Older community residents with depression: long-term treatment with sertraline

Randomised, double-blind, placebo-controlled study

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Background Despite a growing use of selective serotonin reuptake inhibitors in older people, only one trial has examined their prophylactic efficacy in people aged 65 years and over.

Aims To examine the efficacy of sertraline in preventing the recurrence of depression in older people living in the community.

Method Participants were openly treated with sertraline and then randomised into a double-blind, placebo-controlled continuation/maintenance study of about 2 years duration. Drug dosage was maintained at levels that achieved remission.

Results No significant difference between the sertraline and placebo groups was found in the proportion of recurrences (−7.9%; 95% CI −28.06 to 12.23). Increased age and minor residual symptoms during the continuation phase were associated with recurrence.

Conclusions Sertraline at therapeutic dosage does not provide significant protection against recurrence.

Declaration of interest The study was sponsored by Pfizer Ltd.

Up to a tenth of people living in the community who are aged 65 years or more suffer from depression severe enough to warrant intervention. Just under 2% suffer from major depression (Beekman *et al*, 1999) likely to be alleviated by antidepressant therapy. Depression is associated with long-term morbidity and increased mortality (Davidson *et al*, 1988). Epidemiological studies indicate that up to 10% of older community residents with depression are treated with antidepressants. There is a growing trend in the use of selective serotonin reuptake inhibitors (Wilson *et al*, 1999), and a recent study has demonstrated efficacy of maintenance with citalopram (Klysner *et al*, 2002) in this age group. This is the first placebo-controlled trial examining the efficacy of sertraline in the prevention of recurrence of depression in older people in the community.

METHOD

Study design

The study consisted of a treatment phase (8 weeks) and a continuation phase (16–20 weeks) during which participants were treated with open-label sertraline prior to randomisation into a double-blind, parallel, placebo-controlled maintenance trial of 100 weeks. During the open phases drug dosage was titrated from 50 mg to 200 mg daily, as clinically indicated. All participants were maintained on their final therapeutic dosage (or placebo equivalent) during the randomised, controlled phase of the study, with the exception of those treated with 200 mg. In the latter cases the maintenance dosage was decreased from 200 mg to 150 mg, and each case was paired (by a third party) with a placebo recipient to maintain double-blind conditions.

Power analyses

The power of the study was initially based on recruiting 300 persons to each group. This was recalculated as the results from a similar study became available (Doogan & Caillard, 1992). This informed a new power calculation, indicating that a group size of 60 would detect a 26% difference between groups with 95% confidence and 80% power, assuming a 50% relapse/recurrence rate in the placebo group. This would also enable detection of relative risk for relapse of 0.5 for sertraline compared with placebo.

Inclusion and exclusion criteria

All participants were aged 65 years or more. Psychiatric diagnoses were established by a trained psychiatrist using criteria including Geriatric Mental State AGECAT depression level 3 or over (Copeland *et al*, 1988), DSM–III–R diagnoses of major depressive disorder (American Psychiatric Association, 1987) and a Hamilton Rating Scale for Depression (HRSD) 17-item score of 18 or over (Bech *et al*, 1981). Exclusion criteria were a Mini-Mental State Examination (MMSE) score (Folstein *et al*, 1975) of 11 or under to exclude people with severe cognitive dysfunction; severe and unstable physical illness; clinically significant alcohol misuse; significant suicidal or delusional experiences; and concomitant drug treatment, including other psychotropic drugs, warfarin and anticonvulsants.

Randomisation, allocation concealment and compliance

A company independent of the sponsor and trialist was responsible for packaging the trial drugs and randomisation. A computer-generated randomisation list was provided by Pfizer Ltd. The list was stratified by dosage and used to produce numbered containers for the identical capsules of either sertraline or placebo. Participants eligible for the maintenance phase were allocated to the next number at their dose level. Codes were maintained in opaque, sealed envelopes. They were broken on trial completion, after locking the study database. External research auditors maintained the security of the codes, and verified data collection and cleaning. Drug compliance was monitored through tablet counting at each assessment and asking the patient if any doses were missed.

Sample recruitment

Participants were recruited from the screening of all patients over 65 years of age at a

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multi-partner general practice, and referrals from: a community survey conducted at the same time as the trial; twenty general practices in Liverpool; and four old age psychiatry teams.

