. 1965) and Michigan Index (Feinberg and Carroll 1982).

Statistical Analysis

Description of Modelling Procedure. A multi-stage step-down linear regression algorithm was used to fit models predicting patient outcome, defined in one case as final Hamilton score, and in the other as final physician's global rating. The predictor variables were classified into several categories, (1) demographic, (2) duration, (3) historical, (4) stressors, (5) symptom profile, (6) traditional symptom predictors and (7) depressive typology/severity. A predictor indicating treatment (placebo vs drug) was always included and in the case of final Hamilton score, the baseline Hamilton score was always included as well. A categorical variable was modelled with $(n-1)$ dummy variables for the n levels it defined and this set of $(n-1)$ dummy variables was always considered and tested as a group in the step-down process.

Varibles considered as predictors included both the main effect of the predictor, to estimate its importance as an effect modifier, and its interaction with treatment group classification, to ascertain if it might also be a significant confounder of outcome. In the step-down procedure, a main effect was never allowed to be deleted unless and until its interaction with treatment had already been deleted from the model.

The initial stage of model fitting consisted of separately fitting the best predictors within categories. This was done for several reasons. Since some data were missing for many of the potential predictors, an analysis which began by simultaneously attempting to fit all predictors would have caused to be deleted any observation in which any one of the predictors was missing, considerably decreasing our data base, and perhaps biasing the results as well. In addition, the model itself, consisting of both main effects, some of which consisted of several dummy variables, and their interactions, would have been quite large and would have taxed, it not exceeded, the capacity of our computing facilities. Finally, it was felt that the initial competition for significance among the predictors should be at a point at which there was a greater homogeneity of predictive power among the predictors.

The order of deletion of the predictors was based on the test of significance of their linear regression coefficients at each stage of the procedure, that variable (or set of dummy variables) showing the least significance being eliminated subject to the requirement stated above concerning interaction with the treatment effect. The step-down procedure stopped when all remaining variables available for deletion remained significant at a probability level ≤ 0.05.

The second stage of the step-down procedure was performed in a similar manner, those variables initially considered being all those which had remained significant in each of the separate category step-downs. Again, the procedure stopped when all eligible variables remained significant at least at a probability level of 0.05.

Results

With respect to category I (demographics), female sex served as a significant main effect modifier in favor of better outcome on both the HDS and CGI (Table 1). Main effects were also noted for drug and for baseline HDS.

Of the historical variables, lack of prior hospitalization was related as a main effect to more favorable outcome, along with active treatment and higher baseline HDS (Table 1).

Duration of illness was unrelated to outcome.

Among the stressor category, concurrent physical illness was found to be a negative effect modifier on both measures of outcome (i.e. was associated with less favorable outcome), while presence of precipitating events was associated as a main effect with better response as measured by the CGI (Table 1).

BPRS type was marginally significant as a main effect with the CGI only (Table 1).

Of the traditional clinical symptoms, distinct quality of mood was a positive effect modifier, and non-reactivity a negative effect modifier on both outcome measures (Table 1). Treatment × predictor interactions were also evident for these two variables (Table 1), as will be described: in the presence of distinct quality of mood, both treatments exerted modest effects, this being somewhat greater for isocarboxazid than for placebo. When distinct quality was absent, there was no change with placebo but marked change with isocarboxazid.

When non-reactivity of mood was present, isocarboxazid produced a substantial improvement whereas placebo was associated with no improvement. When mood reactivity was preserved, isocarboxazid again resulted in good improvement, while there was minimal change with placebo.

Table 1. Variables predictive of positive outcome ($n = 130$)

