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How Long Should the Elderly Take Antidepressants?
A Double-Blind Placebo-Controlled Study of Continuation/Prophylaxis Therapy with Dothiepin
OLD AGE DEPRESSION INTEREST GROUP

Of 219 elderly patients with a major depressive disorder (meeting RDC), 69 recovered sufficiently and consented to enter a two-year double-blind placebo-controlled trial of dothiepin. Survival analysis revealed that dothiepin reduced the relative risk of relapse by two and a half times. Past but not current serious physical illness was also associated with a favourable outcome, whereas a prolonged index depressive illness trebled the relative risk of relapse. In the light of previous research on prognosis it is suggested that elderly persons who recover from a major depressive illness should continue with antidepressant medication for at least two years, if not indefinitely.

The prognosis of depression in the elderly has been the subject of quite extensive controversy (e.g. Murphy, 1983, 1987; Baldwin & Jolley, 1986; Cole, 1990). It is possible to extract from the debate two main issues. Firstly, data on prognosis are derived from research that is flawed. Cole (1990) and Ames & Allen (1991) have provided comprehensive reviews of the subject. Cole made ten recommendations for improving the quality of data which were, in summary: selection from community samples; categorisation by history of depression; selection by explicit diagnostic criteria; prognostic factors such as physical illness described by valid and reliable measures; minimum of two-year follow-up; specific, mutually independent outcome categories; blind outcome assessment; treatment to be related to outcome; separate categorisation of physical illness/disability and cognitive impairment; demonstrated reliability in all phases of a study. Cole's proposals are highly commendable, but probably represent an ideal that the practicalities of research would make difficult to achieve. For the present, it would certainly be wrong to use the argument of flawed method to avoid making any judgements about the prognosis of depression in old age.

The second issue from the debate is that deciding what is a 'good' or 'bad' prognosis of depression in old age is essentially subjective. Indeed, Murphy (1987), in her answer to Baldwin & Jolley (1986), asserted that the data from their respective studies were not greatly different, but their dispute amounted simply to one side calling pint pots half full while the other called them half empty. To illustrate this point, an optimist, quoting Cole's (1990) analysis of ten studies, could state that approximately 60% of elderly patients who suffer a depressive illness stay well after recovery or recover after subsequent relapses, whereas only about 25% are continuously ill. A pessimist, however, would argue that only approximately 20% stay free of illness whereas about 80% either remain ill or suffer one or more further relapses.

Even at younger ages, the long-term prognosis for depression serious enough to warrant hospital admission is poor. In an 18-year follow-up of depressed patients, all bar two of whom were under 65 at admission to the Maudsley Hospital, 95% of those surviving the period of study had relapsed, and 10% of the index sample had suffered unnatural deaths, of which the majority were adjudged suicide or open verdicts (Lee & Murray, 1988).

Whether or not one bases an optimistic view on the fact that most episodes of depression respond to vigorous treatment, all clinicians would agree that prevention of relapse is of the utmost importance. Major depression in the elderly is probably a chronic disorder but if not that, certainly a recurrent one. Generally speaking, any major depressive episode has to be measured in months which, for an elderly person, is too long to subtract from a relatively short expectation of life.

Most elderly people receive specific antidepressant medication for an acute episode of depression, some in conjunction with electroconvulsive therapy (ECT). The most obvious ways of preventing relapse would seem to be continuation or maintenance antidepressant therapy. The former is continuation of treatment after recovery from an index episode, the latter is treatment given to prevent recurrent episodes. The evidence in favour of continuation therapy in the elderly is scant. There have been studies of younger patients, but not of the elderly. Mindham et al (1973) found amitriptyline superior to placebo in preventing relapse over only a six-month follow-up.
Other workers using different antidepressants in younger patients for different time periods, of up to two years, have had similar results (Kay et al., 1970; Prien et al., 1973; Stein et al., 1980; Glen et al., 1984).