Assessments and interviews

A trained psychiatrist conducted the initial, end-of-phase and final assessments, including DSM–III–R criteria and final HRSD scores. Initial assessment included research diagnostic and entry criteria, a physical examination and laboratory investigations, comprising blood count, vitamin B_{12} and folate measurements, and thyroid and liver function tests. Research staff conducted follow-up assessments. Staff undertook regular training and instrument standardisation throughout the study. Subsidiary instruments included the Montgomery and Åsberg Depression Rating Scale (MADRS; Montgomery & Åsberg, 1979) and the Burvill Physical Health Scale (Burvill *et al*, 1990). Domiciliary interviews were conducted fortnightly during the first two phases of the study, monthly for the first 6 months of the maintenance phase and subsequently every 2 months. All participants entered into the maintenance phase were followed up, including those subsequently withdrawn from the trial.

Outcomes

Entry into the continuation phase required a 50% reduction in baseline HRSD score by 8 weeks. An HRSD score of 10 or less had to be maintained for a period of 4 weeks during the continuation phase prior to randomisation into the double-blind, placebo-controlled maintenance phase of the study. The continuation phase could be extended up to 20 weeks, depending on assessment scores. Recurrence during the maintenance phase was defined as an HRSD score of 13 or over as well as meeting DSM–III–R criteria for major depressive disorder as determined by a trained psychiatrist.

Analysis

Analysis was carried out independently of the funding body. The initial analysis compared clinical and demographic characteristics of the experimental sample with individuals withdrawn or excluded from the study before the maintenance phase. Follow-up data are provided for participants subsequently excluded because of recurrence during the maintenance phase. In the main analysis, primary outcome variables were subjected to survival analyses using Kaplan–Meier and hazard ratio calculations. The distribution of rate of recurrence across the maintenance phase is described. A Cox proportional hazards regression model was used to explore the potential influence of baseline and experimental variables in determining outcome.

Ethical approval

The study was granted ethical approval by the local ethics committee. Each participant was provided with written and verbal information. Informed consent was required prior to trial inclusion. Primary care physicians were informed of the trial and provided with a full psychiatric assessment, care programme and regular updates concerning clinical progress, for each participant.

RESULTS

Study sample

Three hundred and eighteen persons fulfilled the depression entry criteria. They had a mean age of 77.7 years (s.d.=7.1) and a mean HRSD score of 20.4 (s.d.=3.2). Sixty-four persons were subsequently excluded from entry into the treatment phase of the trial: 28 refused consent, 9 were excluded because of severe, unstable physical illness, 7 took contraindicated drugs, 1 had had a previous adverse reaction to sertraline and 6 were excluded because of protocol violations; the reasons for 13 exclusions were unrecorded. The study population (those taking at least one dose of sertraline and receiving at least one follow-up visit) consisted of 254 persons (65 men and 189 women) with a mean age of 77.6 years (s.d.=6.6). Of these, 141 failed to meet the entry criteria for the maintenance phase (Fig. 1). The remaining 113 participants were randomised to

