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Late-onset major depression: clinical and treatment-response variability

Henry C. Driscoll[1], James Basinski[1], Benoit H. Mulsant[1], Meryl A. Butters[1], Mary Amanda Dew[1], Patricia R. Houck[1], Sati Mazumdar[2], Mark D. Miller[1], Bruce G. Pollock[1], Jacqueline A. Stack[1], Mary Ann Schlernitzauer[1] and Charles F. Reynolds III[1]*

[1]*Intervention Research Center for Late-Life Mood Disorders, Western Psychiatric Institute and Clinic, Pittsburgh, PA, USA*
[2]*Department of Biostatistics, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA, USA*

SUMMARY

Objective To explore clinical and treatment-response variability in late-onset *vs* early-onset non-bipolar, non-psychotic major depression.

Methods We grouped patients from a late-life depression treatment study according to illness-course characteristics: those with early-onset, recurrent depression ($n = 59$), late-onset, recurrent depression ($n = 27$), and late-onset, single-episode depression ($n = 95$). Early-onset was defined as having a first lifetime episode of major depression at age 59 or earlier; late-onset was defined as having a first episode of major depression at age 60 or later. We characterized the three groups of patients with respect to baseline demographic, neuropsychological, and clinical characteristics, use of augmentation pharmacotherapy to achieve response, and treatment outcomes.

Results Rates of response, remission, relapse, and termination were similar in all three groups; however, patients with late-onset, recurrent major depression took longer to respond to treatment than those with late-onset, single-episode depression (12 weeks *vs* 8 weeks) and had more cognitive and functional impairment. Additionally, patients with recurrent depression (whether early or late) were more likely to require pharmacotherapy augmentation to achieve response than patients with a single lifetime episode.

Conclusion Late-onset, recurrent depression takes longer to respond to treatment than late-onset single-episode depression and is more strongly associated with cognitive and functional impairment. Further study of biological, neuropsychologic, and psychosocial correlates of late-onset, recurrent depression is needed.

KEY WORDS — major depression; late-onset; treatment outcome

The relationship of lifetime age at onset to both the clinical and treatment response variability of late-life major depression remains incompletely understood. Different studies implicate early-onset (e.g. Brodaty *et al.*, 1991; Dew *et al.*, 1997; Reynolds *et al.*, 1998), late-onset (Alexopoulos *et al.*, 1996), or neither type (Baldwin *et al.*, 1993; Flint and Rifat, 1997) of late-life depression as being more difficult to treat. For example, some studies have reported that patients with early-onset, recurrent illness have a slowed speed of response and higher relapse rates than patients with late-onset depression, i.e. depression beginning after the age of 60 (Reynolds *et al.*, 1996; Reynolds *et al.*, 1998). These treatment response characteristics may reflect prior illness course, including the greater number of previous episodes in patients with early-onset disease. While patients with early-onset depression may also have an increased genetic liability to depression, other factors associated with recurrent episodes may also moderate treatment response, including the effects of recurrent depression on brain structure and function (Whyte *et al.*, 2004), as well depletion of interpersonal and psychosocial resources

*Correspondence to: Dr C. F. Reynolds III, Intervention Research Center for Late-Life Mood Disorders, Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15213. Tel: 412-246-6414. Fax: 412-246-5300. E-mail: reynoldscf@upmc.edu

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attendant to chronic and recurrent depression (Karp *et al.*, 1993; Reynolds *et al.*, 1998).

In contrast, other studies have reported lower response rates and greater brittleness of response (i.e. greater tendency to relapse) in late-onset depression (Alexopoulos *et al.*, 1996; Kalayam and Alexopoulos, 1999). Late-onset depression is heterogeneous in etiology, presentation, and treatment response, with medical comorbidities such as cerebrovascular or neurodegenerative disorders influencing illness characteristics, including greater disability, cognitive impairment, and higher relapse rates (Alexopoulos *et al.*, 1997). Other studies support the relationship between late-life depression, cognitive impairment, and treatment response: e.g. prefrontal dysfunction has been associated with diminished treatment response; and executive dysfunction has been found to predict relapse and recurrence in some (Kalayam and Alexopoulos, 1999; Alexopoulos *et al.*, 2000), but not all studies (Butters *et al.*, 2004a). Clearly, the relationship of cognitive impairment to treatment response variability in late-life depression is more complicated than the earlier view that the former represents benign and reversible 'pseudodementia,' (Kiloh, 1961; Wells, 1979). We now understand that cognitive impairment in late-life depression persists despite improvement in depressive symptoms and may progress despite maintenance of recovery (Butters *et al.*, 2000; Alexopoulos, 2003; Nebes *et al.*, 2003). Some studies suggest that late-onset depression is prodromal to dementia (Schweitzer *et al.*, 2002). Late-onset depression has also been associated with white matter disease, possibly a correlate of diminished response to antidepressant treatment (Hickie *et al.*, 1995; Simpson *et al.*, 1998).