	Outcome Measure				
	Effect	Final Hamilton		Final CGI	
		B Coefficient	*P* value	B Coefficient	*P* value
1. Demographic	Intercept	0.482	0.926	3.310	0.000
	Baseline Hamilton	0.721	0.000	*	*
	Treatment (drug)	−7.214	0.000	−0.774	0.000
	Sex (Female)	−5.217	0.009	−0.607	0.002
2. Historical	Intercept	0.017	0.997	3.353	0.000
	Baseline Hamilton	0.751	0.000	*	*
	Treatment (drug)	−7.420	0.000	−0.796	0.000
	No past hospitalization	−5.971	0.003	−0.663	0.001
3. Stressors	Intercept	−2.111	0.685	3.211	0.000
	Baseline Hamilton	0.651	0.000	*	*
	Treatment (drug)	−6.402	0.001	−0.801	0.000
	Physical illness	6.061	0.011	0.439	0.056
	Precipitants	*	*	−0.332	0.007
4. BRPS Type	Intercept	*	*	3.370	0.000
	Baseline Hamilton	*	*	*	*
	Treatment (drug)	*	*	−0.777	0.000
	Type	*	*	5 levels	0.049
5. Traditional Symptoms	Intercept	3.770	0.499	3.340	0.000
	Baseline Hamilton	0.598	0.000	*	*
	Treatment (drug)	−10.356	0.002	−1.408	0.000
	Distinct quality	−5.733	0.051	−0.766	0.010
	Non-reactivity	10.389	0.011	0.837	0.036
	Treatment × Distinct quality	8.434	0.040	1.288	0.002
	Treatment × Non-reactivity	−13.475	0.013	−1.074	0.043
6. Severity/Endogenicity	Intercept	0.009	0.999	2.203	0.000
	Baseline Hamilton	0.470	0.010	*	*
	Treatment (drug)	−9.778	0.000	−1.029	0.000
	Michigan Index Score	0.268	0.026	0.033	0.001
	Minor Depression	−3.602	0.268	−0.238	0.0458
	Treatment × Minor Depression	8.807	0.050	0.823	0.063

* Not entered in this model

Table 2. Variables predictive of outcome: combined category ($n = 130$)

Effect	Outcome Measure			
	Final Hamilton		Final CGI	
	B Coefficient	*P* value	B Coefficient	*P* value
Intercept	0.305	−0.952	4.077	−0.000
Baseline Hamilton	0.772	0.000	*	*
Treatment (Drug)	−6.794	0.000	−1.524	0.000
Sex (Female)	−3.995	0.044	−0.442	0.019
Percipitants	*	*	−0.409	0.001
No previous hospitallization	−3.967	0.049	*	*
Concurrent physical illness	5.579	0.016	*	*
Distinct quality	*	*	−0.762	0.006
Non-reactivity	*	*	−0.742	0.049
Treatment × Distinct quality	*	*	1.346	0.000
Treatment × Non-reactivity	*	*	−1.243	0.015

* Non entered in this model

Among the criteria of severity and endogenicity, the Michigan score served as an effect modifier on both scales (i.e. lesser response at higher levels of endogenicity). A treatment × RDC depressive type interaction occurred at a borderline level of significance (Table 1). Modest improvement was noted for both treatments, which did not differ, if the patient exhibited minor/intermittent depression. Clear-cut improvement occurred with isocarboxazid in major depression, as compared with minimal effect with placebo.

Stage 2 of the analysis is shown in Table 2, in which each significant predictor from the different categories was entered into the model. Using final HDS as the outcome variable, significant main effects were noted for baseline HDS and drug. Additional main effects were observed for sex (women showed better response), absence of previous hospitalization (better response) and presence of concurrent physical illness (worse response). With CGI as the dependent variable, main effects were found for drug, sex, precipitating factors and distinct quality (all predicting better response), and non-reactivity predicting poorer response.

Treatment and predictor interactions were evident for distinct quality and non-reactivity, with the latter of these predicting MAOI effect.

The overall variance (R^2) accounted for by this model was fair, being 0.31 for the HDS and 0.33 for the CGI.

The use of linear regression places a strain on assumptions of continuity and linearity on a dependent variable with limited distribution. An ordinal logistic model was fitted to the same variables found in the linear regression model for CGI, and this yielded extremely similar probability levels for each independent variable. These levels were as follows: drug treatment (0.0001), female (0.0064), precipitants (0.0022), distinct quality (0.0082), non-reactivity (0.0654), treatment × distinct quality (0.0005), treatment × non-reactivity (0.0229).

Discussion

This study provided barely any support for the existence of specific symptoms predicting response to MAOI therapy, once the effect of other variables had been taken into account. Our limited findings even contradict clinical wisdom, in that non-reactivity of mood was the only specific predictor of good outcome with MAOI. A finding such as this may partly be explained by the sample, since we selected patients for the study on the basis of having symptoms that were presumed to be MAOI responsive. In such a population, "endogenous" symptoms may have a different interactive effect upon outcome from that in a group of melancholic inpatients. Support for this idea is provided by our previous report of response and non-response to isocarboxazid in depressed inpatients (Davidson et al. 1988); in these patients non-reactivity of mood and phobic symptoms were associated with a greater likelihood of non-response to the drug.

