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CURRENT OPINION

Major Depressive Disorder in Older Adults: Benefits and Hazards of Prolonged Treatment

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Abstract Antidepressants have been shown to reduce the risk of depression recurrence in adults, justifying prolonged antidepressant maintenance therapy for most if not all patients. However, older depressed adults may be at increased risk for antidepressant adverse effects. This article discusses the benefits and hazards of continued treatment in elderly depressed patients, and indicates which patients should and should not receive maintenance phase antidepressants. Most clinical trials conducted so far suggest that prolonged antidepressant use in older adults is efficacious to reduce recurrence rates. The benefits of prolonged antidepressant use may not be restricted to preventing recurrence but also include preservation of overall well-being, social functioning, reduced mortality risk from medical disorders, and reduced risk of dementia. Although generally safe, the prolonged use of antidepressants has been associated with higher risk of osteopenia/osteoporosis (in particular the selective serotonin reuptake inhibitors) and cardiovascular toxicity (tricyclic antidepressants). Fewer data are available for special populations, like those with multiple medical comorbidities or those with dementia; thus, the benefits of prolonged antidepressant use are not clear in these individuals.

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1 Introduction

Depressive disorders are common and disabling in the elderly. In a recent work, Byers and colleagues [1] found that the prevalence of major depression and dysthymia in older adults was 4 % and 0.9 %, respectively. However, the prevalence of subsyndromal depression is higher and may reach up to 40 % of community-dwelling elderly subjects [2, 3]. Late-life depression (LLD), referring both to depression that recurs in old age (having begun earlier in life) and that which appears de novo in the elderly, is linked to several negative health outcomes, including a higher risk of cognitive impairment [4], functional impairment [5], and development of Alzheimer's disease and vascular dementia [6]. LLD is also associated with a higher burden of medical illnesses (especially cardiovascular and cerebrovascular) and risk of death, independent of lifestyle factors or socioeconomic status [7, 8]. All of these negative, downstream consequences of LLD impose added caregiver burden upon the family members of those affected.

The identification and treatment of LLD is very important in clinical practice, especially in general medical or primary care practice (because it is here, and not in specialty mental health practice, that common mental disorders in the elderly are treated) and may delay or prevent at least in part, some of the negative health outcomes related to this disorder. In this article, we provide a narrative review of the current state of the art of the treatment of late-life depressive disorders, focusing on the benefits and hazards of prolonged, or maintenance, treatment to prevent relapse and recurrence of major depressive episodes. Our fundamental clinical perspective is that getting well is not enough; rather, it is staying well that counts. Depression in old age is most often a relapsing, chronic

condition, necessitating a long-term perspective on its management to ensure the well-being of both patient and family caregivers. We begin first with a brief review of short-term antidepressant pharmacotherapy in LLD and then focus on the benefits and risks of long-term treatment.

2 Short-Term Antidepressant Treatment on LLD

The main goals of antidepressant treatment are to achieve remission of depressive symptoms, to prevent relapse and recurrence of a depressive episode, and to yield functional recovery. Treatment outcomes rely on several factors including an appropriate diagnostic assessment that includes the identification and management of comorbidities and underlying psychosocial factors, which affect the correct choice of available treatment options and resources [9]. Many short-term, randomized, placebo-controlled clinical trials, as well as systematic reviews and meta-analyses, have addressed the efficacy of antidepressant treatment in major depression in older adults.

