

GUEST EDITORIAL

The prognosis of depression in late life versus mid-life: implications for the treatment of older adults

Depression in late life is extremely common. Of those aged 65 years or older, 2–5% have syndromal depression, but up to 20% of elderly people have depressive symptoms (Horwath *et al.*, 2002). Both syndromal and subsyndromal depression carry a high risk of long-term complications and both are associated with elevated risks of morbidity and mortality (Penninx *et al.*, 1999). Despite repeated alerts, depression is consistently under-recognized in acute medical settings, in nursing homes and in primary care (Volkers *et al.*, 2004). For reasons that are inadequately understood, late-life depression seems to be under-treated to an even greater extent than depression in mid-life (Mackenzie *et al.*, 1999). This issue is particularly important, given that effective and safe treatments for depression are available (Bartels *et al.*, 2003), even though the evidence regarding maintenance therapies in older people is inconsistent (Geddes *et al.*, 2003; Wilson *et al.*, 2003). Recent evidence suggests that a package of care can improve the care of older depressed patients in primary care settings (Bruce *et al.*, 2004) and in nursing homes (Ciechanowski *et al.*, 2004). This has led to the development of several clinical guidelines specifically for late-life depression (Baldwin *et al.*, 2003; Charney *et al.*, 2003; Lebowitz *et al.*, 1997). Yet, in the recent National Institute of Clinical Excellence (NICE) guidelines for the management of depression in primary and secondary care, no distinction was made between early, middle and late-life depression (Malone and Mitchell, 2005).¹

What remains unclear is whether the treatment of late-life depression should be any different from the treatment of depression earlier in life. Over several years, careful observers have noted that only a minority of patients presenting in late life remain well subsequently (Murphy, 1983; Post, 1972). A high proportion undergo future relapses, cognitive decline, disability, and even early death (Jorm, 2001; Lenze *et al.*, 2001; Schulz *et al.*, 2002). Yet, even with this observation, an astute reader will ask whether the rate of these complications is higher in those with a first onset of depression in late life compared to those with a first onset in mid-life? To answer this, we must look carefully for differences in prognosis for cohorts stratified by age and matched for other factors.

¹Unfortunately, a number of studies in those aged over 65 years old were excluded from this document and therefore not reviewed.

Such studies are indeed rare and there are major methodological difficulties underlying such comparisons. First, age at commencement of treatment or recruitment into studies is typically different from the true age of first onset (that is, the first symptom of depression). This is important because a patient with depression in old age may have an early first onset and long illness duration, or a late age of onset and short illness duration. Illness duration and number of past episodes are among the most important predictors of prognosis. Second, most of the studies in this area have relied on naturalistic methodology in which patients receive treatment as usual. This means that it cannot be assumed that cohorts were given comparable interventions, particularly when the cohorts have been assessed in different arms of a service, at different times. Ideally, what is needed are studies of inception cohorts, where patients who are recruited differ only by the factor of interest (such as age of onset) at the same time into a standardized treatment protocol. Third, most studies are relatively small, raising the possibility of type II errors when assessing differences in outcome. With these caveats in mind, it is logical to examine inception cohort studies of comparative samples, ideally divided by age of first episode onset.

At this stage the results of these studies are intriguing but should not yet be viewed as conclusive. Evidence seems to suggest that response (and remission) rates to pharmacotherapy and electro-convulsive therapy (ECT) are not sufficiently different in well-matched, late-onset depressions and mid-life-onset depressions to be clinically significant (unless rates of medical comorbidity differ) (Musetti *et al.*, 1989; Philibert *et al.*, 1997; Reynolds *et al.*, 1998). Regarding relapse, older patients at study entry (that is, those with unselected past histories) seem to be at higher risk of having further episodes (Reynolds *et al.*, 1999). Age of onset plays a surprisingly complex role. Elderly patients with an *early* age of first episode onset are more likely to accrue a higher number of lifetime episodes by the time of recruitment, and this adversely influences prognosis (especially chance of future relapse) when compared to elderly depressed patients with late onset of illness. Thus early first-onset and older current age are linked with relapse. Yet elderly patients with a late age of first episode onset (late-onset depressions) are at increased risk of medical comorbidity (Lavretsky *et al.*, 1998; Tupler *et al.*, 2002). When present, medical comorbidity (including clinical or subclinical vascular brain disease) is often a risk factor for either inferior treatment response, chronicity (Heiden *et al.*, 2005) or poor antidepressant tolerability (Iosifescu *et al.*, 2003; 2004; Yamashita *et al.*, 2001). It is not clear how age of onset influences the likelihood of cognitive decline following depression and whether illness duration is an independent risk factor, but a late first-onset is a risk factor for mortality in depressed patients,

presumably due to an interaction with physical comorbidity (Philibert *et al.*, 1997; Taylor *et al.*, 2004). For example, both vascular brain disease and vascular risk factors are more common in those whose first episode of depression begins in late life (Camus *et al.*, 2004).

If there is some convergence of evidence showing that depression with a late-life first onset or with an early-life onset and recurrence after the age of 65 years has a poorer prognosis than other subtypes of depression, what are the implications for treatment? First, patients who experience their first episode in late life should be examined closely for physical health problems, particularly for conditions where treatment is available, such as vascular disease. Treatment of both physical and psychiatric components together will probably be more successful than treatment of either alone (Taragano *et al.*, 2001). Second, when medical comorbidity (including subclinical brain disease) is present, antidepressant treatment should be chosen carefully given a higher rate of adverse effects, a higher rate of discontinuation and the recognized dangers of unmonitored polypharmacy (Enns *et al.*, 2001). However, several large trials in those over 60 years of age show that antidepressants are effective even in those with medical comorbidity (Sheikh *et al.*, 2004). Appropriate treatment of depression in the context of physical disease may improve not only mood and quality of life, but also the course of underlying physical disease (Glassman *et al.*, 2002; Hitchcock *et al.*, 2004; Jorge *et al.*, 2003). Third, when medical comorbidity is absent, individuals with late-life depression who experienced a first onset in early life and recurrence in late life may require a longer period of maintenance treatment than working-age adults (Hitchcock *et al.*, 2004). Fourth, no health professional should assume that the depression in late life is likely to be refractory to treatment based on age alone. This could be a hidden explanation underlying why a higher proportion of elderly patients are under-treated. Indeed, some work has shown that those with a first episode of depression in late life without comorbidity have a preferentially good outcome (Brodsky *et al.*, 1993).

In summary, the balance of evidence to date seems 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, although such differences are more modest than many suppose. Accumulating evidence suggests that several measurable factors, including a large number of previous episodes (in early onset depressions) and increased neurobiological factors/medical comorbidity (in late-onset depressions), as well as disproportionate attrition from dementia and mortality, account for differences in prognosis. Treatment decisions that are based on these factors are those most likely to have long-term benefit.

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