Minor depression was another specific predictor of poorer response to drug. Lack of antidepressant drug effects in RDC minor depression or other forms of mild depression has been previously observed for desipramine (Stewart et al. 1983) and for amitriptyline (Paykel et al. 1988). A certain level of symptom severity seems necessary for antidepressant benefits to become apparent. It is possible that side effects of high dose drug therapy outweigh benefits at very low levels of symptom severity, and that lower doses would yield different results.

General predictors of good outcome, all of which appeared less significant than the effect of drug, included severity of symptoms, being female, having no previous hospitalizations and the presence of precipitants. Concurrent physical illness was predictive of poor response.

We take our findings to be more consistent with the view that isocarboxazid is an effective antidepressant in most types of depression, with the possible exception of psychotic subtypes (Davidson et al. 1982), and that the search for quintessentially "MAOI specific" atypical symptoms continues to be elusive: it may even prove to be a mirage. Numerous studies (Raft et al. 1979; Vallejo et al. 1988; Nolen et al. 1986; Quitkin et al. 1988; Liebowitz et al. 1984; Davidson et al. 1986; Kayser et al. 1988), have shown an MAOI to be superior to a tricyclic or other antidepressant, both in full samples and in post hoc derived subgroupings, but no common thread can be discerned from these different samples, other than the superior effect of an MAOI. They span melancholic/typical and non-melancholic/atypical depression, men and women, young and old, outpatients and inpatients, mood reactive and mood non-reactive patients.

Some data were missing for individual observations in a scattered fashion. In the multivariate model, absence of data served to eliminate that observation from use at that point. This was the reason for doing the step-down procedure in several stages, to regain as many observations as possible in the latter stages of the process in

order to maximize the power and minimize the problem of possible bias.

It is important to recognize a number of important factors in any study of predictors, because failure to do so may result in misplaced confidence as to the validity of a finding. Our study is no exception in this regard.

Among the questions that need to be asked are the following:
(1) How is the sample characterized: are they outpatients, inpatients, treatment resistant, drug-naive, old or young?
(2) For how long has treatment been administered? Findings based on 4 weeks' treatment may well yield different predictors from a 10- to 12-week trial.
(3) What dose of treatment was used? A daily tricyclic dose of 150 mg/day may yield different outcome and response predictors than a dose of 300 mg/day. Different interactions between depressive type and outcome have been noted by us for high and low doses of isocarboxazid (Davidson et al. 1986).
(4) Is the comparison made between or within treatments? Caution should be used in generalizing results of one form of comparison to another.
(5) Was a placebo condition used? Without a placebo or non-treatment control, it is impossible to differentiate those predictors which are drug specific from those which merely indicate good prognosis depression, or those likely to respond to non-pharmacological treatments.
(6) How homogeneous is the sample? The criteria for major depression cover a broad spectrum and include some depressions which are not responsive to tricyclic (Carroll 1984) or MAOI therapy (Davidson et al. 1989).
(7) How is response measured, and how are the groups defined? Use of the two categories, responder or non-responder, while having clinical utility, may be a less sensitive index than using a continuous measure of response.
(8) In a model which results from a multiple step-down procedure, it is important to remember that the significance of any given variable is that calculated when there are simultaneously other variables in the model exerting effects both on each other and the dependent variable. Tests of the significance of a specific variable under these circumstances are not the best of the relationship of that single variable to outcome. It may be competing with another variable which is virtually identical and either of which, by themselves, might be highly related to outcome but which in combination with each other each fail to share a significant amount of variance. Removing either will immediately cause the other to jump in significance. It would be wrong to say that either lacks a significant relationship to outcome, except when in combination with each other.
(9) Interpretation of predictor studies needs to take into account the question of sample size (Kraemer and Thiemann, 1987). Clearly the power to identify a real predictor as significant is related both to the magnitude of its real relationship to outcome and to its incidence in a surveyed population. If it is rare in the population being tested it may well be difficult to establish a real relationship as significant. The intent of this paper is to identify probable predictors from a large pool of potential predictors in a population that was selected to test the effect of drug treatment on outcome, an effect which was shown to be highly significant.

In conclusion, our study has provided little support for clinically useful MAOI-specific predictors, or for a characteristically MAOI-responsive depressive type. It has raised a number of issues on the matter of predicting antidepressant response, and taken with our previous report (Davidson et al. 1988), supports the view that isocarboxazid, a hydrazine MAOI drug, is a useful antidepressant in both melancholic and atypical forms of the illness. Like Paykel et al. (1988), we believe that severity of illness remains the single most important predictor of an antidepressant drug's short-term efficacy relative to placebo.

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