

How long should older people take antidepressants to prevent relapse? Por quanto tempo os idosos devem tomar antidepressivos para evitar recaídas?

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Abstract Patients with depressive disorder have a high risk of relapse after recovery from a depressive episode. Can the relapse of depressive disorder be prevented or delayed for older adults? This paper reviews the evidence from randomised clinical trials and open label trials of the effectiveness of maintenance antidepressant therapy for older adults with depressive disorder. It also examines the evidence for the effectiveness of psychosocial and psychotherapeutic interventions. The paper concludes with recommendations for clinical practice and future research.

Keywords Review literature. Depression. Aged. Therapeutics. Primary prevention.

Resumo *Pacientes com transtorno depressivo apresentam alto risco de recorrência e recaída. É possível prevenir a recaída ou a recorrência do episódio depressivo ou retardá-lo em fases tardias da vida? Este artigo revisa ensaios clínicos aleatorizados e não-aleatorizados com o objetivo de estabelecer se o tratamento antidepressivo de manutenção reduz o risco de recaída e recorrência de depressão em idosos. O artigo também examina a evidência atualmente disponível sobre a eficácia das intervenções psicossociais e psicoterapêuticas. O artigo conclui com recomendações para a prática clínica e pesquisas futuras.*

Descritores *Literatura de revisão. Depressão. Idoso. Terapêutica. Prevenção primária.*

Introduction

Depressive disorder is the fourth most important cause of global disability,¹ and a common psychiatric condition in later life.² Depression is associated with considerable adverse consequences with increased mortality and suicide,³ greater disability⁴ and increased health care costs.⁵ Patients with physical illness and nursing home residents have a particularly high prevalence of depressive disorder.⁶ There may be cultural differences in the prevalence of depressive disorder with lower rates of depression reported in Japan than in the United Kingdom or United States.²

It is generally accepted that most patients with an acute depression episode improve with antidepressant treatment.^{7,8} Recent research confirms that acute episodes of depression can be effectively treated for up to twelve months.^{9,10} Even very old patients with major depression have a high response rate, although those with co-existing dementia may be less likely to respond to antidepressants.¹¹

Natural history of depressive disorder in older adults

The prognosis of depression in older people is controversial.^{12,13} Cole¹³ criticised the methodology of studies on the prognosis of depression in older people, which usually have small sample sizes and may not be representative of the range of patients seen in clinical practice, because of stringent exclusion criteria. Additionally, there is a lack of consensus on what constitutes a favourable or unfavourable outcome.¹⁴ Is a good outcome a reduction in the score on a rating scale, no longer meeting the diagnostic criteria for caseness, or should outcome be defined in terms of improved social functioning or quality of life?

The short-term prognosis of depression in older adults seems favourable. Most older people recover from depression, although even after 1 year up to 19% relapse.¹⁵ However, with longer-term follow up for up to five years the outlook is less good¹⁶⁻¹⁹ with only 10-34% of patients remaining well. The

remainder either had persistent or recurrent depression, and about 25% of subjects in each sample died.¹⁶⁻¹⁹ Poor prognostic features include female gender, severe depression, impaired functioning, poor current health, anxiety, deficient social support and high service use.¹⁹ One study found no difference in outcomes between younger and older cohorts with depressive disorder.²⁰ At one year follow-up 25% had recovered and at four years 41% had recovered.²⁰

Antidepressants are an effective acute treatment for depressive disorder in older adults. However, treatment resistance, recurrence and mortality are common, and only a minority of patients remain well. The goal of improving the prognosis of older people with depressive disorder appears both reasonable and feasible. The question addressed in this paper is, 'How can elderly patients with recurrent depression be kept well?'

Search strategy

The author conducted a literature search using the key words 'depression', 'older adults', 'controlled trial' and 'treatment' using Medline and the Cochrane Database. Further references were located using the original search results and from previous reading. This strategy was repeated omitting 'controlled trial', so that open label studies could be located. Studies of less than twelve months follow-up were excluded.

Randomised clinical trials (RCT)

An early placebo-controlled comparison of nortriptyline and phenelzine recruited 51 subjects.²¹ Those taking phenelzine had lower rates of relapse (13.3%), than those receiving nortriptyline (53.8%) or placebo (65.2%).²¹ This study was criticised because of the maintenance of nortriptyline levels, which was below the accepted therapeutic range.²²

More evidence in favour of antidepressant continuation therapy came from a multi-centre randomised placebo controlled study in the UK.¹⁴ The study recruited 69 subjects who met the Research Diagnostic Criteria for Depression. Patients with dementia, cognitive impairment and significant physical illness were excluded. Patients who received Dothiepin 75mg daily had less than half the rate of relapse than controls after two years follow up.¹⁴

A recent 2 x 2 randomised, double-blind placebo controlled study, compared nortriptyline and interpersonal therapy (ITP) in the prevention of recurrence of depression in older adults with recurrent non-psychotic depression.²² Subjects were excluded if there were contraindications to the use of nortriptyline, psychiatric co-morbidity and delusional depression. Patients attended a clinic each month and received either nortriptyline (with nortriptyline levels maintained in the range 80-120 ng/ml), placebo, IPT with placebo or ITP with nortriptyline.²² The recurrence rate at three years was better for nortriptyline and ITP 20% (95% confidence interval [CI], 4%-36%), nortriptyline alone 43% (95% CI, 25%-61%), ITP plus placebo 64% (95% CI, 45-83%) than placebo 90% (95% CI, 79%-100%). Reynolds and colleagues²² concluded that 'maintenance therapy with nortriptyline or ITP is superior to

placebo in preventing or delaying recurrence' of depression in older adults, and recommended that combined nortriptyline and ITP 'appears to be the optimal clinical strategy'.