Nortriptyline is a tricyclic antidepressant commonly used in older adults. In an early placebo-controlled randomized clinical trial, nortriptyline was significantly superior to placebo or moclobemide in reducing depressive symptoms, and a greater proportion of subjects in the nortriptyline arm achieved remission compared to moclobemide or placebo [10]. Several clinical trials have evaluated the efficacy of selective serotonin reuptake inhibitors (SSRIs; fluoxetine, sertraline, citalopram, escitalopram, paroxetine, fluvoxamine) and serotonin and noradrenaline reuptake inhibitors (SNRIs; venlafaxine, duloxetine, desvenlafaxine) for the acute treatment of LLD. A meta-analysis including 13 randomized placebo-controlled trials of second-generation antidepressants (fluoxetine, escitalopram, sertraline, paroxetine, citalopram, venlafaxine, duloxetine, and bupropion) demonstrated a small advantage of active medication over placebo, with a number needed to treat (NNT) of 13 [11]. The meta-analysis showed that subjects on active medication had a significantly higher chance of having an antidepressant response [odds ratio (OR) = 1.40, $CI_{95\%}$ (1.24–1.54)] or to achieve remission [OR = 1.27, $CI_{95\%}$ (1.12–1.44)] compared to placebo. Finally, a more recent meta-analysis confirmed that antidepressants (tricyclics, SSRIs, and SNRIs) are more effective than placebo for treatment of major depressive episodes in older adults and that no drugs evaluated in this meta-analysis showed superiority to any other [12]. In addition, the use of antidepressants was not significantly associated with severe adverse effects. Therefore, the evidence to date supports the use of antidepressants for the acute treatment of older adults with major depression.

The hazards of acute antidepressant pharmacotherapy are relatively few with the use of SSRIs and SNRIs. These are limited primarily to the occurrence of SIADH (syndrome of inappropriate antidiuretic hormone secretion) in those over the age of 75 years (especially in those with baseline serum sodium levels of 135 mEq/l or lower) [13]; and to supervening sinus bradycardia, especially in those with pretreatment heart rates of less than 60 bpm and in the presence of beta blockers. It is also noteworthy that the US Food and Drug Administration published a "Medwatch" in August of 2011, warning about increased incidence of torsade de pointes in older adults administered citalopram in doses above 20 mg/day [14].

Another important concern is drug interaction at the CYP450 level. SSRIs and SNRIs are metabolized by the CYP450 enzymatic complex in the liver (in particular CYP2D6, CYP2C19, and CYP2C9). The subject's metabolizer status (e.g., poor or ultrarapid metabolizer) and the coadministration of other drugs that are also metabolized by this enzymatic complex may significantly influence antidepressant response or the emergence of adverse side effects in a given patient [15]. This is of particular importance in older adults under a polypharmacy regimen. CYP polymorphism testing may be necessary for some patients; in particular, those who do not show antidepressant response with usual drug doses (e.g., CYP450 ultrafast metabolizers), those with severe side effects at low antidepressant doses, or those under a polypharmacy regimen [16]. The emergence of suicidal thoughts and attempted suicide after SSRI treatment (usually in the first 2 months of treatment) is a major concern in clinical practice, in particular with adolescents and younger adults [17, 18]. However, a recent meta-analysis does not suggest that SSRI treatment increases the risk of suicide in older adults [19].

3 Benefits and Hazards of Long-Term Antidepressant Treatment

Relapse and recurrence of a depressive episode is common after acute antidepressant treatment [20]. In the majority of older adults, long-term antidepressant treatment may be necessary to maintain the antidepressant response, and prevent some of these negative outcomes. Several studies have evaluated the benefit of maintenance antidepressant treatment for LLD. A clinical study evaluated maintenance antidepressant treatment in 84 older adults whose major depression remitted after nortriptyline or nortriptyline plus lithium [21]. All subjects maintained the same drugs and doses that were necessary to achieve remission in the acute treatment phase. The authors showed that the cumulative

probability of remaining free of depressive episodes was 74 % after 2 years of follow-up. In an open-label clinical trial including 27 older adults with severe depression, Reynolds and colleagues [22] observed that 85 % of the subjects who were maintained on nortriptyline pharmacotherapy did not present recurrence of a depressive episode after 13 months. Similarly, a small open-label study showed that most subjects, who were on paroxetine or nortriptyline treatment, were euthymic for up to 18 months after the remission of the index episode (90 and 80 %, respectively) [23]. Bump and colleagues [24] found similar results in an open continuation trial of paroxetine versus nortriptyline with 18 months of follow-up. In this study, recurrence of a depressive episode was 16 % for paroxetine and 10 % for nortriptyline; this difference was not statistically significant.

The results from open-label continuation trials encouraged the execution of randomized placebo-controlled clinical trials to evaluate the benefits of long-term maintenance treatment in LLD.