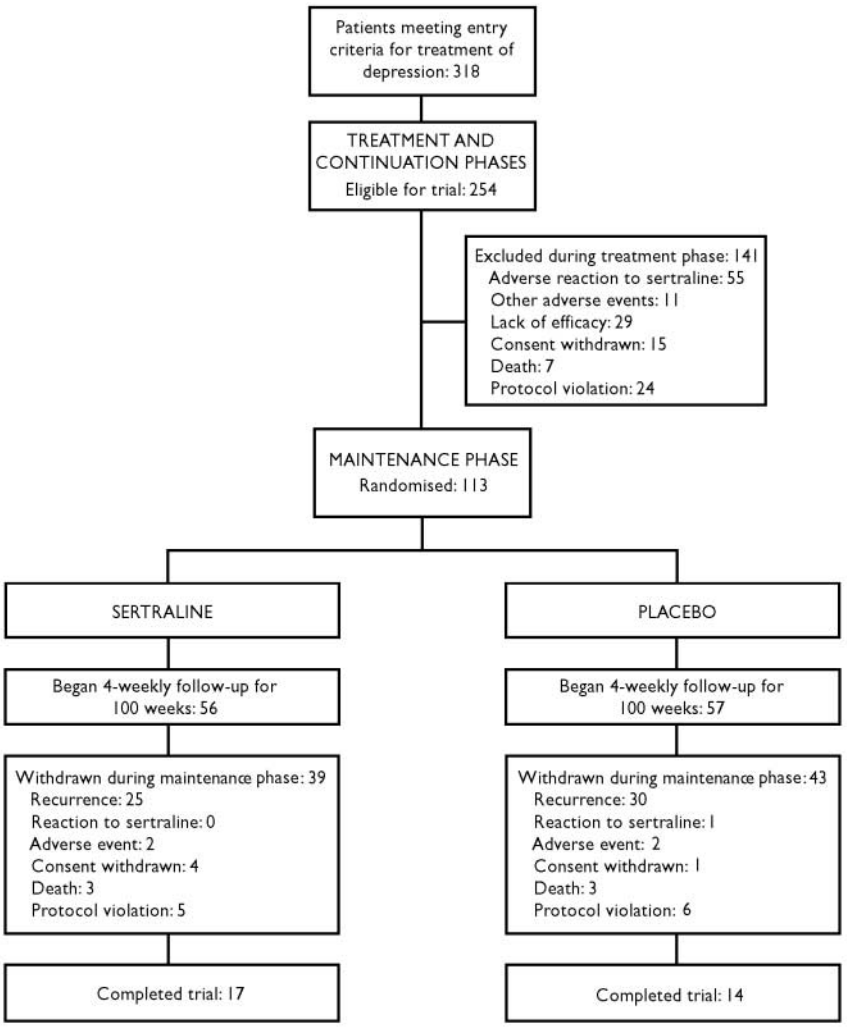

Fig. 1 Study profile.

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Table 1 Demographic and baseline clinical characteristics of study participants entering analyses (double-blind, placebo-controlled maintenance phase); *n*=113

	Treatment group (*n*=56)	Control group (*n*=57)
Age (years)		
Mean (s.d.)	76.6 (6.6)	76.8 (7.0)
25th percentile	71	70.5
Median	76	77
75th percentile	83	82.5
Gender (*n*)		
Male	19	14
Female	37	43
HRSD score: mean (s.d.)	20.7 (3.7)	20.3 (3.3)
MADRS score: mean (s.d.)	26.48 (6.5)	26.0 (5.4)
BPHS score: mean (s.d.)		
Severity: acute	0.1 (0.3)	0.2 (0.7)
Severity: chronic	2.97 (2.1)	2.7 (1.8)
Disability: acute	0.13 (0.3)	0.2 (0.6)
Disability: chronic	2.58 (2.1)	2.5 (2.0)
First episode of depression (%)	71.4	73.6
Duration of episode (weeks)		
Mean (s.d.)	23.6 (29.4)	24.4 (52.1)
25th percentile	6	6
Median	12	12
75th percentile	36	24
MMSE score (out of 35): mean (s.d.)	31.1 (4.7)	30.4 (4.6)

BPHS, Burvill Physical Health Scale; HRSD, Hamilton Rating Scale for Depression; MADRS, Montgomery & Åsberg Depression Rating Scale; MMSE, Mini-Mental State Examination.

receive sertraline (*n*=56) or placebo (*n*=57; Table 1). Recruitment source did not predict likelihood of entry into the maintenance phase (Pearson χ^2=3.0, d.f.=3, *P*=0.4). However, those not meeting maintenance phase entry criteria had significantly higher baseline HRSD scores (2.42, 95% CI 1.10–3.74).

Of those who were withdrawn during the maintenance phase, 84 consented to open follow-up. These included people experiencing recurrence and protocol violations. Two-thirds of this group (*n*=57) accepted subsequent antidepressant therapy of at least 8 weeks duration: 12 (21%) achieved remission (MADRS score of 6 or less), 19 (33%) remained depressed, and the remaining 26 (46%) had varying levels of improvement. Seventeen (20%) of the 84 died prior to the end of the follow-up period of 2 years.

Trial drug dosage and medication compliance

Tablets were delivered to the participants' homes, and tablet counts were conducted at each assessment. Participants were maintained on the dosage that achieved remission of presenting episode: 73% of the sertraline group and 75% of the placebo group received 50 mg daily, while the others received 100 mg daily. None received 150 mg (or placebo equivalent) during the maintenance phase.

