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Is Diazepam an Antidepressant?

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In double-blind sequential study, diazepam was compared with the proven antidepressant moclobemide, in patients with atypical depression. Both agents significantly improved depression ratings over eight weeks of treatment. Diazepam was a significantly better antidepressant than moclobemide at four weeks, although not at eight weeks. All patients ceased diazepam within one year and none reported withdrawal reactions. These data suggest the need to reconsider that benzodiazepines may be antidepressants and to study their possible antidepressant actions.

Benzodiazepines (BZDs) were not regarded as having antidepressant properties by the Committee on the Review of Medicines (1980). This opinion is supported by research studies, notably the 1980 Medical Research Council study (Johnstone *et al*, 1980) and the Lipman *et al* (1986) and Kahn *et al* (1986) comparisons of imipramine and chlordiazepoxide in depressive and anxiety disorders. The review of studies of benzodiazepines in depressive illness by Johnson (1983) reaffirmed their ineffectiveness in depression, but added that data claiming benzodiazepines can cause depression was anecdotal and without substantial proof.

The condition endogenous, endomorphogenic or major depression with melancholia forms a subtype of depression which is likely to respond to tricyclic antidepressants (TCAs) and electroconvulsive therapy (Klein, 1974; Stern *et al*, 1980). The report of Liebowitz *et al* (1984) showing the superiority of phenelzine over imipramine in atypical depression suggested a subtype of depression responsive to monoamine oxidase inhibitors (MAOIs). It was decided to test the efficacy of the reversible, MAO-A-selective antidepressant moclobemide (p-chloro-N-(2-morpholinoethyl)benzamide, Roche) in atypical depression. Moclobemide has been shown to be an effective antidepressant in both open and double-blind placebo-controlled studies of depressed patients (Stefanis *et al*, 1982; Cassachia *et al*, 1984). It has comparable antidepressant activity to amitriptyline in endogenous and reactive depression (Norman *et al*, 1985), to clomipramine in patients with chronic, episodic, or atypical depression (Larsen *et al*, 1984), and to desipramine in unipolar, bipolar and other depressions (Stefanis *et al*, 1984).

In studying a new antidepressant, it is desirable to compare it with placebo. There are, however, arguments that it is unethical to have patients on inactive preparations for prolonged periods, with the risk of increased morbidity and mortality, when there are effective antidepressants. This problem is commonly resolved by comparing the new antidepressant with an established antidepressant. There may be flaws in such comparisons. The proportion of patients not responding to tricyclics can be 30% (Medical Research Council, 1965) to 40% (Prien *et al*, 1984). Data shows that tricyclic antidepressants were not superior to placebo in 35% (Morris & Beck, 1974) and 41% of studies (Thomson, 1982). Furthermore, inactive placebo is associated with significant improvement in 30% (Morris & Beck, 1974) to 50% (Medical Research Council, 1965) of depressed patients. One must determine comparison doses and dose schedules of antidepressants, and consider that unique side-effects of one medication can confound attempts to achieve blindness in assessments by astute clinicians.

In the assessment of moclobemide in atypical depression it was decided to compare it with diazepam, an agent stated to have no intrinsic antidepressant activity. Diazepam could relieve some anxiety in these patients and as a consequence relieve some distress for the minimum four weeks needed to determine antidepressant efficacy (Baldessarini, 1985), and, it was hoped, for up to eight weeks. Diazepam was regarded as an inactive placebo for antidepressant activity. A closed repeated significance test (RST) sequential design was used (Armitage, 1975), considering antidepressant score alone. This design would stop the trial as soon as one agent proved significantly better than the other or when a no-significant-difference boundary was reached. This design was a compromise allowing for scientific and ethical considerations.

Method

Patients

In-patients and out-patients at the Royal Melbourne Hospital who met the following criteria for atypical depression were considered for the study:

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(a) Research Diagnostic Criteria (Spitzer *et al*, 1978) for major, minor, or intermittent depression
(b) maintained mood reactivity while depressed
(c) two or more of the following: increased appetite or weight gain while depressed, oversleeping or spending more time in bed while depressed, severe fatigue creating a sensation of leaden paralysis or extreme heaviness of arms or legs while depressed; and rejection sensitivity as a trait during adulthood (Liebowitz *et al*, 1984).