In a randomized placebo-controlled clinical trial, 121 older adults in remission after acute and continuation (8 and 16 weeks, respectively) antidepressant treatment with citalopram were randomized to continue on citalopram treatment (dose regimen from 20 to 60 mg daily, $n = 60$) or to receive placebo ($n = 61$) for an additional 48 weeks [25]. Participants on the citalopram arm had a lower risk of recurrence of a depressive episode than those on placebo [hazard ratio of 0.32, $CI_{95\%}$ (0.19–0.56)]. Long-term citalopram treatment was safe and participants experienced mild adverse events (tremor, sweating, and fatigue were the most common).

A randomized, double-blind, placebo-controlled clinical trial (the "MTLD-1" trial), using a 2 × 2 factorial design comparing four maintenance options [nortriptyline with supportive care, interpersonal psychotherapy (IPT) with pill placebo, nortriptyline + IPT, and placebo with pill placebo] with 3 years of follow-up included 107 older adults with remission of a depressive episode after acute antidepressant treatment with nortriptyline [26]. All of the participants in this clinical trial had had recurrent episodes of major depression and were thus at high risk for further recurrences. The mean age of the participants was about 68 years. The authors reported that all study arms were significantly superior to placebo in preventing the recurrence of depressive episodes over the 3 years of follow-up. However, the recurrence rate in the nortriptyline + IPT arm was significantly lower (20 %) than the nortriptyline with supportive care (43 %) and the IPT with pill placebo arms (64 %). The recurrence of a depressive episode in the placebo arm was 90 % (Fig. 1).

The results were similar after stratifying the sample according to age (≤69 years old or >70 years old). It is worth noting that half of the recurrences in the nortriptyline arms were associated with low pharmacotherapy adherence, thus highlighting the importance of adherence to achieve the potential benefits of treatment. In another study from the same group, older adults using higher doses of nortriptyline (plasma levels of 80–120 ng/ml) experienced fewer residual depressive symptoms but did not differ in rates of recurrence compared to those at lower doses of nortriptyline (plasma levels between 40–60 ng/ml) [27]. These results highlight the importance of combined pharmacotherapy and psychotherapy, as well as the use of adequate antidepressant drugs and adherence to treatment to prevent the recurrence of depressive episodes. However, another long-term randomized placebo-controlled clinical trial did not find any significant benefit of sertraline treatment compared to placebo over 2 years in reducing the recurrence of depressive episodes in older adults [28].

The "MTLD-2" trial at Pittsburgh evaluated whether long-term maintenance treatment with paroxetine, interpersonal psychotherapy, or its combination, were associated with lower recurrence rates over 2 years of follow-up [29]. About half of the participants in this trial were in their first lifetime episodes of major depression, and many were recruited from primary care settings; the mean age was about 77 years. The authors found that the relative risk of recurrence of a depressive episode in the placebo group was 2.4 times higher than in the paroxetine group (NNT ∼4.0) after adjusting for the effect of psychotherapy. In this study, monthly sessions of interpersonal psychotherapy did not prevent the recurrence of depressive episodes compared to placebo. Remarkably, even participants in their first lifetime episodes demonstrated the benefit of maintenance paroxetine on recurrence prevention, relative to placebo, over a 2-year period (Fig. 2).

In this study, long-term recurrence prevention was moderated by medical comorbidity, with more brittle long-term responses among those with greater medical burden (Fig. 3).

Two recent meta-analyses addressed the potential of continuing antidepressant treatment for preventing relapse or recurrence of a depressive episode. Kok and colleagues [30] included eight double-blinded randomized controlled trials (RCTs) of continuation and maintenance treatment with a total of 925 elderly participants. They showed that antidepressant treatment was efficacious to reduce relapse or recurrence of a depressive episode compared to placebo with an NNT of 3.6 ($CI_{95\%}$ of 2.8–4.8). The NNT for tricyclic antidepressants was 2.9 ($CI_{95\%}$ of 2.2–4.6) and 4.2 ($CI_{95\%}$ of 3.2–5.9) for SSRIs. Both tricyclic antidepressants and SSRIs were well tolerated. On the other hand, Wilkinson and Izmeth [31] included seven clinical trials with a