Analysis of recurrence

Kaplan–Meier survival analyses showed no significant difference (log rank test 1.55, d.f.=1, *P*=0.21) between sertraline and placebo in prevention of recurrence. The sertraline group had a cumulative survival function of 39% with a median survival of 92 weeks. The placebo group had a cumulative survival function of 31% with a median survival of 48 weeks (Table 2). There was a reduction in risk of recurrence of 8.4% over 100 weeks for people taking sertraline compared with those taking placebo during the maintenance phase.

Over half of those experiencing recurrence did so during the first 26 weeks of the maintenance phase: 15 (60%) in the placebo group, 16 (57%) in the sertraline group. Approximately a quarter (32% placebo and 16% sertraline) experienced recurrence between 27 weeks and 52 weeks. The remainder experienced recurrence during the second year of follow-up. We examined the relative rate of recurrence across time, and compared the proportion of eligible participants experiencing a recurrence at each assessment. Three main 'peaks' were identified (at 15 weeks, 30 weeks and 50 weeks) at which 8% or more of eligible participants experienced recurrence. However, at least three other peaks (at 8 weeks, 64 weeks and 72 weeks) were identified at which 5–6% of eligible participants experienced a recurrence.

Cox's regression analysis

Clinical and demographic variables were entered into a stepwise analysis (backwards

Table 2 Cumulative recurrence[1] of depressive disorder during the 2-year maintenance phase

	Sertraline Total *n* randomised=56			Placebo Total *n* randomised=57		
Week	Patients under observation (*n*)	Cumulative recurrences (*n*)	Cumulative survival[1] (%)	Patients under observation (*n*)	Cumulative recurrences (*n*)	Cumulative survival[1] (%)
4	54	2	96.43	51	6	89.47
8	46	8	85.30	42	11	80.63
12	45	9	83.45	42	11	80.63
48	28	19	63.09	20	26	49.00
100	15	25	38.64	12	31	31.10

1. Estimated difference in proportion of participants experiencing recurrence: −7.9% (95% CI −28.06 to 12.2%).
2. Based on Kaplan–Meier estimates.

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elimination) to investigate models of recurrence prediction. Eleven items were entered into the first stage of the regression. Of these, sertraline *v.* placebo, MMSE score, length of presenting episode, previous number of episodes, Burvill scores (of which there are four separate sub-scores) and gender were dropped. Dosage of maintenance medication was associated with baseline severity of depression: high dosage did not protect against recurrence. Age (in 5-year increments) and pre-randomisation MADRS score were predictive of recurrence (Table 3). Each 5-year increase in age has a hazard ratio of 1.30 (95% CI 1.04–1.61). A one-point increase in pre-randomisation (end of continuation phase) MADRS score has a hazard ratio of 1.11 (95% CI 1.02–1.20) for recurrence.

DISCUSSION

This is the first maintenance study to challenge the assumption that the dosage of an antidepressant that achieves remission also provides protection against recurrence. We examine our findings in terms of design limitations and in the context of contemporaneous literature.

Limitations of the study

Studies of a similar nature (Ardern *et al*, 1993) have been criticised for selection bias, excluding a large percentage of the eligible sample and not supplying information about those who were excluded or follow-up of those who experienced recurrence during the trial. We recruited participants from four different sources, reducing the likelihood of selection bias. Recruitment source did not influence eligibility to enter the maintenance phase and was not associated with outcome. In this study, relatively few people were excluded because of concomitant physical illness (n=9). However, analysis demonstrates that those with more severe depression were excluded from entry into the maintenance phase. Consequently, our findings reflect the prophylactic efficacy of therapeutic doses of sertraline in older people in the community who are suffering from mild to moderate severity of DSM–III–R major depressive disorder. Of those who did experience recurrence, two-thirds accepted a second antidepressant or increased dose of sertraline, of whom under a quarter had a good outcome, while the remainder showed some improvement. However, the mortality rate over 2 years was high in this group.

The design of this study may be criticised because of its relatively short continuation phase. Guidelines suggest that the continuation phase should be up to 6 months' duration, based on the assumption that a depressive episode lasts 6–9 months in those treated as out-patients (Kupfer & Frank, 1992). However, as in the study by Klysner *et al* (2002), there was no significant peak of recurrence within the first few months of the maintenance phase in the placebo group, as would be expected if participants were experiencing relapse as opposed to recurrence.