There are also data on prophylactic or maintenance therapy in younger patients. In the most thorough of these, Frank et al. (1990) followed for three years a group of 128 patients with a mean age of 39.5 years (median 38) suffering from recurrent depression, and found that imipramine in full therapeutic dosage of 200 mg was significantly effective in preventing relapse. In one study of elderly patients, Georgeotas et al. (1989) found phenelzine to be superior to placebo and nortriptyline over one year of maintenance, but nortriptyline was not superior to placebo.

These results are interesting, but monoamine oxidase inhibitors (MAOIs) are not commonly used in either treatment or prophylaxis of depression in old age. In a study of 15 patients, Cook et al. (1986) found a high relapse rate in elderly patients withdrawn from long-term tricyclics by placebo substitution. This study accords with clinical experience and with earlier reports (Post, 1972), but the sample size was too small to draw firm conclusions.

The question of how long elderly patients should take antidepressant medication after an acute episode is not an easy one to answer from the available data, because studies in younger patients are not necessarily applicable. Furthermore, the elderly are particularly susceptible to the unwanted effects of antidepressants, some of which, such as postural hypotension and cardiac arrhythmias, are potentially life threatening. Nevertheless, most clinicians would agree with the World Health Organization’s (1989) consensus statement, not drafted with the elderly specifically in mind, that treatment should be continued for at least six months after recovery. The question remains as to how long medication should be continued after that. Ames & Allen (1991) advocated “until evidence to the contrary is presented it would seem prudent . . . to be liberal in the dispensation of prophylactic medication,” but these authors do not suggest how much and for how long.

Our impression, for which we cannot adduce evidence, is that psychogeriatricians divide roughly into two groups: those whose policy is to stop antidepressants after a continuation phase of about 6–12 months from recovery; and those who advise that antidepressants be continued for much longer, sometimes indefinitely. The purpose of this study was to examine which of these policies is likely to lead to a better outcome; or, put more simply, to determine how long elderly patients should continue to take antidepressants after a major episode.

**Method**

Fifteen centres participated in the trial. Investigators were asked to identify all patients aged over 60 years coming to their service with a major depressive illness defined by the Research Diagnostic Criteria (RDC; Spitzer et al., 1978). Demographic and clinical data were collected. The severity of depression was assessed by the Montgomery and Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979), which was slightly modified for our elderly patients: under item 9 (pessimistic thoughts) investigators were asked to rate any ideas or delusions considered relevant to the psychopathology of the patient’s depression (e.g. nihilistic delusions) and not to restrict the rating of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin, as the MADRS specifies.

Patients were treated in whatever way the participating investigator wished. Thus, no restriction or specification was made as to particular drugs or ECT.

Recovery was defined as a MADRS score of less than 11. It was considered unethical to give a placebo immediately on recovery from a major depressive illness. Patients therefore continued their normal clinical treatment for a further eight weeks before entry into the trial.

Those patients who did not fall within the exclusion criteria (see below), who were still recovered (as defined by a MADRS score < 11), and who gave informed consent, entered the trial. All other psychotropic medication was stopped except a hypnotic, if prescribed. Patients were randomly assigned on a double-blind parallel-group basis to take either dothiepin in a single fixed dose of 75 mg daily or placebo. In the randomisation patients were stratified to ensure that those who had received ECT for the index illness were evenly divided between groups.

Patients to whom the following conditions applied were not entered into the trial: those considered by their investigator to be unsuitable; allergy to dothiepin or related drugs; history of significant physical disorder which might be complicated by dothiepin (e.g. glaucoma or cardiac arrhythmias); renal or hepatic impairment; clinical evidence of dementia; a Mental Test Score (Hodkinson, 1973) of less than 25 at the point of potential entry. Investigators were asked to record reasons for not entering the trial.