Patients were aged over 17 years, had been symptomatic for a minimum of one month, were medically stable, and scored over 17 on the 17-item Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960) after at least seven days without drugs. Patients meeting the above criteria were admitted to the study after giving informed consent according to the guidelines of the National Health and Medical Research Council (1983).

Study design

A double-blind sequential trial with paired patients was carried out. Patients were paired according to sex, age (±5 years), and HRSD (±5 points), and allocated to treatment by one of the authors (KM), who was not involved in the clinical assessments. Those patients who were not matched immediately were allocated to treatment on a random basis and matched with the next suitable patient. All patients followed dietary and medication restrictions as for standard irreversible non-selective MAOI antidepressants.

Assessments

Depression was assessed using the observer-rated HRSD and the subject-rated Carroll Depression Rating Scale (CDRS; Carroll *et al*, 1981). Each patient was classed by the Newcastle Scale (Holden, 1983) as endogenously depressed (score 6 or more) or neurotically depressed (score <6). An open-ended side-effects check-list was completed at each assessment. Only emergent side-effects, not present at baseline, were included in the final analysis. Ratings were completed at baseline and after one, four and eight weeks of treatment.

Medication

Following a drug-free week, an initial total daily dose of 15 mg of diazepam or 150 mg of moclobemide was started with equally divided doses three times a day. A double-dummy technique was used, each patient taking active tablets of one medication and inactive placebos made to look like the other medication. The daily dose of medication could be increased, as tolerated, on clinician judgement up to maximum daily doses of 45 mg of diazepam or 450 mg of moclobemide. The 45 mg maximum dose of diazepam was to relieve anxiety in the severely agitated, although it was expected that few would take more than 20–30 mg daily. Nitrazepam (5–10 mg) was permitted as a hypnotic for all patients as required.

Analysis of results

The dimensions of the RST sequential plan were set as $\theta = 0.80$, power 0.95 and overall significance 0.05. Preferences for either drug were based on changes in the HRSD scores, a decrease of 8 points being considered a clinical improvement (Norman *et al*, 1985). Ties were not recorded on the plan, and separate analyses were done at weeks 4 and 8. In addition, the two groups were compared at baseline and weeks 1, 4 and 8 using Student's *t*-tests. The finding of diazepam's antidepressant activity resulted in an analysis, not in the initial design, of specific items of the HRSD to try to preclude anti-anxiety effects being regarded as antidepressant effects.

Results

Sequential analysis

Forty patients with atypical depression entered the study and 31 completed four weeks' treatment. Of these, 28 could be paired for the sequential analysis (including three pairs with age differences of 6, 7 and 10 years). When the week 4 HRSD plan reached a significance boundary, intake for the study ceased as designed, the result showing that diazepam was significantly better (Fig. 1). The results for the 14 pairs included two ties, eleven wins for diazepam and one win for moclobemide. By week 8, the number of tied results had increased from two to seven, and thus the plan did not reach any boundary (Fig. 2).

Comparison of drug groups

For the 14 pairs of patients who completed four weeks' treatment, there were no significant differences at baseline between treatment groups in sex, mean age, HRSD, CDRS,

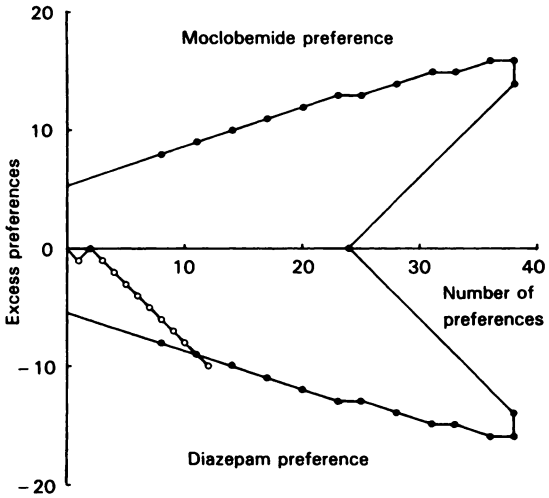


FIG. 1 Sequential analysis of diazepam and moclobemide after four weeks of treatment.

