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Out-patient Compliance With Antidepressant Medication

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A total of 89 depressed out-patients were randomly allocated to one of three groups: group A received one dose of antidepressant medication at night; group B received three doses of medication during the day; group C were allowed to choose either A or B above. Compliance with medication was assessed at three, six, nine and 12 weeks by interrogation and pill count; at the same time, depression and side-effects were rated. No overall significant difference was found between doctor-prescribed and patient-chosen regime, or between once-a-day and three-times-a-day dosage. However, compliance was significantly better in those patients who were allowed to choose, when they selected the three-times-a-day regime. There was a significant decline in compliance for all regimes over the 12 weeks. There was no evidence that better compliance produced a better therapeutic result, and possible reasons are given for this finding.

Inadequate compliance with medication regime is an important cause of ineffective pharmacotherapy (Porter, 1969; Sackett & Snow, 1979; Becker, 1985). Among the factors that have been put forward as affecting compliance is the number of doses to be taken per day (Gatley, 1968; Brand *et al*, 1977). Compliance is particularly low in patients with psychiatric disorders (Haynes, 1987) but the influence of the number of doses to be taken per day on compliance in such patients has been little studied. It was decided to examine this relationship in patients suffering from depression. There has been no research into the effectiveness of allowing patients to choose their own dosage regime, although for practical and theoretical reasons this might be expected to have benefits (Eiser, 1986), so patient choice was also investigated. In addition, it was possible to study the progress of compliance over 12 weeks and the relationship of compliance to therapeutic outcome.

Method

The sample comprised 89 consecutive patients attending a psychiatric out-patient clinic and fulfilling the following criteria: a diagnosis of primary or secondary depression according to the criteria of Feighner *et al* (1972), a score of at least 11 on the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960), no clinical evidence of dementia, at least average intelligence as judged by clinical interview, no retardation, and judged to be non-suicidal.

The study was approved by the District Ethical Committee. Consecutive patients were randomly allocated to each of the three groups, the number allocated to group C being double that of A and B.

Group A: One dose of amitriptyline 75 mg or mianserin 30 mg to be taken at night.

Group B: Three doses of amitriptyline 25 mg or mianserin 10 mg to be taken during the day.

Group C: Either A or B above as chosen by the patient. Those who chose A were designated Group Cn and those who chose B were designated Group Cd.

Mianserin was prescribed rather than amitriptyline if there was considered to be any risk of overdose, albeit without suicidal intent.

All patients received information about the drugs, including side-effects to be expected (Myers & Calvert, 1984). Patients were asked to take no *new* medication unless absolutely necessary. They were asked to return at three-weekly intervals for 12 weeks, and at each visit they received a supply of tablets to last until the next appointment. If, at the six-week point, the patient was judged not be improving, the medication could be increased to 150 mg amitriptyline or 60 mg mianserin per day. Starting patients on the lower dosage reflects current clinical practice.

At the initial visit, patients were rated according to the HRSD and the Asberg side-effects scale (Asberg *et al*, 1970). At subsequent visits, these scales were repeated and the following measures of compliance carried out:

(a) Interrogation using a standardised schedule to assess three separate aspects of compliance (see Appendix).
(b) Pill count. At each visit patients received a number of tablets in excess of those required, this number being known only to the pharmacy. Patients were instructed to bring back the bottle with any remaining tablets in it. These were counted and a compliance ratio (CR) calculated. Compliance was regarded as satisfactory if the CR lay between 80% and 120%.

The results were analysed to determine:

(a) The point-biserial correlation between the two measures of compliance
(b) Significant differences between the groups in respect of compliance using χ^2
(c) Differences in clinical response and compliance over time using repeated ANOVA.