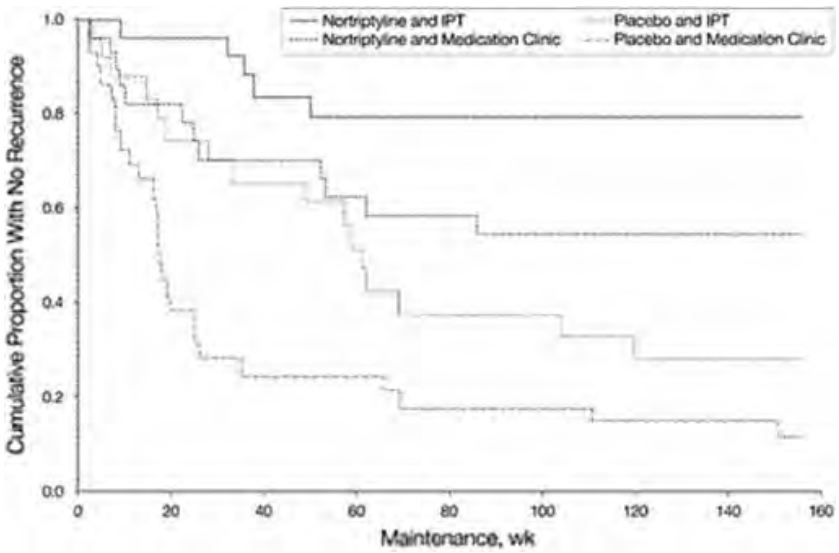

Fig. 1 Recurrence rates of major depressive episodes [27]. Survival function of four treatment groups (log-rank statistic = 34.31; df = 3; $P = 0.001$). On pairwise analysis, each of the three active treatment groups was significantly better than placebo. IPT indicates interpersonal psychotherapy (reprinted with permission from American Medical Association)

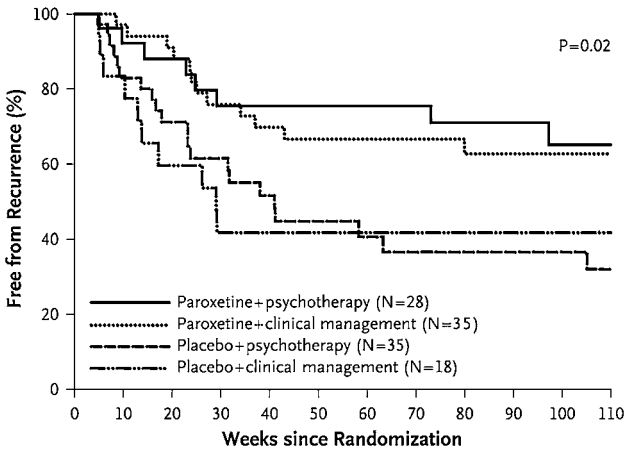

Fig. 2 Time from randomization to recurrence [29]. The relative risk of recurrence among patients receiving placebo was 2.4 times that among patients receiving paroxetine ($P = 0.02$; chi-square statistic = 9.77; df = 2). No effect of maintenance psychotherapy on recurrence was detected. Kaplan–Meier survival analysis with log-rank chi-square statistics was used to test for overall differences in recurrence rates among the groups. *P* values were based on the log-rank chi-square test (reprinted with permission of the Massachusetts Medical Society)