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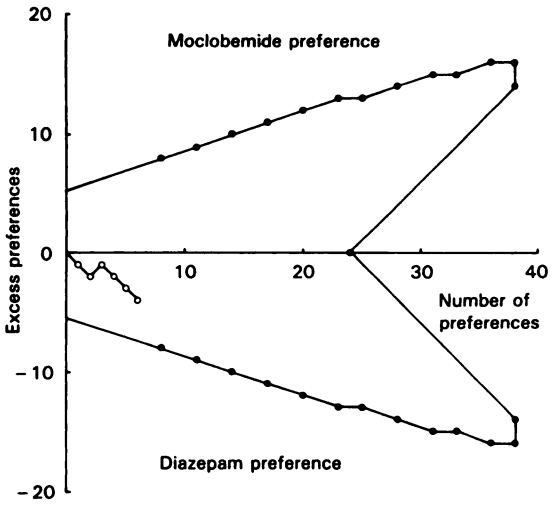


FIG. 2 Sequential analysis of diazepam and moclobemide after eight weeks of treatment.

Newcastle Scale score, or side-effects ratings. There were 14 females and 14 males, with an age range of 21–66 years. All patients met the Newcastle Scale criteria for neurotic depression, the mean score for patients in the diazepam group being 1.0 (s.d. 1.8) and for those in the moclobemide group 1.2 (s.d. 2.0). Results on parameters other than the HRSD and CDRS are reported elsewhere (Tiller *et al*, 1989).

There was a significant decrease in the HRSD and CDRS ratings for the diazepam group from baseline to weeks 1 and 4, and for the moclobemide group from baseline to week 4 (Table I).

The diazepam group had significantly lower HRSD ratings at both weeks 1 and 4 than the moclobemide group, and had a significantly lower CDRS rating at week 1 (Table I).

A separate analysis was made of the ten pairs who completed eight weeks' treatment. Results at weeks 1 and 4 were similar to those obtained for the 14 pairs described above. For both treatment groups, significant decreases in HRSD and CDRS ratings were observed from baseline to week 8 (Table II). At week 8, no significant difference in HRSD scores was found between the two treatment groups, but the CDRS score for the diazepam group was significantly lower than that for the moclobemide group.

TABLE I
HRSD and CDRS scores for the 28 paired patients completing four weeks of treatment

Agent and week		*Diazepam*			*Moclobemide*			*t*	P
		Mean	*s.d.*	*95% CI*	*Mean*	*s.d.*	*95% CI*		
HRSD	0	22.9	4.5	20.3–25.6	23.1	4.0	20.8–25.5	0.25	0.806
	1	13.1***	6.6	9.4–16.9	23.0	5.1	20.1–25.9	4.45	0.001
	4	9.1***	6.8	5.2–13.1	16.1**	6.3	12.4–19.7	2.82	0.014
CDRS	0	25.8	6.1	22.3–29.3	27.4	5.0	24.5–30.3	0.72	0.487
	1	15.1**	9.7	9.6–20.7	27.9	6.8	24.0–31.3	3.30	0.006
	4	14.4*	12.5	7.2–21.7	21.9*	9.8	16.2–27.5	1.63	0.126

1. CI = confidence interval.
*$P<0.05$, **$P<0.005$, ***$P<001$ for change from baseline (1-tailed).

TABLE II
HRSD and CDRS scores for the 20 paired patients completing eight weeks of treatment

Agent and week		*Diazepam*			*Moclobemide*			*t*	P
		Mean	*s.d.*	*95% CI*	*Mean*	*s.d.*	*95% CI*		
HRSD	0	22.1	4.7	18.7–25.5	23.0	4.4	19.8–26.2	0.83	0.430
	1	12.0***	5.9	7.8–16.2	23.2	5.9	19.0–27.4	4.83	0.001
	4	6.3***	2.3	4.6–8.0	14.6***	5.9	10.4–18.8	4.64	0.001
	8	6.1***	3.5	3.6–8.6	11.3***	6.1	6.9–15.7	2.17	0.058
CDRS	0	25.4	6.4	20.8–30.0	27.9	5.1	24.2–31.6	1.06	0.316
	1	12.2**	7.0	7.2–17.2	28.0	6.9	23.1–32.9	4.35	0.002
	4	9.1***	7.7	3.6–14.6	21.3**	9.8	14.3–28.3	2.93	0.017
	8	9.0***	7.1	3.9–14.1	18.6**	11.0	10.7–26.5	2.39	0.040