Table 1
Age and sex distribution ($n = 89$)

	Sex		Age	
	m	f	Mean	s.d.
Group A	7 (37%)	12 (63%)	52.9[1]	12.2
Group B	8 (33%)	16 (67%)	45.0	11.0
Group Cn	8 (25%)	18 (75%)	40.0[1]	12.9
Group Cd	5 (23%)	17 (77%)	45.5	12.3

1. Group A v. Group Cn: $F = 4.1$, 3,85 d.f., $P < 0.01$.

Results

There were no differences between the groups in the proportion of males to females. However, patients prescribed once-daily treatment (group A) were significantly older than those who chose once-daily medication (group Cn).

The interview questions were combined so that an answer of 'no' to any of the questions indicated non-compliance. This measure correlates significantly with the pill count up to the nine-week point (Table 2) for those patients for whom both measures were available. In calculating the correlations, the pill count was transformed into a measure of compliance deviation, this being the absolute deviation of the compliance ratio from 100, irrespective of sign.

Answers to the compliance questionnaire revealed that:

(a) 20% of the total sample did not remember to take the tablets on every occasion that they were supposed to (Question 2)
(b) 18% failed to take the tablets for the full three weeks in at least one of the three-week periods (Question 4)
(c) 6% varied the number of tablets taken per dose (Question 1).

These results concealed more complex effects over the 12 weeks, in that:

(a) during the first three weeks, non-compliance was due more to stopping taking the medication – 23% of total sample according to Question 4
(b) in the middle periods of treatment non-compliance was more a matter of forgetting to take the tablets – 31% according to Question 2 – and was less affected by stopping the medication (11%)
(c) in the final three weeks, varying the dose had become relatively more frequent – 8%.

Table 2
Correlation between questionnaire and pill count measures of compliance

Assessment point	n	r
3 weeks	59	0.54**
6 weeks	40	0.33*
9 weeks	37	0.51**
12 weeks	28	−0.09

*$P = 0.02$, **$P = 0.001$.

The differences are statistically significant (χ^2 13.6, 6 d.f., $P < 0.05$).

Compliance, differing regimes and therapeutic response

These results were analysed on an 'intention to treat' basis (Friedman *et al*, 1982), such that non-compliers included those who had failed to keep their appointments and those who had to be withdrawn from treatment because of side-effects or changes of medication made by the general practitioner. Administrative problems meant that 13 patients were lost to the study, and these have been excluded from the analysis. Where the pill count was not obtained, compliance was assessed by the interview.

Table 3 shows the percentage of compliers with each regime overall and the pattern of compliance over the 12 weeks. There are significant differences between the regimes overall ($\chi^2 = 8.32$, 3 d.f, $P < 0.05$) with greatest compliance where patients chose to take one tablet three times a day (group Cd). Table 3 also shows a significant decline, for all four regimes, in the proportion of compliers over the four consecutive three-week periods ($\chi^2 = 17.55$, 3 d.f., $P < 0.001$). There were no significant differences between the regime groups in the drug prescribed or in the initial scores on the HRSD. The statistically significant difference in age between groups A and Cn (Table 1) is probably not of significance in the interpretation of these results because there was no overall indication that age was related to compliance ($r = -0.06$). The most compliant group also had the highest pre-treatment side-effect score.

Table 3 also shows the progress over 12 weeks of treatment, and demonstrates the considerable loss to therapy through withdrawal from treatment for medical reasons (usually side-effects) – 24% – and through defaulting from appointments – 32% – excluding those withdrawn for administrative reasons.

Table 3
Percentage compliance with each regime and progress of patients over 12 weeks

	3 weeks	6 weeks	9 weeks	12 weeks	Overall
Compliance: %					
A	68	63	50	40	56
B	74	55	45	30	52
Cn	58	43	43	39	58
Cd	82	76	58	50	68
Progress: no. of patients					
Continuing in treatment	79	53	41	34	
Defaulted	7	17	21	24	
Withdrawn for medical reasons	2	12	16	18	
Withdrawn for administrative reasons	1	7	11	13	
Total	89	89	89	89	

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Table 4
Average HRSD score at each visit in relation to subsequent compliance status

Weeks	Average HRSD score			
	Compliant	Non-compliant	Defaulted	Omitted for medical reasons
3	15.4	13.9	13.7	19.0*
6	11.4	11.2	11.0	14.3
9	9.3	10.3	8.5	9.5
12	7.6	8.5	4.0	15.0**

*$P<0.02$, **$P<0.01$.