Other studies

Flint and Rifat^{23,24} maintained 38 patients with recurrent depression on full-dose antidepressant treatment for four years. Patients with schizophrenia, dementia or a neurological disorder were excluded.²³ The acute episode of depression responded to either nortriptyline or phenelzine, and additionally four patients had lithium augmentation and one patient electro-convulsive therapy (ECT). Relapse was defined as meeting the criteria for major depression and having a score of 16 or above on the Hamilton Rating Scale for Depression.²⁵ Ten patients (26.3%) had a recurrence and ten patients (26.3%) withdrew from the study (two died and two developed hypomanic episodes²⁵). Most of the relapses occurred in the first two years of treatment^{24,25}.

Depression in older adults is under-treated.^{26,27} In a follow-up study of community-dwelling older adults with depression only 10.9% took antidepressants, and 59.6% of those who took antidepressants were prescribed sub-therapeutic doses.²⁶ In another study²⁷ only 17% were treated and at three year follow up over half remained depressed. Benzodiazepines are often used to treat depressive symptoms inappropriately.²⁶ Other studies proposed that lithium may reduce the risk of relapse from recurrent depression.²⁸

Non-pharmacological approaches

Domiciliary psychogeriatric services may improve outcomes for older people with depression by providing case-management and monitoring compliance with antidepressant medication.²⁹ Other psychosocial interventions that may prevent recurrence of depression in older adults include patient education,³⁰ psychological adaptation to institutional care³¹ and social support.³² Some psychological approaches, which can contribute to reducing the risk of relapse of depressive disorder in older adults include interpersonal therapy,^{22,33} cognitive therapy³⁴ and life review.³⁵ A combination of psychotherapy and antidepressants may be more effective at preventing relapse of depressive disorder than antidepressants alone.^{22,24}

Discussion

There are three randomised placebo-controlled studies on the effect of treatment on the recurrence of depressive disorder in older adults,^{14,21,22} which included a total of 227 patients. The main methodological issue with these studies is generalisability.²² Exclusion criteria mean that the samples may not be representative of the complexity seen in routine practice. In addition results from specialist services may not be applicable to general practice. The evidence from the studies suggests that antidepressant therapy is effective at preventing and delaying the relapse of depressive disorder in older adults. The combination of antidepressant prophylaxis with psychotherapy²² or domiciliary support by a mental health

team²⁹ may be more effective than pharmacological treatment alone, although data in this area remains sparse.

There is uncertainty about how long to continue antidepressants after recovery from an acute episode.¹⁴ The Old Age Depression Interest Group¹⁴ recommended that after recovery from an acute episode full-doseage antidepressant treatment should be continued for at least two years, if not indefinitely. Depression is associated with significant adverse consequences for patients, their families and their community with increased mortality and suicide rates,³ greater disability⁴ and increased health care costs.⁵ Without treatment only about 10% of patients remain well, while most studies^{14,21-24} found that the majority of patients remain well with longer-term antidepressant treatment.

The randomised trials reviewed in this paper^{14,21,22} used tricyclic antidepressants (nortriptyline or dothiepin) or a mono-amine oxidase inhibitor (MAOI; phenelzine), which may not reflect current clinical practice. The benefits of antidepressants need to be balanced with their risks. Older people are more likely to have side effects from antidepressants,³⁶ which may be compounded by the effects of polypharmacy. Older patients are prone to cardiovascular³⁷ and anticholinergic side effects.³⁸ Therefore, some authors have recommended that serotonin-reuptake inhibitors (SRIs) should be prescribed in preference to tricyclic antidepressants.⁸ However, there is no current evidence available to support the efficacy of SRIs or other newer antidepressants in the prevention of relapse for older adults.

Conclusion

Late life depression is a common disorder with serious consequences for patients, their families and society. Depression in older people typically presents as a complex clinical challenge with medical co-morbidity, adjustment to role changes, multiple losses, social disadvantage and interpersonal stresses. Therefore it is not surprising that older

patients with depressive disorder have high rates of treatment resistance and mortality. There is evidence that treatment and follow up is not always of the highest standard. However, when patients take antidepressant medication for up to three years relapse can be prevented and delayed. Some preliminary evidence suggests that the combination of antidepressant prophylaxis with psychotherapy or domiciliary support may be even more effective.

Guidelines for clinical practice

Older patients with recurrent depression should continue to take full dosage (i.e. the dosage necessary to produce recovery from an acute episode) antidepressants for at least three years, if not indefinitely, after recovery from an acute depressive episode. Where possible patients should receive also receive augmentation with psychotherapy (ITP or cognitive therapy) and domiciliary support by a community mental health team.

Recommendations for future research

This review raises more questions than it answers. How effective are SRIs and other newer antidepressants in the prevention of recurrence of depressive disorder in older adults? What factors influence the efficacy of psychotherapy in the prevention of recurrence of depression in older adults? Which psychotherapies are most suitable for which patients? How effective are other interventions such as community day therapy, group therapy and psycho-education. Are there cultural differences that influence the outcome of depression in older adults? Will the effectiveness of a domiciliary mental health team for older people be replicated in other settings?

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