Prognosis of Depression in Old Age Compared to Middle Age: A Systematic Review of Comparative Studies

Alex J. Mitchell, M.R.C.Psych.

Hari Subramaniam, M.R.C.Psych.

Objective: Depression in old age has a poor long-term prognosis; equal evidence shows that the same is true of depression in middle age. The authors sought to identify research that has compared the prognosis of depression in late life with depression in midlife under similar conditions.

Method: The authors separated studies that examined age at presentation/recruitment from studies of age at first episode of depression, studies that examined remission/response from those that examined relapse/recurrence, and those that examined mortality/risk of dementia.

Results: Evidence suggests that response and remission rates to pharmacotherapy and ECT are not sufficiently different in old-age depression and middle-age depression to be clinically significant. Older patients at study entry appear to have a higher risk of further episodes, which informs the debate about the duration of continuation treatment for depression in older people. However, older patients and patients with late-onset depression are at increased risk of medical comorbidity. Medical comorbidity is a risk factor for inferior treatment response and poor antidepressant tolerability. Elderly patients with early-onset depression are more likely to have had a higher number of previous episodes, which also adversely influences prognosis compared to elderly depressed patients with late onset of illness.

Conclusions: With control for confounding variables, remission rates of depression in patients in late life are little different from those in midlife, but relapse rates appear higher. Findings underline the importance of assessing factors related to patient age and not just to age itself in evaluations of risk factors for poor prognosis.

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There has been considerable debate concerning the outcome of depression in the elderly compared to middle-age sufferers. The first two studies, in 1959 (1) and 1965 (2), suggested that older patients may have a preferential response to ECT. However, in the subsequent two decades, influential reports hinted at a relatively poor prognosis when judged by the chances of subsequent relapse (3, 4). These apparently conflicting results were followed by a series of attempts to confirm or refute the idea that late-life depression has a particularly pernicious outcome. Data from 12 studies conducted both in primary care and in community secondary care were synthesized into a meta-analysis (5) that showed that after 2 years, 21% of elderly depressed patients had died and among survivors, almost half remained depressed. However, during the same period, evidence had accumulated that depression in middle age also has a poor prognosis (6). Therefore, it is surprising that few groups have directly compared outcomes in older and middle-age patients. Indeed, only a limited number of reports have specifically examined whether age is a marker of poor prognosis, and most have limited consideration to a cohort with a narrow age range. Several of these studies have suggested that older age is a predictor of reduced likelihood of remission in both middle-age and elderly depressed patients (7–12). There is a temptation to infer from this that the prognosis must be more hazardous in elderly patients than in younger patients. However, this is not necessarily the case for several reasons:

1. The magnitude of the effect of age varies considerably across studies, in part due to different outcome measures and in part due to variability of confounding factors.
2. The putative effect size could be different in those who are middle age compared to those who are elderly.
3. Studies have not typically distinguished age at the commencement of treatment from the first age at onset of depression.
4. Most critically, no studies have ensured that older and younger patients had received equivalent management strategies.

Given these issues, we were interested in locating and examining studies that have attempted to directly compare cohorts of elderly and middle-age depressed patients. In doing so, we encountered several methodological concerns.

First, is it important to discover whether age at onset of mood disorder influences the prognosis of the patients entering old-age (geriatric) psychiatry services? If this is the case, then it is necessary to examine studies that have divided elderly depressed patients by age at onset. Alternatively, is it the age at the time of the current episode that is of interest (in effect, comparing the people who enter general adult psychiatry services with those who enter old-age psychiatry services)? In which case is it necessary to examine studies that have divided and treated first-onset cases separated into old and middle age?

Second, how can one be sure that any differences in outcome are not explicable by differences in the type of treatment offered (as opposed to treatment response), differences in past psychiatric history, psychosocial stressors, or differences in current comorbidity? Clearly, it is desirable for studies to attempt to control important possible confounding factors.

Third, there is the issue of a clear definition of prognosis. We chose to divide studies into those that considered early prognosis (treatment response) and those that consider later prognosis (relapse and recurrence). We also examined the influence of age on later mortality and dementia because these are increasingly recognized as important adverse outcomes of major depression. With these factors in mind, we conducted a systematic review of the evidence concerning the prognosis of depression in old age compared to midlife.

Method

We conducted a systematic review for primary data studies relating to the differences in clinical outcome of depression according to age. We limited our study to comparative work looking at depressed patients in late life and depressed patients with an index (presentation) or first episode in midlife. We allowed studies to define late life as 60 years or older. We allowed studies to define midlife as less than 60 years or as less than 65 years (and all cutoff ages in between). We further defined our area of interest using the following three constructs.

Construct A: Age

We examined age in relation to depression using three definitions.

1. Age at presentation (or index episode): the age at the time of recruitment into a study or first contact with psychiatric services, regardless of past number of episodes
2. Age at first admission: the age at the time of first clear episode of psychiatric inpatient admission, often abbreviated to "early onset" and "late onset" when it is considered categorically
3. Age at the time of first affective symptoms: the true age at illness onset (regardless of admission age)

Construct B: Prognosis

We defined prognosis using the criteria suggested by Frank and colleagues (13). Response was defined as a substantial (usually 50%) decrease in baseline rating scale severity score. We examined time to remission or proportion of patients who attained remission (early treatment response) and time to relapse (during acute or continuation therapy) or recurrence (during maintenance therapy) and the proportion of patients who suffered a relapse, recurrence, or later dementia or mortality.