Only those patients taking dothiepin or placebo were subject to continuing assessment, which was made by the clinician/investigator who had entered the patient in the trial. Assessments were made at one month and subsequently at three-monthly intervals from entry (i.e. commencement of dothiepin or placebo). At each assessment the MADRS was administered and data on unwanted drug effects recorded. Patients were asked to bring any remaining tablets from the previous assessment to be counted. From this and by discussion with the patient, the investigator recorded an estimate of compliance as good, moderate, or poor.

Patients were considered withdrawn from the trial on first relapse (a clinical judgement or a score on the MADRS of > 10).
Data were analysed using the personal computer statistical packages SPSS/PC (Norusis, 1988) and SPIDA (Lunn & McNeil, 1991).

Results

Of the 219 patients with major depressive disorder identified, 72 were considered suitable and gave consent to take part in the trial. Three of these 72 withdrew or were withdrawn at the point of entry, so that 69 patients finally participated. A further 11 patients were lost during the course of the trial for reasons such as termination of consent, default from follow-up, moving away, and death. Therefore 58 patients either completed two years on medication or were withdrawn because of relapse. Of the 11 lost by attrition, three died from natural causes (not suicide). A further patient who had relapsed in the trial died of natural causes within a month of being withdrawn. No death was attributed to the trial medication. Although more were lost from the dothiepin group than placebo group (8 v. 3), this was not related to any factor which could be attributed to the active drug, such as side-effects or compliance. There was no association between the attrition rate and particular treatments for the index illness, such as ECT.

Table 1 shows some general characteristics of the group as a whole and of the subsamples. Means and standard deviations are given where distributions were normal. It can be seen that those who entered the trial differed from those who did not only in having significantly more late-onset cases.

The reasons for not entering the trial were: failure to recover sufficiently from depression (27%); non-consent (16%); death (8%); physical illness (7%); miscellaneous reasons (10%); reason not given (32%).

The length of the index illness before entry into the trial between the dothiepin and placebo groups was not significantly different (median 16 weeks for both, with interquartile ranges of 7.0 and 9.5 respectively). These groups did not differ with respect to MADRS score at identification (see Table 1) or at entry (median 2.5 for dothiepin and 3.0 for placebo, with interquartile ranges of 3 and 4 respectively).

Drug effects

Table 2 shows the number of subjects relapsing in each group against the month from entry by which relapse had occurred. The beneficial effect of the active drug can be seen to emerge from the first month. Using serial chi-square tests, the difference between the two groups did not reach significance until 12 months. Significance just disappeared (p<0.07) by 21 months because of attrition from the dothiepin group. However, chi-square tests are cross-sectional analyses which fail to take account of the longitudinal nature of the data. Furthermore, they fail to assess the importance of covariates. For this reason it is more appropriate to use techniques of survival analysis.

The data were therefore subjected to regression analysis using Cox’s proportional hazards model (Cox regression) (Cox & Oakes, 1984) with time of relapse as the response variable. The following 12 covariates were introduced initially into the analysis: drug/placebo; age; sex; length of index illness; family history of affective disorder; personal history of depression; number of previous episodes of depression; age at first affective episode (before or after 65); history of physical illness involving the central nervous system (CNS); history of non-CNS physical illness; ECT for index illness; MADRS score at identification. Backward elimination and exhaustive search produced identical best subsets of covariates for an optimum fit to the proportional hazards model. These were: drug/placebo; age; history of serious non-CNS physical illness; and length of index illness, which was log-transformed to remove skewness. Table 3 shows the Cox regression data.

The P values in Table 3 show that all the coefficients are significantly different from 0. The Cox proportional hazards model is one of the family of generalised linear models which incorporate covariates by means of a simple linear sum, comprising the product of each coefficient with its covariate. Thus, although the coefficient for age is an order of magnitude smaller than those for drug/placebo or history of physical illness, the covariate of age itself is an order of magnitude larger. For example, drug/placebo and history of physical illness, being indicators, vary between 0 and 1, whereas age varies typically over a range of the order of ten years. All products of the coefficients and covariates in Table 3 are therefore of comparable influence in the model.