**$P<0.005$, ***$P<0.001$ for change from baseline (1-tailed).

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TABLE III

HRSD (5 items) for the 20 paired patients completing eight weeks of treatment: the items were depressed mood, guilt, suicidal thoughts, retardation, and loss of libido

	Baseline		*Week 4*		*Week 8*		*Difference from baseline*
	Mean	*s.d.*	*Mean*	*s.d.*	*Mean*	*s.d.*	
Diazepam	4.6	1.7	2.1	1.3	1.6	1.5	$P<0.001$
Moclobemide	6.1	2.0	4.4	2.3	3.0	2.4	$P<0.001$
Difference between groups	NS		$P=0.025$		NS		—

TABLE IV

HRSD item 1 (depressed mood) for the 20 paired patients completing eight weeks of treatment

	Baseline		*Week 4*		*Week 8*		*Difference from baseline*
	Mean	*s.d.*	*Mean*	*s.d.*	*Mean*	*s.d.*	
Diazepam	2.3	0.6	1.1	0.8	0.9	1.0	$P<0.01$
Moclobemide	2.6	0.5	2.1	0.8	1.3	0.9	$P<0.02$
Difference between groups	NS		$P=0.002$		NS		—

Analysis of five HRSD items clinically regarded as most specific to depression and not anxiety also showed significant reductions with diazepam and moclobemide (Table III). These items were depressed mood, guilt, suicidal thoughts, retardation, and loss of libido.

A further analysis was effected considering only the item 'depressed mood' from the HRSD: this also showed significant reductions with diazepam at both weeks 4 and 8 (Table IV).

Dose

Medications were not increased after a clinical response was apparent. Though the maximum allowed diazepam dose was 45 mg, the mean dose used was 32 mg (s.d. 12 mg). For moclobemide the mean dose was 450 mg, as all had reached maximal dose on study criteria before a response was apparent.

Hypnotics

The study patients were not using benzodiazepines at entry to the study apart from two using hypnotics, one temazepam (20 mg at night) and the other nitrazepam (10 mg at night). The numbers of patients using hypnotics at weeks 4 and 8 respectively in the diazepam group were one and none, and in the moclobemide group seven and seven, a significant difference in hypnotic use. Over the whole study, only two of fourteen in the diazepam group used hypnotics, compared with ten of fourteen in the moclobemide group. The maximum hypnotic dose was used in every case. There were no significant differences in depression or anxiety ratings at baseline between those who subsequently used hypnotics and those who did not. At the week 8 assessment of the moclobemide group there were no significant differences in depression or anxiety ratings between the seven on hypnotics and the three on no hypnotics, but the trend was for slightly higher depression and anxiety scores in the group on hypnotics.

Side-effects

Both drugs were well tolerated and side-effects were minimal. The number of reported side-effects decreased during the study for both drugs, as reported in Tiller *et al* (1989). All patients ceased medication within 12 months. Medication was generally ceased by slow reduction, and no patients reported withdrawal reactions with either drug.

Drop-outs

There were no significant differences in age or baseline ratings between the nine drop-outs and the 28 patients completing four weeks treatment. Eight drop-outs completed at least one week of treatment. At week 1 their mean HRSD score (23) was significantly higher than for the 28 completers (18, $P=0.03$). Seven of the eight were on moclobemide, and all but one dropped out before week 4. No drop-out or exclusion was related to adverse medication effects. Seven were due to non-cooperation or non-attendance, one patient had a compensation case which was concealed at entry to the study, and one patient was excluded due to missing data.

Discussion

The results show that diazepam reduced depressive symptoms. This finding was unexpected both in its occurrence and persistence. It was expected that the anxiolytic effects of diazepam would reduce HRSD anxiety items, but not the five selected core depression items nor the item 'depressed mood' alone. These

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results differ from those of Cassano *et al* (1985), who reported differences between TCAs and BZDs, the former showing significantly greater improvement with depressed mood and the latter with agitation. The authors reported overlap in action for 30% of the subjects in the groups treated with BZDs ($n = 178$) or TCAs ($n = 209$).

