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Are there predictors of outcome in depressed elderly nursing home residents during treatment with mirtazapine orally disintegrating tablets?

J. Craig Nelson[1]*, Karen Holden[1], Steven Roose[2], Carl Salzman[3], Steven B. Hollander[4] and James V. Betzel[4]

[1]*University California San Francisco, San Francisco, CA, USA*
[2]*Columbia University, College of Physicians and Surgeons, New York, NY, USA*
[3]*Massachusetts Mental Health Center, Harvard Medical School, Boston MA, USA*
[4]*Organon Pharmaceuticals USA Inc., Roseland, NJ, USA*

SUMMARY

Background Treatment studies of depression in residential care are limited. Reports of predictors of response are rare. In the largest nursing home prospective antidepressant trial reported, we examined predictors of response.

Methods This was a 12-week open-label study of mirtazapine orally disintegrating tablets performed in 30 US nursing homes. Subjects were men and women aged ≥70, with a Mini Mental State Exam (MMSE) score ≥10, who had a depressive disorder that required antidepressant treatment. Mirtazapine was started at 15 mg at bedtime, and adjusted to 15–45 mg/day. A 16-item Hamilton Depression Rating Scale was used to assess depression at baseline, weeks 2, 4, 8, and 12 or early termination.

Results One hundred and twenty-four patients received at least one dose of study drug and of these, 119 had at least one post-drug assessment. Mean age was 82.9 years and 72% were female. Response rates at 12 weeks were 47% on the HAMD and 54% on the CGI. Age, sex, MMSE score, medical burden, history of prior depression, and baseline HAMD severity were not significantly associated with HAMD response (≥50% improvement) and in most cases correlations were trivial, <0.1. Advanced age, medical burden, and cognitive impairment did not predict adverse events.

Conclusions In this sample of depressed nursing home residents treated with mirtazapine orally disintegrating tablets, advanced age, medical illness, and cognitive impairment did not predict response. The findings suggest that these variables need not be viewed as obstacles to treatment. Copyright © 2007 John Wiley & Sons, Ltd.

KEY WORDS — late life depression; nursing home; mirtazapine

INTRODUCTION

Depression is a common disorder among nursing home residents that has serious consequences. Prevalence estimates of depression in this population range from 15 to 60% (Rovner and Katz, 1993). Depression not only causes suffering and reduces quality of life (Bondareff *et al*., 2000), but it increases risk of suicide (Conwell, 2004), impairs ADLs (Bruce *et al*., 1994b), and is associated with increased mortality (Rovner *et al*., 1991; Bruce *et al*., 1994a; Pulska *et al*., 1998; Whooley and Browner, 1998). Yet studies of the use of antidepressants for treatment of this population are quite limited. Antidepressant treatment studies of more than ten patients include only three double-blind placebo controlled trials (Katz *et al*., 1990; Magai *et al*., 2000; Burrows *et al*., 2002), two double-blind comparison studies (Streim *et al*., 2000; Oslin *et al*., 2003), four open studies (Trappler and Cohen, 1998; Oslin *et al*., 2000; Rosen *et al*., 2000; Weintraub *et al*., 2003) and the current study (Roose *et al*., 2003). Of this previous group, three

*Correspondence to: Dr J. Craig Nelson, 401 Parnassus Ave Box 0984-F, San Francisco, CA, 94143, USA.
E-mail: craign@lppi.ucsf.edu

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studies had samples of 69, 52, and 50 patients. The other six included samples of 31 patients or less.

An important question, seldom addressed in this literature, is whether there are predictors of response. Given the frail and complicated nature of these patients, most of these factors might be expected to *interfere* with treatment and thus to be precise, be predictors of poor response or adverse events. Although there are limited data from residential care facilities, findings in older adults in all settings suggest that older age (Salzman, 1999; Mitchell and Subramaniam, 2005), cognitive impairment or dementia (Trappler and Cohen, 1998; Kalayam and Alexopoulos, 1999; Streim *et al*., 2000; Alexopoulos *et al*., 2005), medical burden (Keitner *et al*., 1991; Evans *et al*., 1997; Katon *et al*., 2002; Iosifescu *et al*., 2003; Lowe *et al*., 2005), depression severity (Gildengers *et al*., 2005), and recurrent depression (Bosworth *et al*., 2002; Driscoll *et al*., 2005) may predict less robust response.

We examined if these variables did predict poor outcome in an open label study of mirtazapine. This sample was the largest antidepressant study in a nursing home setting reported. Drug treatment and ratings of response were standardized. The naturalistic design included relatively typical patients with cognitive impairment, medical illness, or advanced age. We also examined if advanced age, greater medical burden, and greater cognitive impairment would predict premature discontinuation.