Construct C: Depression

We defined depression as any operationally defined and validated type of depression. We included major and minor depression (e.g., according to DSM-III, DSM-III-R, DSM-IV); mild, moderate, and severe depression (e.g., ICD-10); dysthymia (e.g., ICD-10, DSM-IV); and depression quantified by validated rating scale scores as well as in-depth structured clinical interviews (e.g., the Schedule for Affective Disorders and Schizophrenia—Lifetime Version).

Literature Search

We conducted a literature search using the following search terms.

Construct A. Age (age or aging; older or younger; elderly or late onset; or 60, 61, 62, 63, 64, or 65 years)

Construct B. Prognosis (prognosis, course or outcome, relapse or remission, response or recurrence, improvement or complications, mortality, or dementia, Alzheimer's disease, or vascular dementia)

Construct C. We searched the following abstract databases for depression ("depressi$," "mood," "affective$," or "dysthymia"): MEDLINE, 1966 to July 2004; PsycINFO, 1887 to July 2004; ASSIA, 1987 to July 2004; Embase, 1980 to July 2004; the National Library of Medicine gateway, accessed July 2004; and CINAHL, 1982 to July 2004. A number of full-text collections, including Science Direct, Ingenta Select, Ovid (full text), and Wiley Interscience were searched. In these online databases, the same search terms were used but as a full-text search. The abstract database Web of Knowledge (1.2, ISI) was searched by using the same terms in a title search and by using key papers in a reverse-citation search.

Systematic Review

Individual studies were reviewed by two raters (A.J.M., H.S.). Studies were evaluated by using the following criteria.

Essential criteria

1. Primary data included
2. Direct comparison of older and younger groups around a cutoff of 65 years (±5 years) or studies that compared a first onset of depression around a cutoff of 65 years (±5 years), even if the subjects were currently over 65
3. Sample size of more than 20 in each group (a sample size of 20 in each group would have the power to detect only a very large [45%] difference in outcomes—for example, an 80% relapse rate in the elderly compared to a 35% relapse rate in the young.)

Optional criteria to assess study quality

4. Older and younger patients received comparable treatment
5. Confounding factors were measured and/or adjusted for
6. Subgroups were recruited at the same time by using a standardized protocol for entry (an inception cohort)

Results

We identified 1,512 documents, of which 121 were reviews. Of these, we identified 36 primary data articles. We excluded two articles because of inadequate sample size (14, 15). We excluded three articles because of an inappropriate age range, such as under 18 years (12, 16, 17). We excluded one article because of the duplicate publication of substantially the same data as previously reported (18).

We excluded three articles that made no direct comparison with a younger age group (7–9, 19) and three articles than made no direct comparison with an older age group (10–12). Of the remaining 24 publications, 17 reports used naturalistic (observational) methods in relation to remission, relapse, or recurrence, and four reports (of three studies) used an inception cohort in relation to remission, relapse, or recurrence. We also identified three studies that examined the risk of mortality or dementia in relation to age.

Episode Remission in Older Versus Younger Patients

Direct comparisons with inception cohort. We identified one inception cohort study that involved ECT, one that used pharmacotherapy, and one that compared nortriptyline with interpersonal psychotherapy.

O'Connor and colleagues (20) studied 253 patients treated with bilateral ECT. The subjects were stratified by recruitment age, regardless of age at onset. Although there was no significant difference between the elderly and middle-aged groups, the younger patients had an inferior response. It is important to note that the younger group also had a significantly greater number of previous episodes of depression, a likely confounder that was not adjusted for. Katon and co-workers (21) studied 282 patients in a methodologically thorough randomized, controlled multicenter trial. This study focused on mild types of depression, but the results were probably generalizable to other forms of depression. Of note, the authors showed that an age younger than 60 years at presentation was associated with a better response to paroxetine but not in the problem-solving subgroup (odds ratio=2.68). Reynolds and collaborators in the Pittsburgh Study of Maintenance Therapies in Late-Life Depression (22, 23) examined time to remission as well as time to relapse in 187 elderly patients, initially over 1 year and then over 3 years. The groups were initially divided by those with age at first onset of less than 60 years and those with an onset at age 60 years or later. Although there were clinical and treatment differences between early-onset and late-onset patients, the authors controlled for previous number of episodes. They found that early-onset patients took longer to achieve initial remission than late-onset patients. By design, early-onset patients with depression in old age had longer illness durations and a greater number of episodes before entry, but this only partly explained the effect on time to remission.

Naturalistic studies. There have been four naturalistic studies that have used ECT, and the remainder have employed pharmacotherapy or mixed treatment methods (Table 1).

1. ECT. Wilkinson et al. (24) found no differences in baseline symptoms, past episodes, or clinical features of depression in 78 patients stratified by age at entry. However, over the course of treatment with ECT, older patients had a preferentially better outcome compared to those less than 65 years. In contrast, using age at first episode onset, Philibert et al. (25) found no differences in the rates of remission, although there were differences in subsequent mortality rates. In a small study, Wesson and coworkers (26) found that 67% of those over 65 years old were well at their 4-year follow-up, compared to only 40% in the younger group, in part because of differences in remission rates. Unfortunately, this study was unable to examine past episode characteristics. In an impressive four-center study, Tew et al. (27) treated 268 patients with suprathreshold right unilateral or bilateral ECT using a standardized protocol. Those ages 59 and younger experienced a significantly lower remission rate than those ages 60 to 74 years (54% versus 73%, respectively); however, those over 75 years had an intermediate rate of response of 67%. However, there were clinical and treatment differences between subgroups, with higher medical comorbidity in older groups. In an Australian study, Brodaty and colleagues (28) examined responses to ECT in a smaller group (of barely adequate sample size) stratified by age into those under age 65, age 65 to 74, and 75 years and older. There were no significant differences in response (or remission) after ECT on the Hamilton Depression Rating Scale, but when the subjects were followed up 3 years later, a higher proportion of the oldest group had developed dementia (35.7%).