The rapid relief of depressive symptoms (within one week) by diazepam was unexpected. Antidepressants can take six weeks to show effectiveness, although improvement may be apparent as early as the first week of treatment (Katz *et al*, 1987). It was expected that any initial benefit of diazepam would be lost with persisting depression (Lipman *et al*, 1986). That was not observed in this study, with HRSD scores falling from baseline to week 8 in both treatment groups.

The rapid effect of diazepam, without the time needed for receptor down-regulation as with other antidepressants, suggests other processes in its mode of action. The elevated levels of the endogenous neuropeptide diazepam-binding inhibitor (DBI) in depression (Barbaccia *et al*, 1986) may represent a functional disinhibition of GABAergic neurotransmission associated with depression. Bartholini *et al* (1986) refer to the direct and indirect evidence for decreased GABAergic function in the pathophysiology of depression, and the efficacy of both direct- and indirect-acting GABAmimetic drugs in treating depression. Diazepam–DBI interactions and their effects on GABAergic transmission may explain why in certain instances benzodiazepines have antidepressant actions, and why the onset of action of diazepam in this study was more rapid and independent of post-synaptic down-regulation.

Hypnotic use was significantly different between the two treatment groups, consistent with the sedative effects of diazepam and the tendency of MAOIs to interfere with sleep. The possibility that apparent antidepressant response, or rapidity of response, in the diazepam group was caused by diazepam blocking benzodiazepine withdrawal symptoms was unlikely, given the limited prior use of benzodiazepines and the fact that the majority of the moclobomide group used a benzodiazepine hypnotic during the study. In the moclobemide group there were no significant differences in response between those taking and those not taking a hypnotic. The trend for slightly higher depression and anxiety scores in the group on hypnotics rendered it unlikely that response in the moclobemide group could be attributed to the hypnotics' actions alone.

Drop-outs were fewer in the diazepam group than the moclobemide group, contrasting with the higher diazepam drop-out rate in the Russell *et al* (1978) comparison with mianserin. Lower early mianserin drop-out may result from mianserin's acute sedative action, which is not present with moclobemide. Most moclobemide drop-out occurred early in treatment, before antidepressant activity was likely to be manifest. Drop-outs were lost to follow-up, with unknown outcomes.

The results showed that both agents were well tolerated, with few side-effects. Sedation was not prominent as an adverse effect with either drug, although patients treated with diazepam had fewer sleep problems and used fewer hypnotics. The gradual increase of drug dosage may account for the lack of sedative side-effects.

Diazepam has been shown previously to be effective in anxious depression (Raskin *et al*, 1974). The Raskin *et al* (1974) study was the only one out of 20 double-blind controlled studies reviewed by Schatzberg & Cole (1978) to show benzodiazepine superiority over an antidepressant in treating depression. Benzodiazepines were equal to antidepressants in nine studies and inferior in ten. Schatzberg & Cole (1978) considered benzodiazepine doses were adequate, but the mean Raskin *et al* (1974) dose (30 mg diazepam) was the highest in their review, and in the present study both maximum and mean doses were higher than in any of their reviewed studies.

Data on the effectiveness of alprazolam as an antidepressant suggests that dose may be of importance. Four such studies (Rickels *et al*, 1982, 1985; Feighner *et al*, 1983; Imlah, 1985) used maximum daily doses of alprazolam of 4.5 mg, 4.5 mg, 4.5 mg, and 3 mg. Considering dose equivalences of 10 mg diazepam to 1 mg of alprazolam (Fabre & McLendon, 1979; Aden & Thein, 1980), the effective doses of alprazolam are similar to those of diazepam in this study. Thus, alprazolam may not have unique antidepressant properties: it is possible that other benzodiazepines, in adequate doses, may be antidepressants.

Diagnosis remains controversial. Anxiety is a common feature of depressive illness (DSM–III) (American Psychiatric Association, 1980), and despite careful study there is still dispute as to whether anxiety and depression are discrete entities (Klerman, 1980) or form overlapping elements in a continuum (Roth *et al*, 1972, Prusoff & Klerman, 1974). This is reflected in different clinicians' concepts of the relationship between anxiety and depression (Goldberg & Simpson, 1985). The use of the term neurosis to describe patients with an admixture of anxiety, depressive and other symptoms has been reconsidered (*British Medical Journal*, 1986).

