Brit. J. Psychiat. (1979), **135**, 73–76

Amitriptyline: Comparison of Three Different Dosage Schedules in Neurotic Depression

By DOMENICO DE MAIO and ALESSANDRO LEVI-MINZI

SUMMARY Three groups of neurotic depressed patients were treated with amitriptyline, one group receiving the customary three daily doses, another a single dose in the morning, and the third a single dose at night. All three groups showed significant decrements of total scores on the Hamilton Scale for Depression and the Zung Self-Rating Depression Scale without significant differences. Patients taking the drug at night showed a lower incidence of side effects.

Introduction

The current trend in drug treatment for depression is increasingly in favour of once-a-day medication, as opposed to the traditional thrice daily schedule. This applies to amitriptyline in conventional tablet form (Ziegler *et al*, 1977a; Murphy, 1977) as well as in sustained-release dosage forms (Rifkin, 1972; Sims, 1972; Sedman, 1973; Murphy, 1977), and also to Dothiepin (Sharma, 1977) and to the fluphenazine-nortriptyline association (Brodie *et al*, 1976). Hollister (1976) recommends shifting to the single daily dose mode after the initial stage of dosage adjustment.

The purpose of this study was to compare the efficacy and side effects of amitriptyline given on different dose schedules to neurotic (plus some psychotic) depressed patients.

The choice of amitriptyline for patients with neurotic depression was dictated by our experience of the purely symptomatic effect of tricyclic antidepressants in general, relatively free from any important nosographic implications (De Maio *et al*, 1975; Simpson *et al*, 1976).

Material and Method

This trial was conducted in three groups of male in-patients with neurotic depression. Two groups were selected randomly for treatment with a single daily dose of amitriptyline to be taken at 9 am (Group A) or at 9 pm (Group B); the third group was not randomized and served as control, receiving the drug conventionally in three daily doses to be taken at 9 am, 2 pm and 8 pm (Group C).

Table I describes the three groups of patients: variance analysis of tabulated data yielded a 'not significant' F value, confirming that the three groups were homogeneous in regard to the involved parameters.

Each patient was evaluated clinically by the Hamilton Scale for Depression and the Zung Self-Rating Depression Scale before and after 20 days of treatment.

Amitriptyline dosages were adjusted individually: the range was 75 to 125 mg daily for Group A (morning medication) (mean doses 85.57 $\pm$ 10.48), 50 to 150 mg daily for Group B (evening medication) (mean doses 87.05 $\pm$ 11.49), and 75 to 150 mg daily for Group C (thrice daily medication) (mean doses 90.33 $\pm$ 21.29).

Statistical evaluation of therapeutic results obtained with the three dosage schedules used the total scores of the Hamilton and Zung scales. The therapeutic result of Group C (control) was compared statistically with that of the other two groups, there being no apparent bias for the type of patients represented in the groups or for the mode of treatment. The statistical method employed was variance analysis for a mixed factorial design plus

TABLE I

Three Groups of depressed men treated with amitriptyline

Group	Mean age	Diagnosis		Total scores before treatment	
		Neurotic depression	Psychotic depression	Hamilton scale (mean ± S.D.)	Zung scale (mean ± S.D.)
A	41 ± 12.47	10	3	25.26 ± 6.87	45.20 ± 12.17
B	42 ± 9.48	10	5	29.60 ± 5.96	53.33 ± 6.30
C	42.12 ± 11.82	13	2	26.56 ± 6.14	48.62 ± 8.55

covariance analysis. This afforded observation of different patterns of improvement during treatment, and brought out the importance of different severity of symptoms before treatment in the groups being compared.

Results

Improvement in the three groups is shown in Table II statistically.