2. Pharmacotherapy or mixed treatment methods. Conwell et al. (29) reported on a sample of 94 elderly patients, stratified by age at first episode into four groups. Although there were differences in the aggressiveness of somatic treatment between groups, early-onset patients had a greater number of past episodes and past hospitalizations. Musetti and colleagues (30) studied 400 consecutive patients seen in secondary care over an 18-month period. Unusually, the authors divided their sample both by age at study entry and by age at onset. The authors found no significant difference in the proportion of patients achieving complete remission by age at time of entry into the secondary care. In a British study, Meats and colleagues (31) found a favorable prognosis in 56 elderly patients compared with 24 younger individuals, although the elderly suffered a greater mortality rate. The difference was accounted for by a higher remission rate (not relapse rate) in the elderly patients. Blazer and co-workers (32) observed 79 depressed patients over 1 to 2 years. Initial remission rates differed little between groups. There was a tendency, however, for younger patients to experience persistent residual symptoms. Hughes et al. (33) conducted a modest-sized naturalistic study examining a selected cohort of patients at the Duke University Clinical Research Center for Depression in Late Life. Six months after entry, the older patients were more likely to have attained remission; however, the younger patients had a significantly greater number of previous episodes in this study, making interpretation difficult. Alexopoulos et al. (34) followed 63 subjects

TABLE 1. Remission (Early Treatment Response) Studies Showing Prognosis of Depression by Age

Study	Year	Measure of Outcome and Diagnosis of Depression	Cutoff or Stratification	Group Size	Subgroup Size	Confounders Measured (or adjusted for)	Methods or Setting (if known)	Finding or Comment
Conwell et al. (29)	1989	Failure of remission (chronic course), residual symptoms; DSM-III criteria	Age at onset, stratified	94 elderly patients	Age 17–41, N=24; age 42–54, N=23; age 55–64, N=23; age 65–81, N=24	Attempt to match subgroups by treatment received but not past history	Naturalistic mixed study, 5-year retrospective review with 18-month follow-up	1) No differences detected in remission between those over 65 and those who were younger; 2) there was little clinical difference between groups, although the older groups were more symptomatic at discharge ($p<0.04$)
Musetti et al. (30)	1989	Remission; DSM-III-R criteria	Age at entry, age at onset, cutoff=65 years; also stratified by age at onset	400 consecutive patients	Age <40, N=12; age 40–59, N=14; age ≥60, N=42	Clinical differences between groups noted but not adjusted for	Naturalistic mixed study, cross-sectional assessment of referrals to a tertiary institute in Italy	Remission rates similar in both subgroups
Meats et al. (31)	1991	Remission, relapse; Feighner criteria	Age at entry, cutoff=65 years	80 inpatients	Age ≥65, N=56; age <65, N=24	Attempt to match subgroups by gender, previous episodes, but differences in treatment remained	Naturalistic mixed study, 1-year community follow-up	1) Older patients had lower remission rate but a higher mortality rate and a similar relapse rate to younger patients; 2) residual symptoms were the best predictor of outcome
Blazer et al. (32)	1992	Remission, residual symptoms, relapse; DSM-III criteria, Center for pidemiologic Studies Depression Scale (CES-D Scale)	Age at entry, cutoff=60 years	79 patients	Age ≥60, N=44; age <60, N=35	Attempt to match subgroups by severity of depression	Naturalistic mixed study, 1–2 year outcome	1) Initial remission differed little between groups; 2) relapse was higher in middle-age patients but not significantly so; 3) residual symptoms were higher in elderly subjects at follow-up (n.s.)
Hughes (33)	1993	Remission; CES-D Scale, DSM-III-R criteria	Age at entry, cutoff=60 years	113 patients	Age <60, N=67; age ≥60, N=46	Younger patients had a lower age at onset and a higher number of episodes	Naturalistic mixed study, 6-month outcome, secondary care	1) At 6 months, mean CES-D Scale scores for the younger patients remained above the depression threshold, but the mean score for the older patients was below the threshold; 2) at 6 months, older patients had similar self-reported rates of partial and complete recovery as younger patients; 3) at 6 months, older patients were less likely to have additional episodes of depression; 4) physical health and subjective social support are significant predictors for younger but not older patients
Wilkinson et al. (24)	1993	Response to ECT; DSM-III-R criteria	Age at entry, stratified	78 patients consecutively referred for ECT	—	Attempt to match subgroups by clinical features and past history of depression	Naturalist ECT study, secondary care	1) 73% of those over 65 years had a response compared to 54% of younger patients (n.s.); 2) positive correlation between age and response ($r=0.96$, $p<0.05$)

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TABLE 1. Remission (Early Treatment Response) Studies Showing Prognosis of Depression by Age *(continued)*