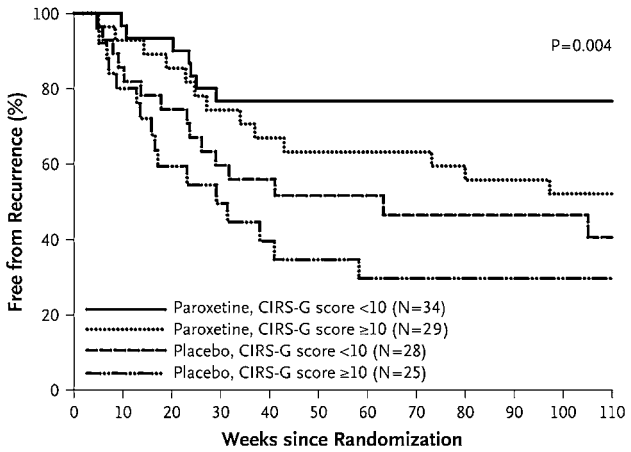

Fig. 3 Effect of the number and severity of concomitant medical illnesses on the efficacy of maintenance therapy with paroxetine [29]. Patients with a greater number and more severe concomitant medical illnesses, as indicated by scores of 10 or more on the Cumulative Illness Rating Scale for Geriatrics (CIRS-G), had higher rates of recurrent depression and did not fare as well during treatment with paroxetine as those with fewer and less severe concomitant medical illnesses. Although both paroxetine use and the score on the CIRS-G affected risk (main or direct effect, $P = 0.004$), paroxetine was more effective in preventing recurrence in patients with fewer and less severe concomitant medical illnesses (interaction effect, $P = 0.03$). Kaplan–Meier survival analysis with log-rank chi-square statistics was used to test for overall differences in recurrence rates among the groups. *P* values were based on the log-rank chi-square test (reprinted with permission of the Massachusetts Medical Society)

total of 803 participants. The meta-analysis results revealed that the benefit of maintenance antidepressant treatment to prevent relapse or recurrence of a depressive episode was more evident in the first 12 months of treatment, although this result was based on only three studies. After 24 months, the benefit was restricted to participants on tricyclic antidepressants; there was no significant benefit of antidepressant treatment after 36 months of continued treatment. The authors concluded that the long-term benefits of maintenance antidepressant treatment in the prevention of relapse or recurrence of depression in older people are not clear and may be restricted to the first year of treatment.

In a pragmatic randomized clinical trial ("PROSPECT": Prevention of Suicide in Primary Care Elderly: A Collaborative Trial) that included 598 older adults from 20 primary care practices in New York, Philadelphia, and Pittsburgh, those in the active intervention group (active practice-based, depression care management) showed a significant reduction in depressive symptoms over 1 year

of follow-up compared to those in the usual care group [32]. In addition, the older adults with major depression in the active intervention group showed a significant reduction in suicidal ideation compared to the usual care group, in particular at 4 and 8 months of active intervention. These results highlight the importance of active depression care management in reducing not only depressive symptoms, but also in reducing the risk of suicidality in older adults with major depression. Follow-up of participants in this trial after a median interval of approximately 8 years showed a reduction in mortality rate of 24 % among participants who had received evidence-based depression care management, as compared with usual care [33]. Mortality reduction reflected reduced deaths due to cancers.

Persistent cognitive impairment is common after successful antidepressant treatment and is associated with worse functional performance, higher risk of recurrence of depressive episodes, as well as cognitive decline and dementia [9]. Acetylcholinesterase inhibitors (i.e., donepezil, rivastigmine, and galantamine) are the main drugs for the treatment of cognitive impairment in Alzheimer's disease and may have a marginal benefit in reducing progression to dementia in older adults with mild cognitive impairment [34, 35]. A recent randomized, double-blind, placebo-controlled clinical trial conducted at Pittsburgh (the "MTLD-3" trial), including 130 older adults with remitted major depression, evaluated whether long-term donepezil (total of 2 years of follow-up) treatment would improve cognitive performance and reduce the recurrence of depressive episodes [36]. Subjects on maintenance antidepressant pharmacotherapy with donepezil augmentation showed a small improvement in episodic memory and executive function performance over 2 years of treatment. In addition, subjects on long-term donepezil treatment showed lower rates of progression to dementia than those on placebo. On the other hand, subjects with mild cognitive impairment on donepezil experienced more recurrent episodes of major depression and adverse events than those on placebo. Thus, the addition of the cholinesterase inhibitor to maintenance antidepressant pharmacotherapy posed both benefits and risks to older depressed patients.