TABLE II

Percentage decline in depression scores after amitriptyline for 20 days

Group	Rating scales	
	Hamilton	Zung
A	−33.5%	−25.6%
B	−44.6%	−21.7%
C	−44.4%	−19.6%

1. The difference between the three groups in terms of improvement, assessed by either rating scale, was not significant ($\chi^2 = 4.85$; $P > 0.05$).
2. There was a highly significant difference ($P < 0.01$) between times, reflecting major improvement of depression, in the results of both rating scales regardless of the model of amitriptyline administration in the three groups.
3. The time/treatment interaction was not significant ($P > 0.05$), indicating a similar pattern of improvement in the three groups.

Side effects

Side effects were reported by 11 of 15 patients of Group A (totalling 14 individual complaints), in 5 of 15 patients of Group B (5 complaints), and in 8 of 16 patients of Group C (9 complaints). The difference between groups is not significant ($\chi^2 = 4.85$; $P > 0.05$). A breakdown of reported side effects is given in Table III.

TABLE III

Side-effects volunteered in three Groups

Complaints	Group A (morning)	Group B (evening)	Group C (t.i.d.)
Somnolence	7	3	3
Asthenia	4	—	—
Insomnia	1	1	—
Dryness of mouth	1	—	3
Headache	—	1	—
Sweating	1	—	1
Dizziness	—	—	1
Constipation	—	—	1

Discussion

The results of this study corroborate earlier reports indicating no difference of therapeutic results whether amitriptyline is administered three times daily or just once a day (Braithwaite *et al*, 1974; Ziegler *et al*, 1977a). In this trial the total score of the Hamilton Scale for Depression elicited after treatment showed a somewhat greater per cent reduction compared to pre-treatment readings than did the total scores of

https://doi.org/10.1192/bjp.135.1.73 Published online by Cambridge University Press

the Zung ratings. This fact, which we reported at an earlier date for other tricyclic compounds (De Maio *et al*, 1975), apparently suggests the greater reluctance of self-administered test scores to move, compared to the more objective Hamilton Scale procedure.

Our experience further confirms that in patients receiving amitriptyline in single daily doses there is no statistically significant difference of clinical improvement whether the dose is taken in the morning or at night. As for the thrice daily dosage schedule, this finds little justification even on merely pharmacokinetic grounds (Ziegler *et al*, 1977a), as is the case also with nortriptyline (Ziegler *et al*, 1977b). Conversely, once-a-day dosing promotes patient compliance (Summers, 1977) and is apparently quite adequate to maintain steady and therapeutically valid blood levels of amitriptyline between consecutive doses (Braithwaite *et al*, 1974), the mean half-life of the drug being between 24 and 48 hours. Yet our own good results obtained with single daily (morning) doses of the non-tricyclic antidepressant, Nomifensine, strongly suggest a mechanism other than pharmacokinetic, since the last-named drug has a half-life of only 2 to 4 hours (Horne *et al*, 1976). One possible explanation, perhaps worth looking into, could be sought in the well-known circadian variations of bioamine concentrations in the brain and blood (Albrecht *et al*, 1956; Reis *et al*, 1968; Scheving *et al*, 1968; Sauerbier and von Mayersbach, 1976). In our three patient groups (two of which were randomized), therapeutic results did not seem dose-dependent; this is at variance with what Simpson *et al* (1976) reported in regard to imipramine in depressed neurotics. Indeed, our mean dosage was respectively 78.57 and 87.0 mg daily in the two once-a-day dosage groups, as opposed to fully 117.5 mg daily, or about 25 per cent more, in the thrice daily group.

If anything, certain differences were observed in terms of side effects, which were complained of by fewer patients in the evening dosage group (B). Obviously, an allowance must be made for the fact that somnolence, for instance, is a noticeable side effect in daytime, but very few patients would complain if it occurred during night hours.

References

Albrecht, P., Visscher, M. B., Bittner, J. J. & Halberg, F. (1956) Daily changes in 5-hydroxytryptamine concentration in mouse brain. *Proceedings Society for Experimental Biology and Medicine*, **92**, 703–6.

Braithwaite, R. A., Nakra, B. R. & Gaind, R. (1974) Steady-state plasma concentrations during single and multiple dosage schedules of amitriptyline. *Psychological Medicine*, **4**, 338–49.