The relative risks associated with each covariate appear in Table 3 with their 95% confidence intervals; because the number 1 is not contained within the limits of any of them, we can conclude that the relative risks for all covariates are significantly different from 1 at the 5% level. Turning to the relative risks themselves, taking dothiepin as opposed to placebo and having a history of non-CNS physical illness

<table>
<thead>
<tr>
<th>Characteristics of samples (at point of identification)</th>
<th>n</th>
<th>Age: years</th>
<th>1st MADRS score</th>
<th>% women</th>
<th>1st onset &lt;65 years: %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole sample</td>
<td>219</td>
<td>75.2 (6.2)</td>
<td>35.3 (9.7)</td>
<td>72</td>
<td>50</td>
</tr>
<tr>
<td>Not entered</td>
<td>150</td>
<td>75.0 (6.2)</td>
<td>35.8 (10.1)</td>
<td>71</td>
<td>55*</td>
</tr>
<tr>
<td>Entered</td>
<td>69</td>
<td>75.7 (6.2)</td>
<td>34.2 (8.8)</td>
<td>77</td>
<td>37*</td>
</tr>
<tr>
<td>Dothiepin</td>
<td>33</td>
<td>75.9 (5.6)</td>
<td>33.6 (9.9)</td>
<td>82</td>
<td>45</td>
</tr>
<tr>
<td>Placebo</td>
<td>36</td>
<td>75.5 (6.8)</td>
<td>34.9 (7.7)</td>
<td>67</td>
<td>29</td>
</tr>
</tbody>
</table>

*First onset <65, for not entered v. entered, χ² = 5.89, P<0.02; no other differences significant.
stand out as better than halving the relative risk of relapse.

On the other hand, a prolonged index depressive illness more than trebles the relative risk of relapse.

The Cox regression (Table 3) used Efron's adjustment (Efron, 1977) to take account of ties. In this case ties are artificially simultaneous relapses, because assessments were made at specified three-monthly intervals during the trial period. Clearly, subjects were relapsing at random times during any given assessment interval, but were necessarily recorded at the distal end of that interval. Even without Efron's adjustment, the Cox regression yielded a good fit to the data, with no evidence against the proportional hazards assumption.

A confirmatory analysis was performed with ordered polytomous regression (McCullagh, 1980) after dividing relapse into four classes: within one month; between one and nine months; between nine and 24 months; no relapse within 24 months. This produced the interesting result that sex replaced length of index illness in the best subset of four covariates.

Although sex had not appeared significant in the Cox proportional hazards model, the results from polytomous regression suggested that it might have played an important role in the quality of fit. Cox regression was therefore repeated, stratifying for sex. This not only improved the quality of fit of the proportional hazards model from a deviance of 215.93 to 182.11 on 64 degrees of freedom, but also further reduced the relative risk of relapse on the drug/placebo covariate. Table 3 shows that stratification lowered the P value and narrowed the confidence intervals for this covariate. With placebo, relapse was 2.49 times more likely than with dothiepin. Figure 1 shows Efron-adjusted Cox survival curves stratified for sex.

No other clinical variables were related either to outcome or to trial medication. In view of Murphy's (1983) findings, we report that pessimistic thoughts or delusional thinking at identification of the index illness did not differentiate those taking dothiepin from those on placebo; nor did it affect outcome (i.e. whether or not they relapsed). Compliance was judged to be good in the great majority of patients at each assessment. Although the number of moderate or poor compliers was small, neither category was associated with a particular outcome.

### Discussion

Sixty-nine patients entering the trial from a potential population of 219 was necessarily a highly selected series. Investigators were asked to collect data on all consecutive patients presenting to their service with major depression until the study coordinator considered that enough had been recruited. Thus, the total of 219 were a representative sample of patients seen in a representative sample of services in England. Recruitment from the 219 into the trial may well have been partly related to the style of service, which must have differed between centres. Selection was, however, more probably determined by other factors, such as stringent regulations as to exclusion of patients with physical illness, and especially to informed consent. Many elderly patients are understandably reluctant to undertake the risk of participation in research.