Study	Year	Measure of Outcome and Diagnosis of Depression	Cutoff or Stratification	Group Size	Subgroup Size	Confounders Measured (or adjusted for)	Methods or Setting (if known)	Finding or Comment
Alexopoulos et al. (34)	1996	Time to remission; Research Diagnostic Criteria (RDC)	Age at onset and age at entry, cutoff=63 years	86 patients	Age ≥63, N=63; age <63, N=23	Differences in antidepressant treatment noted but not adjusted for	Naturalistic mixed study, follow-up for 18.2 months, secondary care	1) Rates of remission similar in older and younger patients; 2) in older patients, age and age at onset predicted slower recovery; 3) in those over 65 years, probability of recovery at 2 years was 64% for late-onset and 90% for early-onset patients of same current age; 4) in younger patients, younger age predicted longer time to recovery
Philibert et al. (25)	1997	Remission rate, mortality rate; DSM-III criteria	Age at onset, stratified	192 subjects	Age <40, N=42; age 40–59, N=47; age 60–69, N=53; age ≥70, N=50	Attempt to adjust for gender effects	Naturalistic mixed study, 7-year follow-up, secondary care	1) Older age at onset linked with higher risk of mortality; 2) age at onset was not linked with remission of depression; 3) patients with late-onset depression were more likely to have physical illness
Wesson et al. (26)	1997	Remission rate, recovery rate, relapse rate; DSM-III-R criteria	Age at entry, cutoff=65 years	63 subjects	Age ≥65, N=33; age <65, N=30	No confounders measured or adjusted for	Naturalistic ECT study, 2–4-year follow-up after index episode, secondary care	1) 67% of those over 65 years were well at follow-up compared to only 40% of the younger group; 2) differences in relapse rates alone were not significantly different; 3) nine of 78 patients died during the follow-up period
Reynolds et al. (22)	1998	Time to remission, relapse rate; Schedule for Affective Disorders and Schizophrenia—Lifetime Version	Age at onset, cutoff=60 years	187 patients	Early onset, N=129; late onset, N=58	Adjustment was made for the number of lifetime episodes, although clinical and treatment differences remained	Inception cohort study, open then randomly assigned nortriptyline and/or interpersonal psychotherapy maintenance treatment in secondary care	1) No difference in remission, recovery, or relapse during the first year of maintenance treatment between the groups; 2) early-onset patients took longer for depression to remit than late-onset ones
Tew et al. (27)	1999	Remission; RDC	Age at entry, stratified	268 patients	Age <60, N=133; age 60–74, N=63; age ≥75, N=72	Adjustment was made for age and medication resistance	Naturalistic ECT study, multicenter secondary care	1) Those ages 59 and younger experienced a significantly lower remission rate than those ages 60 to 74 years (54% versus 73%); 2) those over 75 years had an intermediate rate of response of 67%
Tuma (38)	2000	Remission, relapse, recovery; DSM-III-R criteria, Feighner criteria	Age at entry, cutoff=65 years	110 patients	Age ≥65, N=54; age <65, N=56	Attempt to match subgroups by treatment received and inpatient duration	Naturalistic mixed study, retrospective 4.5-year follow-up	1) Recovery rate was lower in old-age than middle-age patients (36% versus 48%) but did not reach statistical significance; 2) rate of mortality was higher in the elderly (33%), as was the rate of dementia (14.8%); 3) current medical illness predicted poor recovery

(continued)

TABLE 1. Remission (Early Treatment Response) Studies Showing Prognosis of Depression by Age *(continued)*

Study	Year	Measure of Outcome and Diagnosis of Depression	Cutoff or Stratification	Group Size	Subgroup Size	Confounders Measured (or adjusted for)	Methods or Setting (if known)	Finding or Comment
Brodaty et al. (28)	2000	Remission, dementia; Global Assessment of Functioning scale, DSM-III-R criteria	Age at entry, stratified	101 consecutive inpatients	Age <65, N=28; age 65–74, N=25; age ≥75, N=28	Attempt to match subgroups by diagnostic subtype, severity, chronicity, and number of prior depressive episodes, but clinical differences remained	Naturalistic ECT study, prospective with 3-year follow-up	1) There were no significant differences in response (remission) after ECT on the Hamilton Depression Rating Scale; 2) 3 years later, a higher proportion of the oldest group had developed dementia (35.7%)
O'Connor et al. (20)	2001	Rate of remission; Structured Clinical Interview for DSM-IV, score >20 on Hamilton Depression Rating Scale	Age at entry, stratified	253 patients	Age 18–45, N=79; age 46–64, N=81; age 65–85, N=93	Higher percentage of psychotically depressed patients in the older group; younger groups had an earlier age at onset and a greater number of lifetime episodes	Inception ECT cohort, secondary care on multiple sites	1) Remission rates were equivalent in those over 65 years and over 45 years; 2) remission rates were lower in those younger than 45 years; 3) age as a continuous variable influenced treatment response
Katon et al. (21)	2002	Remission rates at 11 weeks; DSM-IV minor depression (dysthymia) criteria	Age at entry, cutoff=60 years	333 patients	Age 18–59, N=40; age ≥60, N=94	Severity of physical illness measured as a possible confounder	Inception pharmacotherapy cohort, 4 weeks of paroxetine or placebo in a multicenter, randomized, controlled 11-week trial, primary care	1) Age younger than 60 years (odds ratio=2.68) were more likely to achieve remission with paroxetine; 2) more serious physical illness was associated with nonresponse; 3) there was an age-by-gender effect; 71% of the younger female sample recovered, compared to 37% of the older women; 4) age effect was significant only in the paroxetine subgroup, not in those using problem-solving therapy
Fischer et al. (36)	2003	Remission; ICD-9 criteria, CES-D Scale	Age at entry, stratified	1,023 patients	Age <35, N=134; age 35–44, N=214; age 45–54, N=264; age 55–64, N=139; age 65–74, N=134; age ≥75, N=138	No confounders measured or adjusted for	Naturalistic pharmacotherapy study, primary care survey with 3-month follow-up	1) Older patients were less likely to have remission at the 3-month follow-up; 2) older patients had more comorbid health problems; 3) older depressed patients were asked about depression, suicide, and alcohol use less frequently than middle-age patients
Zanardi et al. (35)	2003	Remission; Hospital Anxiety and Depression Scale, DSM-IV criteria	Age at entry, cutoff=60 years	327 patients	Age <61, N=354; age ≥61, N=174	Older subjects had a higher number of episodes	Naturalistic pharmacotherapy study, consecutively admitted inpatients	Better antidepressant (fluvoxamine) response in younger than older subjects