METHODS

Design

This was a 12-week open-label study of mirtazapine orally disintegrating tablets performed in 30 US nursing homes. Details of the study methods have been previously described (Roose *et al*., 2003).

Subjects

Men and women aged 70 or older, residing in the nursing home, who had a depressive disorder that the attending physician thought required treatment with an antidepressant, and had a Mini Mental State Exam (MMSE; Folstein *et al*., 1975) score of 10 or greater, were eligible.

Treatment

Patients started treatment with mirtazapine orally disintegrating tablets, 15 mg at bedtime. Dose could be increased to 45 mg/day and adjusted thereafter based on side effects and response within the 15–45 mg range.

Assessments

At baseline the physician or nurse coordinator performed a 16-item Hamilton Depression Rating Scale (HAMD) modified for this population (Hamilton, 1960). The item for decreased sexual interest was deleted. Details of the rating procedure have been provided previously. Briefly the physician or nurse coordinator interviewed nurses or other caregivers in daily contact with the patient to obtain information used to complete the HAMD, the Cornell Scale for Depression in Dementia (CSDD; Alexopoulos *et al*., 1988), the Clinical Global Impressions severity scale (CGI-S), and for subsequent ratings, the CGI-improvement (CGI-I) scale (Guy, 1976). Ratings were performed at baseline and at weeks 2, 4, 8, and 12 or at the time of early termination. Medical illness was assessed using the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) (Linn *et al*., 1968). Cognitive function was assessed with the MMSE.

Analysis

The association of response with predictors was examined in patients in the intent-to-treat (ITT) sample with at least one post-treatment rating using the last observation carried forward. The primary definition of response for this analysis was 50% or greater improvement on the HAMD rating. CGI response ('much' or 'very much' improvement) was employed as a second measure. Point biserial correlations were determined for associations with continuous variables and phi coefficients for categorical variables. We recognized the hazard of performing multiple comparisons, but given the paucity of data on this topic preferred to avoid a type I error. We postulated that advanced age, greater medical burden, greater cognitive impairment, greater baseline severity, and history of recurrent episodes would be associated with lack of response. We also hypothesized that advanced age, higher medical burden, and greater cognitive impairment would predict premature discontinuation.

RESULTS

One hundred twenty-four subjects were enrolled and received study drug. Of these, 119 subjects had at least one post-drug efficacy rating. Details of the

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Table 1. Characteristics of the patients

Number of patients enrolled	127
Number in ITT sample	119
Age (mean, SD, range)	82.9 ± 6.6, 67–98
Female sex (%)	72%
History of prior depression (%)	30%
MMSE score (mean, SD)	21.9 ± 5.4
CIRS-G total (mean, SD)	11.4 ± 4.8
Baseline CGI-severity	4.0
Baseline HAMD (mean, SD)	15.7 ± 6.3

Table 3. The correlation of predictor variables with premature discontinuation (any reason) or premature discontinuation for adverse events is shown below

Predictor	Correlation with any premature discontinuation*	*p*	Correlation with discontinuation for adverse event*	*p*
Age	−0.11	0.24	−0.04	0.64
CIRS	−0.11	0.22	−0.08	0.39
MMSE	0.03	0.71	−0.05	0.55
Sex	0.11	0.99	0.02	0.78

*Degrees of freedom = 122 for items 1–3; and df = 1 for sex.

outcome have been provided previously. Briefly, 43 subjects discontinued prematurely, 14 of these due to adverse events. The mean dose of mirtazapine was 19.4 mg ± (SD) 6.3 mg. The response rate on the HAMD was 47% at week 12. Response on the CGI was 54%. Characteristics of the sample are shown in Table 1.

Correlations of response on the HAMD (≥50% improvement) with predictor variables are shown in Table 2. None of these variables predicted poor outcome. Similar correlations using the CGI to define response were also performed but again, none were significantly associated.

The associations of predictor variables with premature discontinuation are shown in Table 3. None of these items were significantly associated with premature discontinuation.

DISCUSSION

In this nursing home sample, advanced age, increased medical burden, cognitive impairment, depression severity and history of recurrent episodes were not associated with a reduced likelihood of response. While the lack of a placebo group limits our ability to predict 'drug response,' these data do appear to provide a valid measure of overall response and non-response. The findings suggest that these variables were not obstacles to treatment.