The benefits of long-term antidepressant pharmacotherapy are not limited to reducing the rates of recurrence of depressive episodes. Long-term antidepressant treatment is associated with preserving overall well-being, social functioning, as well as dealing with emotional problems [37]. In a recent post-hoc analysis of the PROSPECT trial [32], long-term management of depression in older adults significantly reduced the risk of dying due to cancer [33], but not of other major medical disorders. (Figs. 4, 5). Finally, case-registry studies showed that long-term

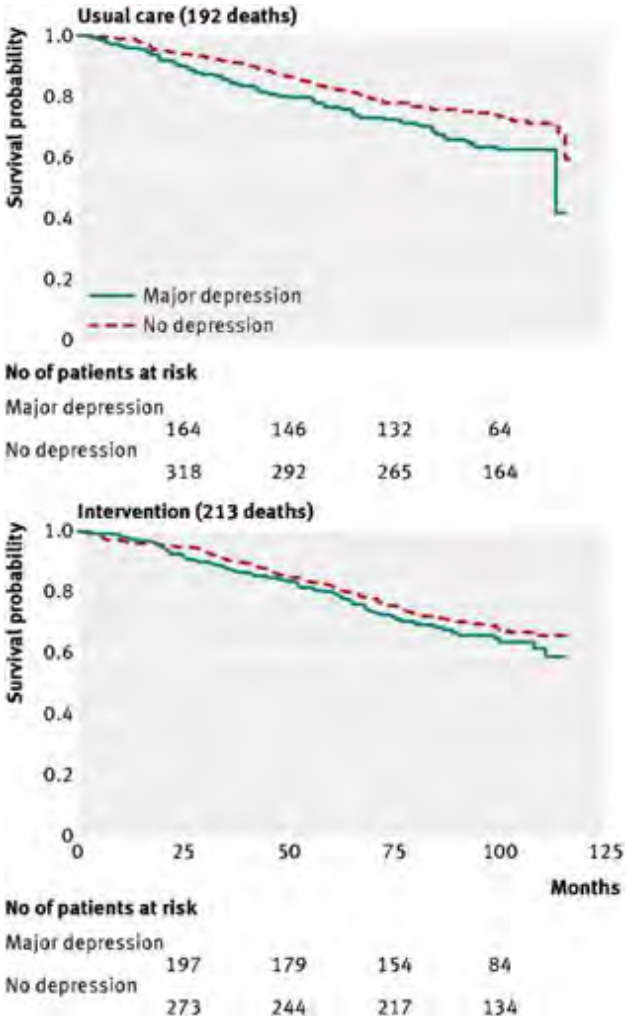

Fig. 4 Survival probability among people with no depression or major depression in practices randomized to usual care (*top panel*) or to intervention (*bottom panel*). Data from PROSPECT (1999–2008) [33]. Reprinted with permission from the *British Medical Journal*

antidepressant treatment may have a protective effect against the development of dementia and Alzheimer's disease [38].

4 Possible Adverse Effects of Long-Term Antidepressant Treatment in Older Adults

Despite the considerable benefits, long-term maintenance antidepressant treatment may also bear some important risk to older adults. Population-based cohort studies have suggested, but not proven, that long-term antidepressant use may be associated with higher risk of osteoporosis, particularly in women [39]. This association seems to be particularly important to the SSRIs [40]. A meta-analysis of cohort and case controls addressing the relationship between SSRIs and the risk of fractures in older adults