Brodie, N. H., McGhie, R. L. & O'Hara, H. (1976) Once daily administration of plephenazine/nortriptyline preparation in the treatment of mixed anxiety/depressive states. *Current Medical Research Opinion*, **4**, 346–52.

De Maio, D., Caponeri, M. A., Mellado, C., Nielsen, P. N. & Scieghi, G. (1975) Scelta e modalità di uso dei farmaci anti-depressivi in rapporto alla valutazione clinico-psicometrica dei diversi quadri clinici. *Acta Neurologica*, **30**, 307–11.

Hollister, L. E. (1976) Clinical use of tricyclic antidepressants. *Diseases of the Nervous System*, **37**, 17–21.

Horne, I., Cavagna, F., Christ, O., Fehlhaber, H. W., Heptner, W., Kellner, H. M. & Rupp, W. (1976) Pharmakinetic und Metabolism von Nomifensin. In: *ALIVAL (Nomifensin): Symposium über Ergebnisse der experimentellen und klinischen Prüfung* (F. K. Schatten Verlag Publ.) Stuttgart (99–102).

Murphy, J. E. (1977) A trial of Triptizol, Lentizol and Ludiomil. *VI World Congress of Psychiatry (Honolulu)*, Abstract N. 1492.

Reis, D. J., Weinbren, M. & Corvelli, A. (1968) A circadian rhythm of norepinephrine regionally in cat brain: its relationship to environmental lighting and to regional diurnal variations in brain serotonin. *Journal of Pharmacology and Experimental Therapeutics*, **164**, 135–45.

Rifkin, A., Quitkin, F. & Klein, D. F. (1972) A single daily dose of a new form of amitriptyline in depressive illness. *British Journal of Psychiatry*, **121**, 457 (Correspondence).

Sauerbier, I. & von Mayersbach, H. (1976) Circadian variation of serotonin levels in human blood. *Hormones and Metabolism Research*, **8**, 157–8.

Scheving, L. E., Harrison, W. H., Gordon, P. & Pauly, J. E. (1968) Daily fluctuations (circadian and ultradian) in biogenic amines of the rat brain. *American Journal of Physiology*, **214**, 166–73.

Sedman, G. (1973) Trial of a sustained-release form of amitriptyline (Lentizol) in the treatment of depressive illness. *British Journal of Psychiatry*, **123**, 69–71.

Sharma, S. D. (1977) Evaluation of one-time nocturnal vis-à-vis thrice daily dosage schedule with Dothiepin (prothiadene) in depressed patients. *VI World Congress of Psychiatry (Honolulu)*, Abstract: *New Research*, 7.

SIMPSON, G. M., LEE, J. H., CUCULIC, Z. & KELLNER, R. (1976) Two dosages of imipramine in hospitalized endogenous and neurotic depressives. *Archives of General Psychiatry*, **33**, 1093–1102.

SIMS, A. C. P. (1972) Trial of a sustained-release form of amitriptyline in the treatment of depressive illness. *British Journal of Psychiatry*, **120**, 65–7.

SUMMERS, W. K. (1977) Encouraging compliance with antidepressant therapy. *Lancet*, *ii*, 35–6.

ZIEGLER, V. E., MEYER, D. A., ROSEN, S. H., KNESEVICH, J. W. & BIGGS, J. T. (1977a) Amitriptyline dosage schedule, sampling time and tricyclic plasma levels. *British Journal of Psychiatry*, **131**, 168–71.

—— KNESEVICH, J. W., WYLIE, L. T. & BIGGS, J. T. (1977b) Sampling time, dosage schedule and nortriptyline plasma levels. *Archives of General Psychiatry*, **34**, 613–15.

Domenico De Maio, M.D., *Professor of Psychiatry, Head of Service*,

Alessandro Levi-Minzi, M.D., *Psychiatrist, Neuropsychiatric Emergency Service 'R. Bozzi', Via Assietta 38, 20161 Milan, Italy*

(*Received 8 March 1978*)