The complex relationship of age of onset and the clinical, neuropsychologic, and treatment response variability of late-life depression is the subject of this report. We report both acute and continuation treatment outcomes in depressed, elderly participants from an ongoing study of the long-term maintenance efficacy of interpersonal psychotherapy and pharmacological treatment with paroxetine. We explore differences among patients with early- and late-onset depression in terms of sociodemographic, illness course, and clinical characteristics, neuropsychological performance, and treatment response variability. We focus particularly on patients with late-onset illness (i.e. lifetime onset at or after age 60), contrasting late-onset patients with single *vs* recurrent depressive episodes. No prior studies to our knowledge have examined illness characteristics among late-onset cases, contrasting single-episode *vs* recurrent illness. We were particularly interested in clarifying whether a subgroup of late-onset patients has a diminished response to treatment and/or greater functional, medical, or cognitive impairment. This study was exploratory, i.e. intended to generate new hypotheses concerning late-onset depression to be tested prospectively in independent study groups.

SUBJECTS AND METHODS

We analyzed data from the second Pittsburgh study of maintenance therapies in late-life depression (MTLD-II), an ongoing, five-year study which enrolled patients from January, 1999 to December, 2003, and which was described in Szanto *et al.* (2003). We screened 363 patients to yield the final study group of 210 who enrolled in the study. Reasons for exclusion included: failure to meet diagnostic, age, and severity criteria; and patients' wishes for other treatment (14/363, 4%). Following University Biomedical Institutional Review Board procedures, all patients entering the study provided written informed consent after receiving explanations about research procedures, risks and benefits.

Subjects

All subjects in the study were age 69 or older, met DSM-IV (American Psychiatric Association, 1994) criteria for non-bipolar current major depressive episode without psychotic features, had a Mini-Mental Status Examination (MMSE) (Folstein *et al.*, 1975) score ≥ 18, and did not have a history of substance abuse in the preceding six months. We used the Structured Clinical Interview for DSM-IV (First *et al.*, 1997) as a guide to data acquisition, for formulation of diagnosis, and ascertainment of illness course (including early *vs* late onset). By allowing Folstein scores as low as 18, it is likely that our study group included some patients with coexisting major depression and dementia. Our rationale for doing so was to capture a study group broadly representative of help-seeking elderly. All subjects had a baseline score on the Hamilton Rating Scale for Depression (HRSD-17 item) (First *et al.*, 1997; Folstein *et al.*, 1975; Mulsant *et al.*, 1994) of ≥ 15 upon study entry. Cognitive function was assessed with the Mattis Dementia Rating Scale (MDRS) (Mattis, 1976) and the Executive Interview (EXIT) (Royall *et al.*, 1992). Total medical burden was quantified using the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) (Miller *et al.*, 1992). Similar to a previous analysis of data from the first Pittsburgh study of maintenance