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Akiskal's (1984) paper on the interface of chronic depression with anxiety considered the role of atypical depression and anxious depression as subgroups of depression, while in the general-practice study reported by Goldberg & Simpson (1985) all the patients with depression had anxiety symptoms. It has been suggested that patients with depression and predominant anxiety should be regarded as having an anxiety disorder, not a depression, and be treated with a benzodiazepine (Schatzberg & Cole, 1978). There may need to be a pragmatic decision to divide depressions into those preferentially responsive to tricyclics and other antidepressants, and those responsive to benzodiazepines.

Davis (1985) suggested that the best procedure to test the antianxiety–antidepressant dimension is to determine if benzodiazepines are effective in a group of 'purely depressed patients'. This procedure ignores the possible effectiveness of benzodiazepines in atypical depression. If benzodiazepines in adequate dosage are effective antidepressants in atypical depression, then it would seem inappropriate to use tricyclics, newer antidepressants or MAOIs as the treatments of first choice, when benzodiazepines have greater safety margins, are better tolerated and have less potential toxicity. The rapid onset of benzodiazepine antidepressant activity could minimise patients dropping out of treatment.

There is the possibility of dependency with higher-dose BZDs for the time needed in these patients. This risk of dependency on benzodiazepines and the importance of patient selection has recently been emphasised (Tyrer, 1989). The studies reported by Higgitt *et al* (1985) and Pecknold *et al* (1988) show that gradual reduction of benzo-diazepine dosage avoids or minimises withdrawal reactions, and none occurred in this study.

Improvements observed may not have resulted from medication but represented spontaneous recovery or the non-specific effects of study interventions. Fairchild *et al* (1986) suggested that certain depressions respond to placebo alone. In this study the patients had persistent disorders for at least a month before entry, and remained with a HRSD >17 after at least one week before treatment started, which was thought to minimise the chance of spontaneous recovery.

These results highlight problems in studying drugs. Despite ethical concerns, should one test new drugs and/or new uses by comparisons with an inert agent, rather than an existing treatment, or with a therapeutically active agent presumed ineffective for the condition or symptoms under study?

Benzodiazepines, in adequate doses as shown, may be safe, well-tolerated antidepressants for atypical depression, and more appropriate than conventional antidepressants. This antidepressant activity needs further study, and despite ethical concerns there is a case for a placebo-controlled study. The results also raise the question: are benzodiazepines in adequate doses effective in other types of depression?

References

ADEN, G. C. & THEIN, S. G. (1980) Alprazolam compared to diazepam and placebo in the treatment of anxiety. *Journal of Clinical Psychiatry*, **41**, 245–248.

AKISKAL, H. S. (1984) The interface of chronic depression with personality and anxiety disorders. *Psychopharmacology Bulletin*, **20**, 393–398.

AMERICAN PSYCHIATRIC ASSOCIATION (1980) *Diagnostic and Statistical Manual of Mental Disorders* (3rd edn). Washington, DC: APA.

ARMITAGE, P. (1975) *Sequential Medical Trials*. Oxford: Blackwell Scientific Publications.

BALDESSARINI, R. J. (1985) Drugs and the treatment of psychiatric disorders. In *The Pharmacological Basis of Therapeutics* (eds A. Goodman Gillman, L. S. Goodman, T. W. Rand & F. Muriad). New York: Macmillan.

BARBACCIA, M. L., COSTA, E., FERRERO, P., *et al* (1986) Diazepam-binding inhibitor. *Archives of General Psychiatry*, **43**, 1143–1147.

BARTHOLINI, G., LLOYD, K. G. & MORSELLI, P. L. (eds) (1986) *GABA and Mood Disorders, Experimental and Clinical Research, LERS*, vol. 4. New York: Raven Press.

BRITISH MEDICAL JOURNAL (1986) Neurosis: another tough old word (Editorial). *British Medical Journal*, **292**, 972–973.

CARROLL, B. J., FEINBERG, M., SMOUSE, P. E., *et al* (1981) The Carroll Rating Scale for Depression: development, reliability and validation. *British Journal of Psychiatry*, **138**, 194–200.