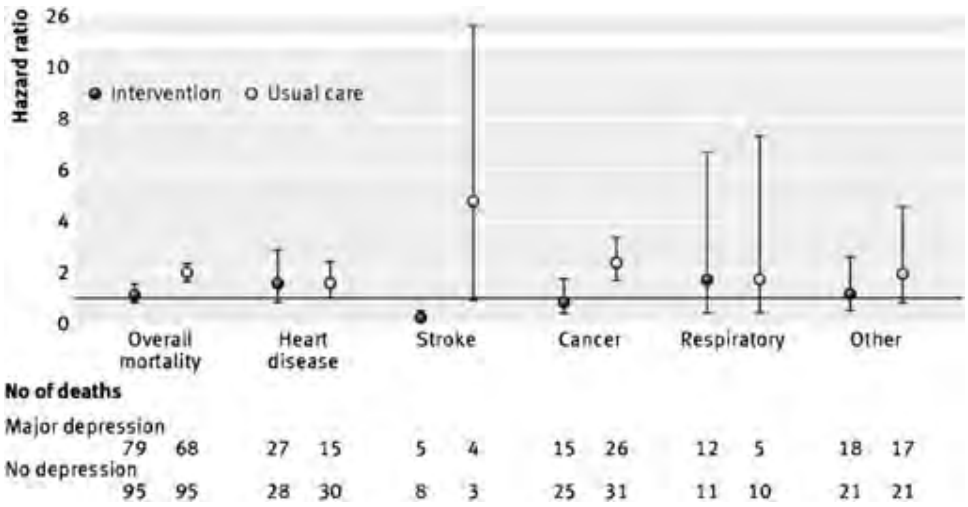

Fig. 5 Adjusted hazard ratios (95 % CI) for specific causes of death comparing major depression with no depression within intervention or usual care practices. Data from PROSPECT (1999–2008). Hazard ratios are from Cox proportional hazards models. Adjusted models included terms for baseline age, sex, education, marital status, smoking, cardiovascular disease, stroke, diabetes, cancer, cognition, and suicidal ideation [33]. Reprinted with permission from the *British Medical Journal*

Table 1 Potential hazards of antidepressant treatment in the elderly

Hazard	Drug class
Osteoporosis and osteopenia	SSRIs
Drug interaction	All antidepressants
CYP450 metabolism induction	SSRIs (more significant with fluoxetine, paroxetine, fluvoxamine)
Bleeding	SSRIs
Hypertension	SNRIs (more significant with venlafaxine)
Orthostatic hypotension	Tricyclic antidepressants
Arrhythmia	Tricyclic antidepressants
Cognitive impairment	Tricyclic antidepressants
Other anticholinergic side effects[a]	Tricyclic antidepressants
Risk of falls	Tricyclic antidepressants

SSRIs selective serotonin reuptake inhibitors, *SNRIs* serotonin and noradrenaline reuptake inhibitors

[a] Dry mouth, excessive sedation, blurred vision, constipation, urinary retention

showed that the use of antidepressants was associated with a significant increase in the risk of fractures [relative risk, 1.72; $CI_{95\%}$ (1.51, 1.95)] [41, 42]. This effect was independent of history of depression and bone mineral density. Despite the evidence of negative interaction between antidepressants and osteoporosis and risk of fractures, there are few analyses of controlled trials in this respect. In a recent analysis of a short-term open-label clinical trial, Shea and colleagues [43] reported that the use of venlafaxine over 12 weeks was associated with increased markers of bone resorption and reduced bone formation in older adults. This effect seems to be particularly prominent in subjects with high-expressing 5HTTLPR genotype and those with the low-expressing HTR1B genotype [44]. As of 2014, it is not possible to infer a causal effect of antidepressant pharmacotherapy on the development of osteoporosis, because of possible confounding by indication, in the absence of data from RCTs specifically investigating this issue.

Many long-term maintenance trials included nortriptyline as one of the study drugs. Although these trials did not show a largely significant increase in major adverse effects, it is worth noting that tricyclic drugs may have serious anticholinergic and cardiovascular-related adverse effects, such as risk of arrhythmia, orthostatic hypotension, and worsening of cognitive performance, which can preclude its long-term use in older adults [45]. Tolerability is also an important issue for long-term use of nortriptyline, because it can be associated with excessive somnolence, dry mouth, constipation, urinary retention, nausea, and vomiting, mostly as results of its anticholinergic effects.

As stated above, drug interaction is also a major concern and may hinder the long-term use of antidepressants in older adults. Most of the antidepressants have hepatic metabolism, in particular by the CYP450 enzymatic complex. This enzymatic complex is also responsible for the metabolism of other drugs commonly used in older adults. Therefore, the benefits and risks of continued antidepressant treatment must be carefully weighted in those subjects with multiple medical comorbidities and using several medications. Table 1 summarizes some of the hazards related to long-term antidepressant treatment in the elderly.