Table 1. Baseline demographic and clinical characteristics

	A. Late-onset, single-episode ($n = 95$)	B. Late-onset, recurrent ($n = 27$)	C. Early-onset, recurrent ($n = 59$)	F or χ^2 [a]	df	P value	Post hoc[b]
Age (years)	77.2 (5.4)	79.2 (7.0)	75.9 (4.7)	3.48	2,178	0.04	BC
%Women	57%	78%	71%	5.67	2	0.06	
%White	96%	78%	90%	8.66	2	0.02	AB
%Married	57%	22%	25%	24.31	4	0.0001*	AB,AC
%Widowed	13%	19%	34%				
%Not married	31%	59%	41%				
CIRS-G Total[c]	10.3 (4.0)	9.5 (4.1)	9.7 (4.0)	0.57	2,178	0.57	
Age at Onset of depression (lifetime)	75.0 (6.4)	71.5 (7.0)	39.9 (12.3)			NA	
Median Duration of current episode (weeks)	52	24	36	13.47	2	0.002*	AB,AC
% with co-morbid existing anxiety disorders	38% (N = 36)	52% (N = 27)	54% (N = 32)	4.47	2	0.11	
Instrumental ADL[d]	11.4 (3.1)	10.2 (3.4)	12.2 (2.2)	4.37	2,175	0.02	BC
Physical ADL[d]	14.3 (1.6)	13.3 (2.2)	14.2 (1.9)	3.01	2,174	0.05	AB
Baseline HRSD[e]	20.5 (3.8)	21.3 (4.0)	20.7 (3.3)	0.58	2,178	0.56	
Baseline suicidality[f]	21%	11%	17%	0.91	2	0.63	
Baseline MMSE[g]	27.6 (2.7)	27.0 (2.7)	28.4 (1.9)	3.47	2,177	0.04	BC
Baseline MDRS[h]	130.3 (11.5)	127.9 (10.6)	134.3 (6.1)	4.84	2,176	0.009	AB,BC
IP subscale[i]	33.6 (4.8)	32.5 (4.7)	34.5 (3.4)	1.99	2,176	0.14	
Memory subscale	21.2 (3.7)	20.0 (3.5)	22.2 (2.8)	3.84	2,176	0.03	BC
Total Scaled Score	8.3 (3.6)	7.2 (3.5)	9.2 (2.4)	3.67	2,176	0.03	BC

*Significant ($p < 0.05$) after step-down Bonferroni adjustment.
[a]Overall test for three groups.
[b]Tukey *post-hoc* comparisons on continuous measures.
[c]Cumulative Illness Rating Scale–Geriatric.
[d]Activities for Daily Living (DARS).
[e]Hamilton Rating Scale for Depression (17-item)
[f]Baseline suicidality is defined as 2 or higher on HRSD item 3.
[g]Mini-Mental State Examination (Folstein *et al.*, 1975).
[h]Mattis Dementia Rating Scale (MDRS).
[i]Initiation/Perseveration score from MDRS.

therapies in late-life depression (Reynolds *et al.*, 1998), based upon SCID interviews, we classified subjects into groups of early and late age of depression onset based upon a cutoff age of 60. These groups were further subdivided by episode type (single/recurrent). Demographic and clinical characteristics of the final study group who began treatment ($n = 181$) are summarized in Table 1.

Treatment Procedures

The study setting was a university-based geropsychiatric research clinic. Subjects received initial acute treatment with open-label paroxetine and weekly interpersonal therapy (IPT). We began paroxetine at 10 mg/day and titrated the dose to 40 mg/day as indicated. Patients were seen weekly during acute-phase treatments. 'Response' was defined as three consecutive weeks of HRSD ≤ 10. Subjects who responded during acute treatment moved from weekly to biweekly continuation treatment for four months. 'Remission' was defined by a HRSD score of ≤ 7 by the end of continuation treatment. 'Relapse' during continuation treatment was defined as having two consecutive weekly HRSD ≥ 15 and meeting SCID criteria for a major depressive episode. After either failing to stabilize with paroxetine and IPT during acute treatment or relapsing after their initial response, subjects received one or more trials of augmentation pharmacotherapy with lithium carbonate, nortriptyline, or bupropion-SR (Whyte *et al.*, 2004). Whenever possible, and depending upon the presence of any medical contradictions to a particular augmenting agent, patients first received lithium (to a serum level of 0.5–0.7 mEq/L), then nortriptyline if needed (titrated to 80–120 ng/ml), and finally bupropion SR (150–300 mg/d). Augmentation pharmacotherapy was employed if patients had not achieved response criteria (HRSD ≤ 10) by week 8 of combined paroxetine and interpersonal psychotherapy. Patients could remain in acute-phase treatment, employing augmentation strategies, for up to 26 weeks. In responders, augmentation pharmacotherapy was then continued for the remainder of a subject's participation in the study. Subjects with a sustained response over

16 weeks were considered recovered and became eligible for the randomized, double-blind, maintenance phase of the study (not included in the present analysis).

Statistical Analyses

All analyses used data from the three study groups: late-onset, single-episode ($n = 95$), late-onset, recurrent episode ($n = 27$), and early-onset, recurrent episode ($n = 59$).