While a larger sample would clearly have been more desirable, ours was nevertheless sufficient to yield highly significant results. The reasons for attrition from the original 219 patients prove interesting in themselves. Of those for whom a reason for not entering was given, the majority (27%) did not recover sufficiently from depression to be considered suitable. This figure is in line with results from the prognosis or natural-history studies summarised by Cole (1990) and Ames & Allen (1991) if one considers that the subgroup included those who remained

### Table 2

<table>
<thead>
<tr>
<th>Month from start of trial by which relapsed</th>
<th>1</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
<th>18</th>
<th>21</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dothiepin</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>8</td>
<td>8*</td>
<td>9*</td>
<td>9*</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Placebo</td>
<td>5</td>
<td>8</td>
<td>14</td>
<td>17</td>
<td>19</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

*P < 0.05 (χ² test).

### Table 3

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Coefficient</th>
<th>P</th>
<th>Relative risk</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug v. placebo</td>
<td>-0.790</td>
<td>0.038</td>
<td>0.454</td>
<td>0.215 to 0.957</td>
</tr>
<tr>
<td>History of non-CNS illness</td>
<td>-0.926</td>
<td>0.015</td>
<td>0.396</td>
<td>0.188 to 0.832</td>
</tr>
<tr>
<td>Age</td>
<td>-0.075</td>
<td>0.035</td>
<td>0.928</td>
<td>0.866 to 0.995</td>
</tr>
<tr>
<td>Log of length of index illness</td>
<td>1.246</td>
<td>0.005</td>
<td>3.475</td>
<td>1.451 to 8.321</td>
</tr>
</tbody>
</table>

**With stratification for sex**

| Drug v. placebo                | -0.913      | 0.019 | 0.401       | 0.187 to 0.861          |
| History of non-CNS illness     | -0.914      | 0.015 | 0.394       | 0.191 to 0.839          |
| Age                           | -0.073      | 0.035 | 0.929       | 0.868 to 0.995          |
| Log of length of index illness | 1.093       | 0.012 | 2.982       | 1.268 to 7.015          |

*1. Significance of difference of the coefficient from 0.*
Patients entering the medication/placebo phase of this study differed from those not entering in only one respect: there were more late-onset cases (first affective episode after 65) in the former group. This may have been a chance result, but other explanations need to be considered. It is possible that more early-onset cases had already been so damaged by recurrent affective disorder that they did not recover sufficiently to enter the trial, or might already have been established on other prophylactic medication, such as lithium. There was a slight trend in favour of this explanation - 21% of early-onset cases being persistently ill compared with 16% of late-onset cases - but the difference was not significant. One might speculate that more early-onset cases had become disillusioned with psychiatric care and withheld consent to participate, but the non-consenting were equally divided between those with a late and early onset. The difference between those entering and not entering cannot be explained by there being more late-onset cases as a whole. Of the 219 patients identified, 103 had their first illness before 65 and 105 after that age (for 11 this information was not available). It is interesting to note that there were more early-onset cases in the dothiepin than placebo group (Table 1), although the difference was not significant. Furthermore, age at onset did not emerge as a significant covariate in the survival analysis.

This study could be criticised for not taking inter-rater reliability into account. As far as diagnosis was concerned, this was probably a negligible factor since RDC were applied. Use of the MADRS is more open to criticism because judgements on ten separate six-point subscales had to be made several times for each patient over the course of the trial by more than 20 raters. It is difficult, however, to conclude that the lack of rater training and measurement of reliability made a significant difference to the implementation or outcome of this trial. The results from all the different centres were remarkably consistent, and none stood out as having discrepant results on the MADRS or other measures, such as assessment of compliance.