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TABLE 1. Remission (Early Treatment Response) Studies Showing Prognosis of Depression by Age *(continued)*

Study	Year	Measure of Outcome and Diagnosis of Depression	Cutoff or Stratification	Group Size	Subgroup Size	Confounders Measured (or adjusted for)	Methods or Setting (if known)	Finding or Comment
Muller et al. (39)	2004	Time to remission, time to relapse; RDC, Schedule for Affective Disorders and Schizophrenia	Age at entry, stratified	332 subjects	Age 17–30, N=119; age 31–50, N=118; age 51–64, N=63; age 65–79, N=32	All patients ages 65 and over were inpatients; physical illness was measured and reported	Naturalistic mixed study, 15-year outcome, secondary care on multiple sites, treatment monitored	1) Significant difference between 51–64-year-olds and 65–79-year-olds (older group had more rapid relapse); 2) older groups had more medical illnesses (including cancer and cardiovascular disease)
Rush and Rothschild (37)	2004	Remission rates (response); DSM-IV criteria (personal communication)	Age at entry, cutoff=60 years	5,453 patients from phase IV trial database	Age ≥60, N=784; age <60, N=4,669	Treatment was standardized, but flexible dosing was allowed	Naturalistic pharmacotherapy study, primary and secondary care on multiple sites	Patients ages 60 or older had a marginally less frequent response rate at week 8 of treatment, although the difference was likely to be not clinically significant

older than 63 years and 23 younger patients with depression over 18 months. After controlling for treatment intensity between the groups, the authors found that in elderly patients, late age at onset was the strongest predictor of prolonged time to remission, whereas in younger patients, weak social support, age-related cognitive impairment, and low intensity of antidepressant treatment were important.

In more recent work, Zanardi and colleagues (35) treated 528 consecutive (nonrandomized) depressed inpatients with fluvoxamine. The time to remission and the proportion attaining remission were significantly lower in those over 60 years compared to younger subjects. In another adequately powered publication, Fischer et al. (36) reported on the outcome of depressed patients from nine primary care clinics across the United States. Of 1,023 patients, 272 were ages 65 years or older at study entry (36). Older patients were less likely to have achieved remission at the 3-month follow-up. However, no confounders were examined in this study, and the older patients had more comorbid health problems. Finally, in an important study yet to be fully reported, Rush and Rothschild (37) examined an impressive database containing 5,453 patients over 18 years, of whom 784 were 60 years or older. Patients 60 years or older had a marginally less frequent rate of response to treatment with escitalopram after 8 weeks of treatment, although the difference (less than 5%) was unlikely to be clinically significant.

Relapse and Recurrence in Older Versus Younger Subjects

We found only one inception cohort study that had examined relapse; the remainder of the studies relied upon naturalistic methods (Table 2).

Inception cohort study. In an ambitious study of open, acute treatment and randomized maintenance treatment, Reynolds and colleagues (23) randomly assigned 107 patients into maintenance treatment with nortriptyline, interpersonal psychotherapy, or placebo. The authors divided the patients by age at onset into 129 subjects with a first onset at age 59 years or younger and 58 subjects with an onset at 60 years or older. They found no differences in the proportion that remitted, recovered, or relapsed in the first year, but old age at the time of study entry was associated with an increased likelihood of recurrence for up to 3 years. Although not specifically controlled, the authors stated that previous episodes, age at index episodes, and degree of medical comorbidity did not predict relapse.

Naturalistic studies. As mentioned in the study by Blazer et al. (32), initial remission rates differed little between groups, but there was a tendency for a higher relapse rate in younger patients. Brodaty et al. (40) studied a consecutive sample of patients referred to a specialist tertiary clinic for mood disorders but found no differences in rates of relapse or rates of persisting residual symptoms. Tuma (38) studied 54 patients 65 years or older and 56 under 65 years at study entry and found no difference in time to remission or proportion who relapsed within 1 year, but fewer elderly patients had made a lasting recovery by 4.5 years, mainly because of attrition to dementia. In addition, current medical illness in the elderly predicted a poor outcome. Recently, an important study has addressed several of the method shortcomings previously noted in a large sample of 332 patients. Using 15 years of prospective data from the National Institute of Mental Health (NIMH) Collaborative Depression Study, Muller and colleagues (39) examined time to recovery and time to recurrence in four cohorts divided by age at the time of enrollment. Assessments were conducted every 6 months for 5 years and then annually thereafter. Survival analysis was used to estimate the time to recovery and first recurrence. Although the median time to recovery was similar between groups, the median time to recurrence was shorter for the oldest versus the 51–64-year-old group. It should be noted that this was not an inception cohort and patients were not all recruited at the first episode. Thus, older patients tended to have a greater number of past episodes, and this influence could not be excluded post hoc. Nevertheless, this important study is still of relevance to clinicians who wish