CASSACHIA, M., CAROLEI, A., BARBA, C., *et al* (1984) A placebo-controlled study of the antidepressant activity of moclobemide, a new MAOA-inhibitor. *Pharmacopsychiatry*, **17**, 122–125.

CASSANO, G. B., CONTI, L., PLACIDI, G. F., *et al* (1985) The overlap of the spectrum of antianxiety and antidepressant drugs: a multivariate approach. In *Psychiatry – Vol. 1. Clinical Psychopathology: Nomenclature and Classification* (ed. P. Pichot). New York: Plenum Press.

COMMITTEE ON THE REVIEW OF MEDICINES (1980) Systematic review of the benzodiazepines. *British Medical Journal*, **280**, 910–912.

DAVIS, J. M. (1985) Antidepressant drugs. In *Comprehensive Textbook of Psychiatry IV* (eds H. I. Kaplan & B. J. Sadock). Baltimore: Williams & Wilkins.

FABRE, L. F. & MCLENDON, D. M. (1979) A double blind study comparing the efficacy and safety of alprazolam with diazepam and placebo in anxious outpatients. *Current Therapeutics Research*, **25**, 519–526.

FAIRCHILD, C. J., RUSH, J., VASAVADA, N., *et al* (1986) Which depressions respond to placebo? *Psychiatry Research*, **18**, 217–226.

FEIGHNER, J. P., ADEN, G. C., FABRE, L. F., *et al* (1983) Comparison of alprazolam, imipramine, and placebo in the treatment of depression. *Journal of the American Medical Association*, **249**, 3057–3064.

GOLDBERG, D. & SIMPSON, N. (1985) The diagnosis of anxiety in primary care settings. In *Drug Treatment of Neurotic Disorders: Focus on Alprazolam* (eds M. H. Lader & H. C. Davies). Edinburgh: Churchill Livingston.

HAMILTON, M. (1960) A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry*, **23**, 56–62.

HIGGITT, A. C., LADER, M. H. & FONAGY, P. (1985) Clinical management of benzodiazepine dependence. *British Medical Journal*, **291**, 688–690.

HOLDEN, N. L. (1983) Depression and the Newcastle scale: their relationship to the dexamethasone suppression test. *British Journal of Psychiatry*, **142**, 505–507.

https://doi.org/10.1192/bjp.155.4.483 Published online by Cambridge University Press

IMLAH, N. W. (1985) An evaluation of alprazolam in the treatment of reactive or neurotic (secondary) depression. *British Journal of Psychiatry*, **146**, 515–519.

JOHNSON, D. A. W. (1983) Benzodiazepines in depression. In *Benzodiazepines Divided* (ed. M. R. Trimble), pp. 247–259. Chichester: Wiley.

JOHNSTONE, E. C., CUNNINGHAM OWENS, D. G., FRITH, C. D., *et al* (1980) Neurotic illness and its response to anxiolytic and antidepressant treatment. *Psychological Medicine*, **10**, 321–328.

KAHN, R. J., MCNAIR, D. M., LIPMAN, R. S. *et al* (1986) Imipramine and chlordiazepoxide in depressive and anxiety disorders – II. *Archives of General Psychiatry*, **43**, 79–85.

KATZ, M. M., KOSLOW, S. H., MAAS, J. W., *et al* (1987) The timing, specificity and clinical prediction of tricyclic drug effects in depression. *Psychological Medicine*, **17**, 297–309.

KLEIN, D. F. (1974) Endomorphogenic depression. *Archives of General Psychiatry*, **36**, 447–454.

KLERMAN, G. L. (1980) Anxiety and depression. In *Handbook of Studies on Anxiety* (eds G. D. Burrows & B. Davies). Amsterdam: Elsevier/North-Holland Biomedical Press.

LARSEN, J. K., HOLM, P. & MIKKELSON, P. L. (1984) Moclobemide and clomipramine in the treatment of depression. *Acta Psychiatrica Scandanavica*, **70**, 254–260.

LIEBOWITZ, M. R., QUITKIN, F. M., STEWART, J. W., *et al* (1984) Phenelzine vs. imipramine in atypical depression. *Archives of General Psychiatry*, **41**, 669–677.

LIPMAN, R. S., COVI, L., RICKELS, K., *et al* (1986) Imipramine and chlordiazepoxide in depressive and anxiety disorders – I. *Archives of General Psychiatry*, **43**, 68–77.