Table 2. Association of predictor variables with HAMD response

Predictor	Correlation with HAMD response[a]	*p*
Age	0.047	0.62
CIRS	0.055	0.56
MMSE	0.030	0.75
Baseline HAMD	−0.018	0.85
Baseline CSDD	0.056	0.55
History of prior episodes	0.157[b]	0.46
Sex	0.162[c]	0.12

[a]Degrees of freedom = 116 for items 1–4, df = 115 for CSDD and df = 1 for items 6 and 7.
[b]Phi coefficient, df = 1, probability assessed with X^2.
[c]$n = 118$.

Our findings differ from previous reports, although these reports vary with respect to whether advancing age, medical burden, and cognitive impairment predict poor outcome (Small *et al*., 1996; Salzman, 1999; Sheikh *et al*., 2004; Gildengers *et al*., 2005; Krishnan *et al*., 2005; Mitchell and Subramaniam, 2005; Roose and Miyazaki, 2005). We suspect that our findings for advanced age, medical burden, and impaired cognition may, in part, reflect the restricted range of these variables in our sample. The typical patient in this study was older (mean age 82.9), medically ill (mean CIRS = 11.4), and had some cognitive impairment (mean MMSE = 21.9). These variables might have been more predictive if examined in a broader range of patients including young healthy patients. For example, Iosefesu *et al*. (2003) demonstrated in an eight-week open trial of fluoxetine that CIRS scores of 6 or greater were associated with lower response and remission rates. In our sample, the mean CIRS score was 11, well beyond the distribution of scores in the fluoxetine study. Alternatively, the advanced age, medical burden, and cognitive impairment of our sample are characteristic of a nursing home population.

Gildengers *et al*. (2005) suggested that depression severity might predict poor outcome. The lack of prediction in our sample may be related to the limited number of patients whose depression was very severe. The mean baseline HAMD was 15.7. On the CGI severity scale, 20% of the sample was judged mildly depressed, 60% as moderately ill, and 20% as markedly or severely depressed. Alternatively, other studies also found severity did not predict outcome (Flint and Rifat, 1997; Rosen *et al*., 2000; Streim *et al*., 2000).

History of recurrent depression has been cited as a predictor of outcome in some reports (Bosworth *et al*.,

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2002; Driscoll *et al*., 2005) but not in others (Flint and Rifat, 1997; Gildengers *et al*., 2002; Lowe *et al*., 2005) or in our sample. A possible explanation is suggested by the placebo-controlled study preformed by Roose *et al*. (2004). In that study, recurrent depression predicted less good response to placebo, while response to drug treatment was relatively unaffected.

In a recent comprehensive review of age as a predictor, Mitchell and Subramaniam (2005) noted the problem of disentangling the association of several age-related variables with poor outcome. For example, older patients with late onset depression may be at greater risk for medical illness, which appears associated with poor outcome. But early onset is associated with more frequent prior episodes, which may contribute to poor outcome. We did perform a multivariate logistic regression with HAMD response as the outcome and the predictor variables cited above as independent variables. We found no interaction among the variables that was obscuring prediction of outcome.

There are various factors that limit our conclusions. The assessment of depression in medically ill, and cognitively impaired patients presents a challenge. However, the reliability of our assessments is supported by a robust correlation of the baseline HAMD and CSDD, $r = 0.89$, $p < 0.001$. Study entry did not require a DSM diagnosis of major depression, but this allowed for recruitment of a sample typical of those receiving antidepressants in this setting and of nine other nursing home studies reported, only two have required a DSM diagnosis of major depression (Trappler and Cohen, 1998; Katz *et al*., 1990). Although broad inclusion criteria were employed to recruit a representative sample, patients with unstable medical illness or a MMSE score <10 were excluded and the number of patients with very severe depression was low. As a result, we do not know if our findings generalize to those groups. The study did not employ a placebo and we cannot determine what portion of response was attributable to mirtazapine, but our determination of overall response *vs* non-response should be valid. Finally, no dosing guidelines were provided for the clinicians who were free to adjust dose between 15 mg/day and 45 mg/day. In fact, the final mean dose was 19.4 mg/day suggesting that clinicians were very cautious adjusting dose in this elderly, medically ill sample. Other dosing strategies might have resulted in different findings. The flexible dosing schedule employed here does not allow us to determine the optimal dosing strategy for this patient group.

KEY POINTS

- Studies of predictors of outcome are rare in depressed nursing home residents.
- This is the largest systematic study of an antidepressant in the nursing home.
- Hypothesized predictors (age, medical burden, cognitive impairment, and depression severity) were not associated with response.
- These variables were not associated with premature discontinuation of treatment.

In conclusion, although there are limitations to the interpretation of the findings, this is the largest systematic study of antidepressant treatment in a nursing home setting. As such, the findings provide hope that depressed individuals can benefit from treatment in the face of medical illness, advanced age, and cognitive impairment.

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