TABLE 2. Relapse Studies Showing Prognosis of Depression by Age

Study	Year	Measure of Outcome and Diagnosis of Depression	Cutoff or Stratification	Group Size	Subgroup Size	Confounders Measured (or adjusted for)	Method or Setting (if known)	Finding or Comment
Meats et al. (31)	1991	Remission, relapse; Feighner criteria	Age at entry, cutoff=65 years	80 inpatients	Age ≥65, N=56; age <65, N=24	Attempt to match subgroups by gender, previous episodes, but differences in treatment remained	Naturalistic mixed study, 1-year community follow-up	1) Older patients had lower remission rate but higher mortality rate and a similar relapse rate as younger patients; 2) residual symptoms were the best predictor of outcome
Blazer et al. (32)	1992	Remission, residual symptoms, relapse; DSM-III critera, Center for Epidemiologic Studies Depression Scale (CES-D Scale)	Age at entry, cutoff=60 years	79 patients	Age ≥60, N=44; age <60, N=35	Attempt to match subgroups by severity of depression	Naturalistic mixed study, 1–2 year outcome	1) Initial remission little different in groups; 2) relapse higher in middle-age patients but not significantly so; 3) residual symptoms higher in elderly at follow-up (n.s.)
Brodaty et al. (40)	1993	Relapse rate; DSM-III criteria for unipolar major depressive episode	Age at onset and age at entry, stratified	242 consecutive referrals	Age ≥60, N=61; age <60, N=181	No confounders measured or adjusted for, although past history and physical illness were measured	Naturalistic mixed study, 1-year and 2–4-year outcome, tertiary clinic	1) No differences were apparent at 1 year; 2) early-onset (first depression <60) patients had a worse prognosis than those with late-onset depression, who had fewer relapses; 3) among the elderly depressed, prior history of recurrent depression was more likely to be associated with a poor outcome than a first episode of depression; 4) physical illness did not affect recovery in the elderly
Wesson et al. (26)	1997	Recovery rate, relapse rate; DSM-III-R criteria	Age at entry, cutoff=65 years	63 subjects	Age ≥65, N=33; age <65, N=30	No confounders measured or adjusted for	Naturalistic ECT study, 2–4-year follow-up after index episode	1) 67% of those over 65 years were well at follow-up compared to only 40% in the younger group; 2) differences in relapse rates alone were not significantly different; 3) 9 of 78 patients died during follow-up period
Reynolds et al. (22)	1998	Time to remission, relapse rate; Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L)	Age at onset, cutoff=60 years	187 patients	Early onset, N=129; late onset, N=58	Adjustment was made for the number of lifetime episodes, although clinical and treatment differences remained	Inception cohort study, open then randomized nortriptyline and/or interpersonal psychotherapy maintenance treatment in secondary care	1) No difference in remission, recovery, or relapse during the first year of maintenance treatment between the groups; 2) early-onset patients took longer to recover than late-onset patients

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TABLE 2. Relapse Studies Showing Prognosis of Depression by Age *(continued)*

Study	Year	Measure of Outcome and Diagnosis of Depression	Cutoff or Stratification	Group Size	Subgroup Size	Confounders Measured (or adjusted for)	Method or Setting (if known)	Finding or Comment
Reynolds et al. (23)	1999	Recurrence rate, SADS-L	Age at entry, cutoff=70 years	107 patients	Age 60–69, N=69; age ≥70, N=38	Clinical and treatment differences were present	Inception cohort study, open then randomized nortriptyline and/or interpersonal psychotherapy maintenance treatment in secondary care	1) No differences according to age at first onset; 2) older patients at study entry had a higher chance of relapse during follow-up
Tuma (38)	2000	Remission, relapse, recovery; DSM-III-R criteria, Feighner criteria	Age at entry, cutoff=65 years	110 patients	Age ≥65, N=54; age <65, N=56	Attempt to match subgroups by treatment received and inpatient duration	Naturalistic mixed study, retrospective 4.5-year follow-up	1) Recovery rate was lower in old age than middle-age patients (36% versus 48%) but did not reach statistical significance; 2) rate of mortality higher in elderly (33%), as was the rate of dementia (14.8%); 3) current medical illness predicted poor recovery
Fischer et al. (36)	2003	Remission; ICD-9 criteria, CES-D Scale	Age at entry, stratified	1,023 patients	Age <35, N=134; age 35–44, N=214; age 45–54, N=264; age 55–64, N=139; age 65–74, N=134; age ≥75, N=138	No confounders measured or adjusted for	Naturalistic pharmacotherapy study, primary care survey with 3-month follow-up	1) Older patients were less likely to have remission at 3-month follow-up; 2) older patients had more comorbid health problems; 3) older depressed patients were asked about depression, suicide, and alcohol use less frequently than middle-age patients
Muller et al. (39)	2004	Time to remission, time to relapse; Research Diagnostic Criteria, Schedule for Affective Disorders and Schizophrenia	Age at entry, stratified	332 subjects	Age 17–30, N=119; age 31–50, N=118; age 51–64, N=63; age 65–79, N=32	All patients age 65 and over were inpatients; physical illness was measured and reported	Naturalistic mixed study, 15-year outcome, secondary care on multiple sites, treatment monitored	1) Significant difference between 51–64-year-olds and 65–79-year-olds (older group had more rapid relapse); 2) older groups had more medical illnesses (including cancer and cardiovascular disease)

to know if patients at age 65 or older have a less favorable prognosis than those under 65 years at the time of presentation (regardless of the number of past episodes).

