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

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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. Copyright © 2005 John Wiley & Sons, Ltd.

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 (Wryte et al., 2004), as well depletion of interpersonal and psychosocial resources.

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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
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 \( \leq 10 \). Subjects who responded during acute treatment moved from weekly to biweekly continuation treatment for four months. ‘Remission’ was defined by a HRSD score of \( \leq 7 \) by the end of continuation treatment. ‘Relapse’ during continuation treatment was defined as having two consecutive weekly HRSD \( \geq 15 \) 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 \( \leq 10 \)) 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

### Table 1. Baseline demographic and clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>A. Late-onset, single-episode (n = 95)</th>
<th>B. Late-onset, recurrent (n = 27)</th>
<th>C. Early-onset, recurrent (n = 59)</th>
<th>F or ( \chi^2 )</th>
<th>df</th>
<th>P value</th>
<th>Post hoc(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>77.2 (5.4)</td>
<td>79.2 (7.0)</td>
<td>75.9 (4.7)</td>
<td>3.48</td>
<td>2</td>
<td>0.04</td>
<td>BC</td>
</tr>
<tr>
<td>%Women</td>
<td>57%</td>
<td>78%</td>
<td>71%</td>
<td>5.67</td>
<td>2</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>%White</td>
<td>96%</td>
<td>78%</td>
<td>90%</td>
<td>8.66</td>
<td>2</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>%Married</td>
<td>57%</td>
<td>22%</td>
<td>25%</td>
<td>24.31</td>
<td>4</td>
<td>0.0001*</td>
<td>AB,AC</td>
</tr>
<tr>
<td>%Widowed</td>
<td>13%</td>
<td>19%</td>
<td>34%</td>
<td>0.57</td>
<td>2</td>
<td>0.57</td>
<td></td>
</tr>
<tr>
<td>%Not married</td>
<td>31%</td>
<td>59%</td>
<td>41%</td>
<td>0.47</td>
<td>2</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>CIRS-G Total(^c)</td>
<td>10.3 (4.0)</td>
<td>9.5 (4.1)</td>
<td>9.7 (4.0)</td>
<td>0.57</td>
<td>2</td>
<td>0.002*</td>
<td>AB,AC</td>
</tr>
<tr>
<td>Age at Onset of depression (lifetime)</td>
<td>75.0 (6.4)</td>
<td>71.5 (7.0)</td>
<td>39.9 (12.3)</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Duration of current episode (weeks)</td>
<td>52</td>
<td>24</td>
<td>36</td>
<td>13.47</td>
<td>2</td>
<td>0.002*</td>
<td>AB,AC</td>
</tr>
<tr>
<td>% with co-morbid existing anxiety disorders</td>
<td>38% (N = 36)</td>
<td>52% (N = 27)</td>
<td>54% (N = 32)</td>
<td>4.47</td>
<td>2</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>Instrumental ADL(^d)</td>
<td>11.4 (3.1)</td>
<td>10.2 (3.4)</td>
<td>12.2 (2.2)</td>
<td>4.37</td>
<td>2</td>
<td>0.02</td>
<td>BC</td>
</tr>
<tr>
<td>Physical ADL(^e)</td>
<td>14.3 (1.6)</td>
<td>13.3 (2.2)</td>
<td>14.2 (1.9)</td>
<td>3.01</td>
<td>2</td>
<td>0.05</td>
<td>AB</td>
</tr>
<tr>
<td>Baseine HRSD(^f)</td>
<td>20.5 (3.8)</td>
<td>21.3 (4.0)</td>
<td>20.7 (3.3)</td>
<td>0.58</td>
<td>2</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>Baseline suicidality(^f)</td>
<td>21%</td>
<td>11%</td>
<td>17%</td>
<td>0.91</td>
<td>2</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>Baseline MMSE(^g)</td>
<td>130.3 (11.5)</td>
<td>127.9 (10.6)</td>
<td>134.3 (6.1)</td>
<td>4.84</td>
<td>2</td>
<td>0.009</td>
<td>AB,BC</td>
</tr>
<tr>
<td>IP subscale(^i)</td>
<td>33.6 (4.8)</td>
<td>32.5 (4.7)</td>
<td>34.5 (3.4)</td>
<td>3.67</td>
<td>2</td>
<td>0.03</td>
<td>BC</td>
</tr>
<tr>
<td>Memory subscale(^i)</td>
<td>21.2 (3.7)</td>
<td>20.0 (3.5)</td>
<td>22.2 (2.8)</td>
<td>3.67</td>
<td>2</td>
<td>0.03</td>
<td>BC</td>
</tr>
<tr>
<td>Total Scaled Score</td>
<td>8.3 (3.6)</td>
<td>7.2 (3.5)</td>
<td>9.2 (2.4)</td>
<td>3.67</td>
<td>2</td>
<td>0.03</td>
<td>BC</td>
</tr>
</tbody>
</table>

\(^a\)Significant (\( p < 0.05 \)) after step-down Bonferroni adjustment.

\(^b\)Overall test for three groups.

\(^c\)Tukey post-hoc comparisons on continuous measures.

\(^d\)Cumulative Illness Rating Scale–Geriatric.

\(^e\)Activities for Daily Living (DARS).

\(^f\)Hamilton Rating Scale for Depression (17-item).

\(^g\)Baseline suicidality is defined as 2 or higher on HRSD item 3.

\(^h\)Mini-Mental State Examination (Folstein et al., 1975).

\(^i\)Mattis Dementia Rating Scale (MDRS).

\(^j\)Initiation/Perseveration score from MDRS.
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 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

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**Table 2. Treatment response characteristics across three groups**

<table>
<thead>
<tr>
<th></th>
<th>A. Late-onset, single (n = 95)</th>
<th>B. Late-onset, recurrent (n = 27)</th>
<th>C. Early-onset, recurrent (n = 59)</th>
<th>$\chi^2$ df = 2</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responded during acute treatment</td>
<td>75/95 (79%)</td>
<td>19/27 (70%)</td>
<td>41/59 (69%)</td>
<td>2.01</td>
<td>0.37</td>
</tr>
<tr>
<td>Terminated during Acute treatment</td>
<td>19/95 (20%)</td>
<td>7/27 (26%)</td>
<td>14/59 (24%)</td>
<td>0.56</td>
<td>0.75</td>
</tr>
<tr>
<td>Remitted during acute or continuation treatment</td>
<td>45/95 (47%)</td>
<td>15/27 (56%)</td>
<td>31/59 (53%)</td>
<td>0.74</td>
<td>0.69</td>
</tr>
<tr>
<td>Relapsed during continuation treatment</td>
<td>18/95 (19%)</td>
<td>7/27 (15%)</td>
<td>10/59 (17%)</td>
<td>0.28</td>
<td>0.87</td>
</tr>
<tr>
<td>Terminated during continuation treatment</td>
<td>17/75 (23%)</td>
<td>4/19 (21%)</td>
<td>10/41 (24%)</td>
<td>0.09</td>
<td>0.96</td>
</tr>
<tr>
<td>Required an augmentation agent</td>
<td>25/95 (26%)</td>
<td>12/27 (44%)</td>
<td>27/59 (46%)</td>
<td>7.17</td>
<td>0.03</td>
</tr>
</tbody>
</table>
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 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, $\chi^2 = 4.18$, $p < 0.05$).

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 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.
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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