MEDICAL RESEARCH COUNCIL (1965) Clinical trial of the treatment of depressive illness. *British Medical Journal*, *i*, 881–886.

MORRIS, J. & BECK, A. (1974) The efficacy of antidepressant drugs. *Archives of General Psychiatry*, **30**, 667–674.

NATIONAL HEALTH AND MEDICAL RESEARCH COUNCIL (1983) *Statement on Human Experimentation and Supplementary Notes*. Canberra: NH&MRC.

NORMAN, T. R., AMES, D., BURROWS, G. D., *et al* (1985) A controlled study of a specific MAO-A reversible inhibitor (Ro 11–1163) and amitriptyline in depressive illness. *Journal of Affective Disorders*, **8**, 29–35.

PECKNOLD, J. C., SWINSON, R. P., KUCH, K., *et al* (1988) Alprazolam in panic disorder and agoraphobia: results from a multicentre trial – III. Discontinuation effects. *Archives of General Psychiatry*, **45**, 429–436.

PRIEN, R. F. & LEVINE, J. (1984) Research and methodological issues for evaluating the therapeutic effectiveness of antidepressant drugs. *Psychopharmacology Bulletin*, **20**, 250–257.

PRUSOFF, B. & KLERMAN, G. (1974) Differentiating depressed from anxious neurotic outpatients. *Archives of General Psychiatry*, **30**, 302–308.

RASKIN, A., SCHULTERBRANDT, J. G., REATIG, N., *et al* (1974) Depression subtypes and response to phenelzine, diazepam, and a placebo. *Archives of General Psychiatry*, **30**, 66–75.

RICKELS, K., COHEN, D. O., CSANALOSI, I., *et al* (1982) Alprazolam and imipramine in depressed outpatients: a controlled study. *Current Therapeutic Research*, **32**, 157–164.

——, FEIGHNER, J. P. & SMITH, W. T. (1985) Alprazolam, amitriptyline, doxepin, and placebo in the treatment of depression. *Archives of General Psychiatry*, **42**, 134–141.

ROTH, M., GURNEY, C., GARSIDE, R., *et al* (1972) Studies in the classification of affective disorders. The relationship between anxiety states and depressive illness. *British Journal of Psychiatry*, **121**, 147–167.

RUSSELL, G. F. M., NIAZ, U., WAKELING, A., *et al* (1978) Comparative double-blind trial of mianserin hydrochloride (Organon GB94) and diazepam in patients with depressive illness. *British Journal of Clinical Pharmacology*, **5**, 57S–65S.

SCHATZBERG, A. F. & COLE, J. O. (1978) Benzodiazepines in depressive disorders. *Archives of General Psychiatry*, **35**, 1359–1365.

SPITZER, R. L., ENDICOTT, J. & ROBINS, E. (1978) Research diagnostic criteria: rationale and reliability. *Archives of General Psychiatry*, **35**, 773–782.

STEFANIS, C. N., ALEVIZOS, B. & PAPADIMITRIOU, G. N. (1982) Antidepressant effect of Ro 11–1163, a new MAO inhibitor. *International Pharmacopsychiatry*, **17**, 43–48.

——, —— & —— (1984) Controlled clinical study of moclobemide (Ro 11–1163), a new MAO inhibitor and desipramine in depressive patients. In *Monoamine Oxidase and Disease: Prospects for Therapy with Reversible Inhibitors* (eds P. Dostert, M. S. Benedetti & K. F. Tipton). London: Academic Press.

STERN, S. L., RUSH, A. J. & MENDELS, J. (1980) Towards rational pharmacotherapy of depression. *American Journal of Psychiatry*, **137**, 545–552.

THOMSON, R. (1982) Side effects and placebo amplification. *British Journal of Psychiatry*, **140**, 64–68.

TILLER, J., SCHWEITZER, I., MAGUIRE, K., *et al* (1989) A sequential double blind controlled study of moclobemide and diazepam in patients with atypical depression. *Journal of Affective Disorders* (in press).

TYRER, P. (1989) Risks of dependence on benzodiazepine drugs: the importance of patient selection. *British Medical Journal*, **298**, 102–104.

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