Rates of Mortality and Dementia in Older Versus Younger Patients

At least 60 studies have examined the association between depression and mortality (excluding suicide) (e.g., see reference 41). Most of these studies controlled for patient age at the time of recruitment but did not examine the effect of age within a depressed cohort. We could only identify two studies that have examined the differential risk of mortality based on age at onset of depression (Table 3). Rabins et al. (42) studied 62 consecutive inpatients over the age of 60, but because there were only eight deaths, the study was underpowered and identified no differences. In a larger retrospective examination Philibert and colleagues (25) found that patients with an onset of depression before age 40 had about half the risk of mortality as patients with late-onset depression, despite a similar recruitment age.

We identified over 30 studies that have examined the relationship between depression and an incident of dementia, but few have examined whether the risk of dementia was different in older versus younger sufferers. Bassuk et al. (19) found a greater risk of dementia in depressed patients ages 75 years or older than in those under 75 years at the time of study entry, but the effect of age at onset was

TABLE 3. Mortality Studies Showing Prognosis of Depression by Age

Study	Year	Measure of Outcome and Diagnosis of Depression	Cutoff or Stratification	Group Size	Subgroup Size	Confounders Measured (or adjusted for)	Method or Setting (if known)	Finding or Comment
Rabins et al. (42)	1985	Mortality rate; DSM-III criteria	Age at onset and age at entry not specified	62 subjects	Not specified	No attempt to adjust for confounding factors	Naturalistic mixed study, 1-year follow-up, secondary care	Age not linked to mortality, but subgroup size too small for analysis
Philibert et al. (25)	1997	Remission rate, mortality rate; DSM-III criteria	Age at onset, stratified	192 subjects	Age <40, N= 42; age 40–59, N= 47; age 60–69, N= 52; age ≥70, N=50	Attempt to adjust for gender effects	Naturalistic mixed study, 7-year follow-up, secondary care	1) Older age at onset linked with higher risk of mortality; 2) age at onset not linked with remission of depression; 3) patients with late-onset depression were more likely to have physical illness
Palsson et al. (43)	1999	Dementia (22.8%); Mini-Mental State Examination	Age at onset	57 patients	Not specified	Years of education	Naturalistic mixed study, community based	1) Early-onset major depression conferred increased risk of cognitive decline; 2) low education was linked with increased risk of cognitive decline

not studied. Indeed, only one report, to our knowledge, part of a longitudinal study in Gothenburg, has examined this. Palsson et al. (43) showed that an early first onset of depression in those age 85 years at the time of study entry was associated with an increased risk of dementia and cognitive decline.

The Influence of Confounding Factors

Naturalistic studies involving ECT must be viewed with caution because there appear to be differences in why clinicians choose ECT according to age. In younger patients, ECT tends to be reserved for treatment-resistant cases, but in older groups, it may be used as first-line treatment more frequently (27).

Where past psychiatric history was examined, the effect usually dominated other risk factors for poor prognosis. For example, several authors found that the prognosis of depression in midlife is more hazardous than depression in old age, but in these studies, depression at a younger age was linked with a greater number of past episodes (e.g., see reference 33).

Numerous studies have demonstrated a higher rate of medical comorbidity (and broadly defined physical disability) in elderly depressed patients than in nonelderly depressed patients (or, indeed, in elderly nondepressed patients) (22, 38, 39, 44–46). It appears that the same relationship holds for age at first-episode onset but with a uniform current age (25, 47, 48). It is possible that elderly depressed patients with a late-life onset have greater comorbidity for some disorders not but others when compared with elderly depressed patients with an early onset (49–51). Therefore, an important subsidiary question is whether comorbidity influences treatment response or treatment selection. A recent Cochrane review (52) showed that antidepressants are effective in patients with physical illness, with a combined number needed to treat of 4.2. However, this review did not examine antidepressant efficacy in the elderly, per se. On this question, most (21, 38, 53–58), but not all (59–61), studies have suggested that medical comorbidity adversely affects treatment response. Furthermore, a meta-analysis of studies in older adults suggested that there is a dose-response relationship, with more serious physical illness associated with poorer treatment response (62). It is quite possible that specific medical conditions influence the outcome of specific subgroups and that specific antidepressants have differential effects in this population. Perhaps the best example is the influence of brain white matter lesions on antidepressant response. However, this link between medical comorbidity and poor antidepressant response is likely to be itself moderated by complex factors, such as adverse events, degree of disability, and effects of social support (63).

Discussion

We conducted a systematic review focusing on robust studies that have directly compared the prognosis of depression in late life versus midlife. This review is fundamentally limited by the quality of the primary data studies. We found that most authors have relied on naturalistic methods with different degrees of homogeneity of treatment. We found only four reports (of three studies) that recruited older and younger patients at the same time into one study with a fixed treatment protocol (an inception cohort) (20–22). We also found that many of the studies (naturalistic and inception) have been underpowered,

raising the possibility of type I and type II errors. We chose to exclude studies with a sample size below 20 per subgroup, but we would advise caution in the interpretation of several studies that showed small differences of questionable clinical importance, as well as studies that did not adequately measure possible confounding variables (26, 28–31, 40). Indeed, it is remarkable how few studies have taken into account whether psychosocial stressors or degree of social support varies by age, despite the likely effects on outcome (34). Nevertheless, we found 23 publications reporting 21 unique studies of remission, relapse, or recurrence of depression (Table 1 and Table 2). Of these, 18 considered age at presentation (or the index episode), and seven considered age at first episode (the categories were not mutually exclusive). Unfortunately, we were unable to identify any studies that have examined age at the time of first onset of affective symptoms, suggesting that more work on the duration of untreated depression is urgently required.