5 Current Limitations of the Literature

The current literature on maintenance treatment for LLD has several important limitations that need to be addressed in future studies. Most of the current evidence relies on a few long-term double-blind RCTs that included a relatively small number of patients. For example, the largest meta-

analysis on this topic included only 8 RCTs with a total of 925 participants [30]. The ideal length of antidepressant maintenance treatment has not been established. The studies with longer follow-up time (e.g., 3 years) have not shown a consistent benefit of antidepressant treatment in reducing relapse and recurrence of depressive episodes [31]. The optimal antidepressant dose regimen for maintenance treatment is also not well defined in the literature, but the majority of the studies maintained the same dose regimen of the acute treatment phase. Thus, we recommend that the same antidepressant regimen that was needed to achieve remission in the acute treatment phase be continued for maintenance treatment.

In addition, most studies have not systematically included the oldest subjects (older adults aged over 85 years). This is the population stratum with the fastest growing rate and there is no evidence-based information for the maintenance of antidepressant treatment in this population. Similarly, other subgroups have not been systematically included in most clinical trials, such as those with multiple medical comorbidities and cognitive impairment. Comorbid depression and anxiety is common in the elderly and anxiety is an independent risk factor for depressive episode recurrence in this population [46, 47]. Therefore, it is important to investigate the role of comorbid anxiety disorders as a potential moderator of the long-term benefits of antidepressants in preventing depression recurrence. At this point, we have no information on how the systematic measurement of biomarkers or pharmacogenetic information can help to define the best drug, dose regimen, or treatment length for antidepressant treatment in individual subjects.

6 Concluding Remarks

Long-term maintenance antidepressant treatment is necessary for the majority of older adults after response and remission of the depressive episode, even in those who report only one lifetime episode of major depression [27]. Data from randomized placebo-controlled clinical trials and meta-analyses showed that long-term maintenance of antidepressants significantly reduces the risk of relapse and recurrence of depressive episodes, with more strong evidence for the first year of treatment. The use of antidepressants is in general safe, with the emergence of few severe adverse effects. The benefits of long-term antidepressant maintenance treatment seem to extend beyond prevention of depression recurrence throughout life. They also encompass better health-related quality of life, improved social adjustment, and better capacity to deal with emotional problems, all of which are major risk factors for major depression in the elderly [48]. Long-term satisfactory depression management in primary care may be associated with reduced mortality risk due to cancer [33]. Prolonged antidepressant treatment and the combination of donepezil with antidepressants may improve cognitive performance and reduce the risk of progression to dementia in older adults [36].

Despite the evidence suggesting the benefits of antidepressant maintenance treatment for older adults, there are still several open questions that have not been addressed. The optimal dose regimen is not well established, but most clinical trials maintained the same antidepressant regimen of the acute treatment phase. Therefore, we recommend the maintenance of the same antidepressant regimen of the acute treatment phase. The length of maintenance treatment is also controversial, but antidepressant should be maintained ideally for at least 1 year after the remission of the depressive episode. The risk for drug interaction should be monitored in all phases of treatment, and in special cases, CYP450 polymorphism analysis may be necessary to help in choosing or adjusting the antidepressant or other drugs.

The actual benefits of long-term antidepressant treatment should be weighed against potential harmful effects. Particular attention should be paid to the risk of osteoporosis and fractures in subjects on long-term SSRI treatment. This is important because falls and fractures are major sources of disability and frailty in the elderly [49]. Future randomized double-blind clinical trials should include bone mineral density measures to control for the potential negative effect of antidepressants on bone metabolism. The negative cardiovascular and anticholinergic side effects of tricyclic drugs, as well as tolerability, may preclude their long-term use. Because long-term maintenance trials followed up the subjects for 2–3 years, the efficacy and safety of antidepressants for longer periods of time need to be determined. Finally, the benefits and risks of long-term antidepressant treatment need to be evaluated in special populations, such as older adults with multiple medical comorbidities, those with persistent cognitive impairment after successful antidepressant treatment, those at more advanced age (e.g., those older than 85 years), and in institutionalized older adults.

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