We performed one-way analysis of variance (ANOVA) on continuous baseline demographic and clinical variables, followed by conservative (Tukey) *post-hoc* comparisons of variables that were significantly different among the three groups. We also compared baseline MDRS scores using published scaled scores (Mattis, 1976) adjusting for age and education as covariates in the three groups. We compared categorical measures (i.e. gender, race, and marital status) with chi-square tests for contingency tables. Significance level was set at two-tailed alpha of 0.05. We also performed a step-down Bonferroni test of statistical significance to adjust for Type-1 error inflation.

Chi-square tests for contingency tables were also used to compare rates of response, remission, relapse, and drop-out. We examined covariates of time to response via Cox survival analysis. An adjusted survival curve was produced from the Cox model using the empirical cumulative hazard function estimate (as described by Ghali *et al.*, 2001). The survival curve adjusted for the average duration of index episode and marital status, since these variables differed among the three groups.

RESULTS

Sociodemographic Characteristics (Table 1)

Most subjects were female, with no significant gender difference among the three groups. A greater percentage of those with late-onset, recurrent depression were African-American compared to late-onset, single-episode patients. Patients with late-onset, single-episode depression were more likely to be married than patients with recurrent depression (either early- or late-onset).

Illness Course and Clinical Characteristics at Baseline (Table 1)

Patients with either early- or late-onset *recurrent* depression had a significantly shorter duration of current depression episode compared to the late-onset, single-episode subgroup. The three groups did not differ on pretreatment medical comorbidity burden (CIRS-G scores). They also did not differ on pretreatment suicidality (based on a score of 2 or more on HRSD Item 3) and depression severity (HRSD score), or rate of coexisting anxiety disorders (per SCID/DSM-IV interviews).

Neuropsychological and Functional Measurements (Table 1)

Despite the absence of differences in severity of depression and suicidality, when compared to patients in the other groups, patients with late-onset, recurrent depression were more functionally impaired in both instrumental and physical activities of daily of living based on lower scores in ADL testing. They also demonstrated more cognitive impairment on Folstein, Mattis Total and Mattis Memory scores. Difference in performance on the Mattis total remained when scores were adjusted for age and educational differences.

Treatment Response Variability (Table 2, Figure 1)

The three groups did not differ in categorical rates of response to acute treatment, remission during acute or continuation treatment, relapse during continuation treatment, or dropout during either acute or

Table 2. Treatment response characteristics across three groups

	A. Late-onset, single ($n = 95$)	B. Late-onset, recurrent ($n = 27$)	C. Early-onset, recurrent ($n = 59$)	χ^2 df = 2	*P* value
Responded during acute treatment	75/95 (79%)	19/27 (70%)	41/59 (69%)	2.01	0.37
Terminated during Acute treatment	19/95 (20%)	7/27 (26%)	14/59 (24%)	0.56	0.75
Remitted during acute or continuation treatment	45/95 (47%)	15/27 (56%)	31/59 (53%)	0.74	0.69
Relapsed during continuation treatment	18/95 (19%)	7/27 (15%)	10/59 (17%)	0.28	0.87
Terminated during continuation treatment	17/75 (23%)	4/19 (21%)	10/41 (24%)	0.09	0.96
Required an augmentation agent	25/95 (26%)	12/27 (44%)	27/59 (46%)	7.17	0.03

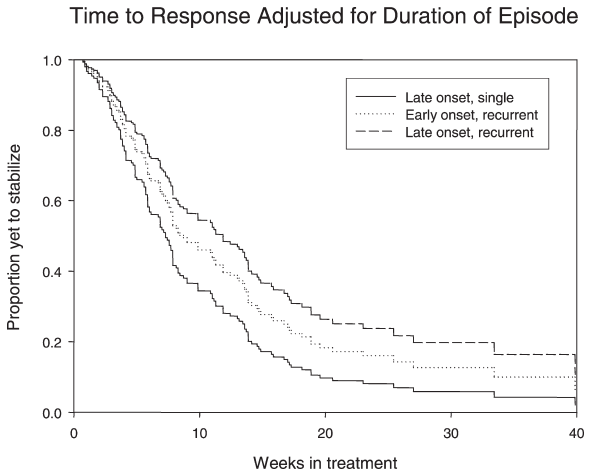

Figure 1. Fitted time to response curves from Cox model adjusted for sample median episode duration of 39 weeks. 'Time to Response' is measured in weeks until patient achieves a HAM-D score of 10 or less for three consecutive weeks. The late-onset group with recurrent depression had a significantly longer time to response compared to the late-onset group with a single episode (median: 12 *vs* 8 weeks; 95% CI = 0.330–0.977, hazard ratio = 0.57, $\chi^2_1 = 4.18$, $p < 005$)