Are Differences Between Older and Younger Patients Clinically Relevant?

Of comparative studies that have examined relapse or recurrence, outcome appears to be poorer in the elderly, but effect sizes have been modest and, hence, this is most clearly demonstrated only by the largest studies. The principal methodological difficulty with most comparative studies is one of comparing like with like because differences in past history (particularly the number of previous episodes), medical comorbidity, psychosocial stressors, and social support will, in themselves, influence prognosis. In addition, systematic differences in treatment of depression by age is an important confounder in naturalistic studies. Examples of recognized systematic differences include low rates of inquiry about depression or suicidal thoughts (36) and differences in the threshold clinicians apply when prescribing ECT (27) in the elderly compared with middle-age groups.

Relapse and Recurrence

In the key study by Reynolds and colleagues (22, 23), despite the fact that cohorts were not identically matched clinically, both groups were randomly assigned to equivalent treatment, and allowance was made for the number of lifetime episodes of depression. The results showed that older patients at study entry had a higher chance of relapse during follow-up. Imperfect matching for background factors is not ideal when testing a research hypothesis but is analogous to the situation in the clinic where past history cannot be controlled. The NIMH Collaborative Depression Study, which also studied patients stratified by age at study entry (again without perfect matching for possible confounding factors), lends support to the hypothesis that older depressed patients have a shorter interval until recurrence. This may be of clinical importance and supports the suggestion from several groups for longer maintenance treatment in the elderly (64–66). Regarding the effect of age at onset itself on relapse, further research is needed because only one study has been reported, to our knowledge, showing no appreciable effect (22).

Treatment Response

The evidence regarding treatment response in relation to age is less consistent. Two large studies have shown that older patients at the time of pharmacological treatment for depression have an inferior treatment response than middle-age patients (35, 36), but a number of other reports have shown the opposite finding (20, 31, 33) or no statistical difference (25, 30, 32, 34). Together this suggests that rates of response are not substantially different between groups, a hypothesis supported by the largest study to date, which showed only a tiny difference in response rates, which is unlikely to be of clinical significance (37). The results from naturalistic ECT surveys (all of which have used age at treatment as the predictor variable) have suggested small or absent differences in treatment response, but interpretation is more difficult because of methodological limitations of relatively small sample sizes and selection bias in the use of ECT itself. Furthermore, although it is possible that the prognostic effect of age may differ according to the type of treatment used, only one study to date, to our knowledge, has hinted at differential effects (21).

Regarding studies of elderly depressed patients stratified by age at first-episode onset, it has been reported that patients with a late onset of first-episode depression have a better treatment response (22) and a lower chance of subsequent relapse (40) or, in contrast, an inferior treatment response (29, 34). These discrepant results may be understood by the effect of two confounding factors working in opposite directions. Elderly patients of the same chronological age but an earlier age at onset than a group with a later age at onset, by definition, have a longer illness duration and a higher probability of a greater number of previous episodes, which is one of the strongest predictors of relapse and recurrence (67). However, medical comorbidity is more likely in people with late-onset depression without a past psychiatric history (47, 48). Evidence from comorbidity studies has demonstrated that time to remission may be longer and rates of remission may be lower when medical comorbidity is present. Thus, a first onset of depression in late life *without* comorbidity may have a preferentially good outcome, but more commonly, a first onset of depression in late life is associated with a higher rate of medical comorbidity than in early-onset patients. Hence, a first episode in late life (with comorbidity) most commonly has a worse prognosis. Therefore, the influence of chronological age and age at onset on prognosis is closely linked with past psychiatric history, as well as current and future comorbidity. Comorbid medical illness (and dementia) is an important reason why patients do worse with increasing age (38). It is already known that age is a risk factor for

dementia, but it is intriguing that an early age at onset (and, hence, a long illness duration) of depression might confer additional risk (43). Additionally, there are hints that patients who go on to develop dementia may respond worse to treatment at baseline (28, 68). It is of interest to note that both late age at onset and older chronological age appear to greatly increase the likelihood of medical comorbidity (25, 37). The clinical implication is that older patients with comorbidity are likely to require more prolonged treatment with antidepressants. Given that older patients may experience a different side effect profile than younger patients (69), antidepressant choice must also reflect agents that are well tolerated in the medically ill older population (70, 71).

In summary, the balance of evidence appears to support the notion that depression in the elderly is equally responsive to initial treatment but has a more adverse longitudinal trajectory than depression in middle age. However, this effect is probably accounted for by factors such as previous episodes and medical comorbidity. If future studies recruit subjects from across the life span rather than concentrating on a narrow age range, our understanding of the complex course of depression will improve. In addition, more attention should be given to the influence of duration of untreated depression on later prognosis. It is already clear that the link between outcome of depression and age is more complex than it first appears, which serves to remind clinicians of the importance of assessing all factors associated with aging and not just age itself.

Received Aug. 1, 2004; revision received Sept. 10, 2004; accepted Sept. 20, 2004. From the Department of Liaison Psychiatry and the Specialist Registrar in Psychiatry for the Elderly, Leicester General Hospital. Address correspondence and reprint requests to Dr. Mitchell, Department of Liaison Psychiatry, Brandon Unit, Leicester General Hospital, Leicester, U.K. LE5 4PW; alex.mitchell@leicspart.nhs.uk (e-mail).

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