O'Neill et al (1991) argued that measurement of compliance is essential in clinical trials with the elderly. Their analysis was critical of the type of method used in this trial because, as they stated, "pill counts and interviews are of low sensitivity and specificity". O'Neill et al advocated monitoring by tablet containers with a microchip memory. This was preferred to measurements on biological fluids (what would have been serum dothiepin levels in this trial) because it "is representative of compliance only over a period which is dependent on the elimination half-time of that substance". We do not disagree with this as an ideal and should prefer microchip tablet containers for future trials. However, we do not consider that poor compliance was a significant factor in this trial. Furthermore, the superiority of active dothiepin over placebo either supports our contention that poor compliance was not a factor or was so marked that any minor compliance effect was over-ridden.

In this trial we chose dothiepin for two principal reasons. Firstly, it has been in use in the UK for many years and its efficacy for an acute depressive illness is now well established. Secondly, we considered it to be the most acceptable choice for a wide number of clinicians with their own preferences in everyday practice, because dothiepin is a 'middle of the road' drug, between the traditional tricyclics, such as amitriptyline or imipramine, and the more recently introduced tetracyclic and related compounds - the newer selective serotonin reuptake inhibitors were not on the market when this trial began. The dose of
75 mg was chosen by the Old Age Depression Interest Group on the basis of clinical experience as the one to strike the best balance between efficacy and safety for elderly patients. However, the unavoidable fixed dosage schedule had the disadvantage that the optimum dose for some patients was likely to have been higher than 75 mg. This disadvantage would perhaps have been more important if the effect of dothiepin compared with placebo had not been so marked, but, given our results, optimum dosage would presumably have increased the difference we have shown.

Researchers working with younger patients correctly distinguish between continuation therapy and prophylactic (maintenance) treatment. The former is consolidation of recovery by continuation of treatment after remission of an index illness. Prophylactic treatment is that given to patients with recurrent episodes of recurrent affective disorder. For research purposes, Frank et al (1990) defined ‘recurrent affective disorder’ as a total of three or more previous episodes and at least one within the preceding two and a half years. Our study intentionally overlaps the divide between continuation and prophylaxis. In younger patients who do not have frequent recurrent episodes, the issue of indefinite treatment does not customarily arise. For them, the relevant question is how long the continuation phase should last. With older patients, the high risk of relapse after one episode or risk of chronic illness prompts many clinicians to merge continuation into prophylaxis by more or less indefinite treatment.

Montgomery (1990) has criticised prophylaxis research (i.e. prevention of recurrent episodes) on the grounds that an insufficient symptom-free period has been allowed before initiating treatment. He proposed four months for the minimum such period. The present study is not strictly a prophylaxis one, as discussed, but adherence to Montgomery’s criterion would probably be feasible in only a minority of elderly patients, who would therefore comprise a highly selected sample. This is because many older people who make a good clinical recovery from an episode suffer from one or two unpleasant residual symptoms. A typical example is diurnal variation of mood: ‘I feel bad for the first couple of hours of the day’. For this study we did not choose a symptom-free recovery but the more realistic one of a cut-off point on the MADRS, which allows for satisfactory clinical recovery but also residual symptoms.

Predictors of relapse
Using modern statistical techniques of survival analysis, dothiepin was found to be two and a half times more effective than placebo in terms of relative risk of relapse over two years, after recovery from a major depressive illness. These results are comparable to those of Frank et al (1990) in their study of maintenance therapy for recurrent depression in younger patients. Our cohort, unlike that of Frank et al, contained both subjects for whom the index illness had been a first episode (42) and those for whom it had been a recurrence (25) (this was not recorded in two instances). Because of the relatively poor prognosis in either condition with elderly patients, it is less important to distinguish between a first onset and a recurrence than it is to prevent a relapse. Evidence that age at first onset of affective disorder was not important in relation to outcome was given by the Cox regression, since it was not a significant covariate (P value 0.91). This finding strengthens the conclusion that taking dothiepin was above all the significant factor in preventing relapse.