The study may also be criticised on the grounds of potential type II error. The power analysis indicated that 60 participants should be recruited into each arm of the post-randomisation phase. Owing to protocol violations identified after recruitment was closed, 6 persons (0.05% of the study sample) were subsequently excluded from the analyses. Statistical modelling indicated that the inclusion of these individuals in the appropriate experimental arms and allocating them to the outcome that favours drug efficacy compared with placebo did not significantly influence the results. Our study is comparable in size to that of Klysner *et al* (2002), which was of a similar design, evaluating an antidepressant from the same class. Other studies in this age group that are of similar design are approximately half the size of our study. Ardern *et al* (1993) studied 58 persons, 25 of whom received dothiepin and 35 received placebo; Reynolds *et al* (1999) studied 53 persons (excluding those receiving psychotherapy), of whom 24 received nortriptyline and the remainder received placebo. Despite being of similar size to our study or smaller, all three studies (Ardern *et al*, 1993; Reynolds *et al*, 1999; Klysner *et al*, 2002) found in favour of antidepressant treatment compared with placebo.

Other potential criticisms lie in the possibility of poor compliance and the use of relatively low dosages of sertraline in a proportion of participants. Reynolds *et al* (1999) demonstrated the prophylactic efficacy of therapeutic levels of nortriptyline. Poor compliance and sub-therapeutic blood levels are thought to explain up to 50% of the recurrence in that study. The authors also suggest that sub-therapeutic blood levels explain the negative findings of other, smaller studies (Georgotas *et al*, 1989) examining the prophylactic efficacy of the same drug. In a small study examining the efficacy of lithium and cognitive–behavioural therapy in the prevention of recurrence and relapse, Wilson *et al* (1995) noted that poor drug compliance resulting in low serum lithium levels confounded the findings.

We believe that low dosage is unlikely to be responsible for the findings of our study. Participants were maintained on the dosage of sertraline at which they achieved remission; three-quarters took 50 mg daily, which is recognised as the optimum dose for treatment (Preskorn & Lane, 1995),

Table 3 Cox regression model predicting recurrence

	Hazard ratio	95% CI
Included variables		
Sertraline *v.* placebo	1.21	0.704–2.082
MADRS score at end of phase 2	1.11	1.019–1.200
Age (5-year increments)	1.30	1.044–1.613
Rejected variables		
Gender (male:female)	0.95	0.52–1.73
Length of episode	1.00	1.0–1.01
Previous episodes	1.01	0.89–1.14
MMSE score	0.93	0.93–1.04
BPHS score:		
Severity: acute	1.00	0.58–1.46
Severity: chronic	0.89	0.89–1.15
Disability: acute	0.90	0.55–1.50
Disability: chronic	1.01	0.93–1.18

BPHS, Burvill Physical Health Scale; MADRS, Montgomery & Åsberg Depression Rating Scale; MMSE, Mini-Mental State Examination.

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and about a quarter were treated with 100 mg. High dosage was associated with increased severity of index depression and did not have an increased protective effect in terms of outcome. Compliance is more difficult to monitor. Compliance was enhanced through domiciliary delivery of medication and supportive, ongoing counselling, emphasising the importance of medication, with tablet counting at each assessment. Analysis failed to demonstrate any difference between tablet returns in those experiencing recurrence compared with those who remained asymptomatic in the sertraline group. There was no difference between those who received sertraline and those who received placebo in terms of compliance monitoring. Blanchard *et al* (1999) demonstrated the importance of generic nurse support in the longer-term management of depression in older community residents. The follow-up in this study was intense, with regular home visits augmented by telephone contact. Members of both placebo and experimental groups received similar support in terms of nature and number of contacts during the experimental period. It is unlikely that differential support influenced the findings.

Our findings in context

We have found two studies that have examined the prophylactic efficacy of sertraline. Doogan & Caillard (1992) found that sertraline was more effective than placebo in preventing recurrence in 144 subjects over 44 weeks. Keller (1998) found similar results in a younger population over 76 weeks. However, the design of both these studies included a facility to increase maintenance dosage (preserving masking integrity) in people who were thought to be showing early evidence of recurrence during the double-blind, placebo-controlled phase. An analysis of presented data suggests that a significant proportion of those experiencing potential recurrence benefited from a subsequent dosage increase in each study. These findings are reflected in the 'treatment of recurrence' study by Franchini *et al* (2000), who found that increasing the dosage of sertraline had a therapeutic role in the management of recurrence in people with depression who were already taking the drug. Our study design did not have the facility of increasing maintenance dosage when early signs of recurrence became obvious; participants were maintained at the dosage of sertraline that achieved remission of the presenting episode. A subsequent search of the Cochrane Database of randomised, controlled trials failed to generate any evidence that the dosage of sertraline required to achieve remission has prophylactic efficacy and that enhanced dosage is probably required for maintenance treatment.