Table 3. Key findings with clinical implications

- Older patients with late-onset (i.e. after age 59) recurrent major depression respond well to treatment but take longer to respond to treatment (12 weeks versus 8 weeks on average) than older patients with late-onset, single-episode depression.
- Older patients with late-onset recurrent major depression are more likely to exhibit cognitive and functional impairments than patients with late-onset single episode depression or early onset recurrent depression.
- Older patients with recurrent depression, whether early- or late-onset, were more likely to need augmentation pharmacotherapy to achieve response and remission than patients with single-episode depression.
- Late-onset recurrent depression may be a clinically relevant subtype of depression in old age, warranting further investigation into both its neurobiologic and psychosocial correlates.

continuation treatment (Table 2). However, roughly 1.4 times as many patients with recurrent depression (either early- or late-onset) received drug augmentation as patients with single-episode depression ($\chi^2 = 7.17$, $p < 0.03$).

We performed a Cox survival analysis to determine differences in time to, and probability of, response to treatment among the three groups (Figure 1). The late-onset, recurrent group had a significantly longer time to response (median = 12 weeks) compared to the late-onset, single-episode group (median = 8 weeks) (hazard ratio = 0.57 $\chi^2_1 = 4.18$ $p < 0.05$), but did not differ from the group with early-onset, recurrent depression (9 weeks). The survival analysis adjusted for differences in marital status and duration of index episode.

DISCUSSION (TABLE 3)

Patients with late-onset recurrent depression took longer to respond to treatment than those with late-onset, single episode depression (12 weeks *vs* 8 weeks). Although baseline severity of depression did not differ, patients with late-onset, recurrent depression also had more cognitive and functional impairment than patients with early-onset, recurrent depression or late-onset single-episode depression. Ultimately, however, the late-onset, recurrent group did not differ from the other two groups in terms of categorical response, remission, or relapse rates. In all, 70–80% of the study participants responded to treatment (with about half ultimately remitting) but differed in how long they took to respond. Both the high rates of response and the similarity of categorical outcomes among the three groups may be attributable to the high-intensity, systematic treatment regimen (paroxetine, interpersonal psychotherapy, and drug augmentation, if appropriate), as also reported in a prior study (Burvill *et al.*, 1991). Additionally, patients with recurrent depression (regardless of age of onset) were more likely to require at least one augmenting agent to achieve stabilization, thus accounting for their longer time to response (4 weeks on average). The results suggest that both recurrent illness course and late age of onset may both affect depressive episode characteristics and treatment response variability; specifically, both recurrence and late age of onset may be associated with longer time to response and greater functional and cognitive impairment.

We have observed cognitive impairment in more than half of elderly, depressed individuals (Butters *et al.*, 2004b), as well as the preponderance of Alzheimer's neuropathological changes (*vs* cerebrovascular changes) in elderly depressed people who had post-mortem brain evaluation (Sweet *et al.*, 2004). Also relevant to late-life cognitive impairment, we reported that elderly depressed subjects with elevated cerebrovascular disease risk factors were more likely to have had onset of their first lifetime depressive episode after age 60, consistent with the hypothesis that depressed elderly patients with high cerebrovascular risk are more likely to have experienced late-onset

depression (Miller *et al.*, 2002). The same study did not find, however, that cerebrovascular risk affected treatment outcomes; the current study similarly finds that cognitive impairment and late-onset, recurrent depression do not presage worse outcome, but rather slower response, in association with increased cognitive and functional impairment. Both clinical and treatment response variability may be related to underlying neurobiology of late-onset, recurrent depression (as well as to the psychosocial context in which old age depressions occur).

Our findings are preliminary, could be due to chance (Type-1 error inflation), and await confirmation using an independent sample. Additional research (e.g. with fMR imaging, diffusion tensor imaging, MR spectroscopy, or measurement of beta-amyloid load) could further illuminate brain differences hypothesized to be relevant to the pathogenesis, illness course, and treatment response variability of late-onset, recurrent depression as a distinct type of depression. The current data may also have clinical utility: clinicians may be well-advised to 'stay the course' in treating patients with late-onset, recurrent depression, who despite taking longer to respond, ultimately demonstrate similar response rates, particularly if augmentation pharmacotherapy strategies are employed.

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