Although sex did not emerge as one of the best subset of four covariates in the Cox regression, ordered polytomous regression showed that a better fit to the proportional hazards model could be achieved by stratifying for sex. From Fig. 1 it can be seen that men had a better outcome than women, although the effectiveness of dothiepin was prominent for both groups. In fact sex has not emerged as a predictive factor from previous studies on prognosis or prophylactic therapy (Post, 1972; Murphy, 1983). Frank et al (1990), in their three-year maintenance trial, did not mention sex specifically, but it can be presumed not to have been a factor since they state ‘neither demographic nor baseline clinical characteristics were shown to be associated with survival time’.

It is not easy to explain our finding with regard to sex, but it should perhaps be treated with some caution since the number of men in the dothiepin and placebo groups (Table 1) was low. However, it is interesting to note that, while the difference was not statistically significant, the proportion of men in the placebo group was higher (33%) than in the dothiepin group (18%). If our finding of a better outcome in men is valid, it might have worked to reduce the difference between the dothiepin and placebo groups. Since stratifying for sex improved the relative risk of relapse, the sex difference therefore offers indirect reinforcement of the effect of the drug.

The distribution of durations of index episode was skewed by some illnesses which were markedly prolonged. For this reason the data were log transformed for statistical analysis. That a long index illness approximately trebled the relative risk of relapse is not surprising. In the functional psychoses, both schizophrenic and affective, it is generally recognised that long illnesses carry a poorer prognosis
than short ones, a clinical observation confirmed in old age depression by the studies of Post (1972) and Murphy (1983).

The most unexpected and perhaps inexplicable finding in this trial is that a history of serious physical illness requiring hospital treatment emerged from the survival analysis as a strong predictor of good outcome. A little over half (38 v. 31) of those who entered the trial had had such a physical illness. It is important not to equate this variable with current physical illness, which has been shown by research (e.g. Murphy, 1983) and is known from clinical experience to be a poor prognostic indicator. Indeed, because of the exclusion criteria, our patients were likely not to have a serious current physical illness. When the details of the histories were examined, it was seen that illnesses varied widely, from appendectomy or tonsillectomy in childhood, through jaundice and dysentery during World War II, to elective hip replacement shortly before the index depression. The subgroup was therefore reanalysed in two ways: by separating physical illness within two years of the index depression from those before two years; and by separating an acute or discrete episode (e.g. herniorrhaphy or prostatectomy) from chronic and persistent illness (e.g. diabetes or osteoarthritis). In neither of these reanalyses did redefined histories of physical illness prove significant. The untransformed history of physical illness therefore remained the important covariate, which is difficult to explain. In view of the negative reanalysis by proximity to the index depression it cannot be said that recovery from the physical illness sustained remission of the mental illness. If our finding is valid, we can offer only the tentative hypothesis that the subgroup consisted of survivors whose successful outcome from physical illness had somehow mentally strengthened them against chronic or recurrent depression. The more likely explanation, however, is that it was a chance result from this cohort and of no general validity in predicting outcome.

Conclusions

A highly significant advantage of dothiepin over placebo was shown, those taking the drug being two and a half times more likely to remain well over the two-year trial. Depression in the elderly is a serious, chronic or recurrent condition, but in this study we have not examined why elderly people with major depression are so prone to relapse. One mechanism might be an age-related functional reduction in biogenic amine neurotransmission. If this is correct it would argue in favour of indefinite continuation of antidepressant therapy. The poor prognosis for major depression at younger ages (Lee & Murray, 1988) does not support the hypothesis, although such patients could differ from their age-matched peers in having a functional impairment of cerebral neurotransmission. In this case they, too, should continue therapy for much longer after recovery – an argument adduced by Lee & Murray in their final sentence.

A conservative interpretation of our results suggests that for those elderly patients who are considered suitable for tricyclic antidepressant drugs, alone, the medication should be continued for at least two years after recovery from an index episode. Many clinicians will conclude that our findings support the argument for recommending indefinite continuation of this treatment.

Acknowledgements

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References


**OADIG**


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**Correspondence**