Predictive variables

As in our study, Reynolds *et al* (1999) found an association between increased age and recurrence. Notably, these observations are independent of the number of preceding episodes experienced by the individual. Follow-up studies of patients referred to secondary services have demonstrated a mixed association between acute and chronic physical illness and handicap (Burvill *et al*, 1991). We were unable to demonstrate any significant correlation between these variables and outcome. Again, our findings concur with those of Reynolds *et al* (1999), who examined these issues in the context of a randomised, controlled trial. Our finding that following remission, residual depressive symptoms predict poor outcome in terms of recurrence has been found in other treatment-controlled studies (Faravelli *et al*, 1986).

Clinical and research implications

A number of research issues are generated by these findings. First, there is no doubt that sertraline is a relatively safe and therapeutically active drug (Finkel *et al*, 2000) which has been examined in the context of prophylactic treatment. Despite these later studies (Keller, 1998; Finkel *et al*, 2000) being positive, our negative findings are consistent when study design is taken into account. In this study we specifically examined the prophylactic efficacy of sertraline prescribed at the dosage required to achieve remission. This differs from other studies, which clearly demonstrate the prophylactic efficacy of sertraline provided that the dosage is increased over and above that required to achieve remission of the presenting episode. These negative findings are important. It is apparent that in the absence of evidence, it cannot be assumed that the dosage of antidepressant required to achieve remission offers protection against recurrence or relapse: in the case of sertraline, the effective prophylactic dosage is likely to be greater than the therapeutic dosage. Second, in comparing this study with other studies conducted on similar populations it is evident that antidepressants differ in terms of maintenance efficacy. A review of the literature indicates that this is not a class-specific phenomenon and emphasises the importance of randomised, controlled trials in establishing prophylactic efficacy (and dosage) before new antidepressants are routinely employed in this fashion. Third, it is evident that extreme age is associated with an increased risk of recurrence of depression over 2 years – in the study by Reynolds *et al* (1999), 3 years. It is important in future that maintenance trials are developed to accommodate these issues, bearing in mind the relatively high levels of morbidity and suicide in this age group.

From a clinical perspective, three specific recommendations can be drawn from our findings. First, this study draws attention to the particular vulnerability of very old people with depression living in the community. It is evident that emphasis must be placed on maximising symptom control during the treatment phase. Even minor (sub-syndromal) residual symptoms are predictive of poor outcome in terms of recurrence. This warrants an aggressive and closely observed treatment plan. Second, it is also apparent that the very old are particularly vulnerable to recurrence. This is independent of the number of previous episodes experienced by the individual. Consequently, these people should be encouraged to take long-term maintenance medication, irrespective of the number of previous episodes. Third, it is not safe to assume (in the absence of evidence) that the therapeutically active dose of an antidepressant that promoted remission has prophylactic efficacy. Increased dosage may be required in the context of long-term, closely followed-up therapy, with counselling and compliance monitoring.

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CLINICAL IMPLICATIONS

- The sertraline dosage required to achieve remission of depression in older people does not have significant prophylactic efficacy. However, research suggests that increasing the dosage at the first sign of recurrence does have a role.
- Residual depressive symptoms after treatment are associated with recurrence, suggesting that complete symptom control should be a priority of treatment.
- Very old people are particularly vulnerable to recurrence of depression (irrespective of physical illness, handicap and number of previous episodes), suggesting that prophylactic treatment should be considered after the first episode.

LIMITATIONS

- The study findings can only be generalised to older people with mild or moderate major depressive disorder, living in the community.
- Compliance was not assessed by measuring serum drug levels.
- This is one of a very few studies reporting that the dosage of an antidepressant required to achieve remission does not have prophylactic efficacy. Replication studies and meta-analysis are required to confirm the findings.

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