Table 4 shows the average HRSD scores at each visit in relation to whether the patient *subsequently* complied or did not comply with medication, defaulted or was omitted for medical reasons. Patients who were compliant over the first three weeks of treatment were more depressed before the start of treatment than those who were non-compliant. At each visit, defaulters were more depressed than at their previous visit. Those omitted for medical reasons (side-effects or lack of improvement), usually had the highest HRSD scores of all at their previous visits. Table 4 shows that average levels of depression dropped progressively over the 12 weeks for compliers, non-compliers and defaulters (no significant difference).

Discussion

No significant differences in compliance were found between doctor-prescribed and patient-chosen regimes or between dosage once a day and three times a day. There was, however, an interaction effect resulting in significantly better compliance when the patient, being allowed to choose, chose the three-times-a-day regime (Table 3). This is contrary to the generally held belief that more frequent dosage leads to poorer compliance and suggests that there might be some personality characteristic that is common to the choice of a more frequent dosage regime and better compliance. One hypothesis is that such patients are of an obsessional type. This group, who chose three tablets a day and were the most compliant, also reported the most side-effects at the initial visit, adding some weight to this hypothesis.

Monitoring compliance at three-weekly intervals over 12 weeks allowed a number of observations to be made.

(a) There is satisfactory agreement between estimates of compliance by interrogation and by pill count for up to nine weeks from the start of treatment. That the absolute correlations are not higher can be attributed in part to the limited range of the answers to the questions ('yes'/'no') compared to the more differentiated pill-count scores.

(b) Variations in the type of non-compliance over the 12 weeks drew attention to what may be 'life-cycles' in the adjustment of patients taking a course of medication. At the beginning, their reaction to any doubts about taking the drug is to discontinue treatment; in the middle period they are more casual about the treatment and often forget; when they become longstanding users they become confident and start to vary the dosage themselves.

(c) There was significant decline in compliance, for all regimes, over the four three-week periods. It is a matter of some concern that so many patients were lost to therapy through defaulting from attendance or through being withdrawn on account of side-effects (3% by three weeks; 16% by six weeks; 21% by nine weeks; 24% by 12 weeks). These results have important implications, not only for therapy, but also for clinical trials of new antidepressants. Feinstein (1979) has shown how failure to take account of non-compliance can seriously distort the findings of a clinical trial. A search through the *British Journal of Psychiatry* from January 1977 to December 1988 by one of the present writers (EDM) revealed that of 12 out-patient, or predominantly out-patient, comparative trials of antidepressants, only 5 mentioned compliance and only one (Rowan *et al*, 1982) gave details of the method used to assess compliance and the results of that assessment.

(d) There is no evidence from this study that better compliance produced a better therapeutic result. This could be because those who were improving most tended to default from further treatment; it could also indicate, as suggested by Quitkin (1985), that the dosages prescribed were too low.

Overall, it would appear that all patients might be given the opportunity to choose their own dosage regime, because this makes no difference to the general outcome, and can increase compliance in a subgroup who choose to take medication three times a day. The results suggest that, both in out-patient clinical practice and out-patient clinical trials of antidepressants, considerably more attention should be paid to the detailed monitoring of compliance to give valid conclusions.

Appendix: Measurement of compliance by interrogation

Question 1: "When you took the tablets, did you take the proper number each time, or did you vary it at all?" (Record actual reply)

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Question 2: "Did you remember to take the tablets every time you were supposed to, or did you sometimes forget?" (Record actual reply)

Question 3: (To be asked if patient admits that he sometimes forgot, but does not say how often.) "How often would you say you forgot?"

Question 4: "Did you take the tablets for the full three weeks since I last saw you, or did you leave off taking them at all?" (Record actual reply and, if appropriate, question further to determine length of periods for which tablets were not taken).

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