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Amitriptyline and Amitriptyline-with-Perphenazine in Depression—A Retrospective Study

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The object of this paper is to assess, in retrospect, the relative effectiveness of amitriptyline ('Triptizol') and amitriptyline with perphenazine ('Triptafen') in the treatment of depressed patients.

Amitriptyline has been shown to be more effective than imipramine (Hordern *et al.*, 1964) and safer than the monoamine oxidase inhibitors which can give rise to many serious side-effects (*Lancet*, 1964, *i*, 506). Although amitriptyline has a proved tranquillizing effect (Browne *et al.*, 1963), we found this to be insufficient in some patients, and therefore administered a tranquillizer concurrently. This need is not really surprising, since many depressed patients have symptoms of agitation, anxiety and tension (Ayd, 1961; Coffee, 1964). When a combination of amitriptyline and perphenazine became available, its use was adopted. It may be noted in this connection that perphenazine has itself been shown to have some antidepressant activity (Hinton, 1959). The preparation we used, containing in each tablet 25 mg. of amitriptyline hydrochloride and 2 mg. of perphenazine, has already been reported upon by Mattey (1963), Smith (1963), and Martins (1966).

Introduction

The Psychiatric Unit attached to Burnley General Hospital serves an immediate population of approximately 200,000. About 98 per cent. of the mental illness arising in this population is treated at the Unit. In addition, about 22 per cent. of the cases treated come from outside the catchment area (Downham, 1965).

All new patients are first seen as out-patients, if clinically possible, when a decision and plan for treatment is made. For severe depressions, as a rule treated as in-patients, electro-convulsive therapy is the treatment of choice. For milder depressions, drug therapy is used first.

As a general policy, drugs are used at minimal dosage to produce an effective response with minimal side-effects as quickly as possible. The response is evaluated rapidly and a decision made as to the value of the drug and indication for its continuation. Dosage times are adapted to specific patients' needs. The side-effects of the drug and their significance are always explained to the patient and his co-operation with the drug requested. The patient is also informed initially that it is not expected that he should remain on the drug for an unlimited period of time, but only so long as the therapeutic effect continues to be achieved and is necessary. The aim is to stop all drugs as soon as clinically practicable. So far as possible, every patient is expected to continue at work or with her domestic duties.

Night sedation is used sparingly and for as short a period as possible.

Psychotherapy is always given concurrently with any other form of physical treatment, very often with the use of abreactive agents.

Methods and Scope of the Survey

All the psychiatric records incepted during 1965 were examined, and all the patients first seen during that year who had started treatment with either of these drugs were included. Any patient who had received any other antidepressant and/or tranquillizer and/or E.C.T. was excluded. The majority of the sample included in the trial had not had any previous psychiatric treatment. The records were examined and information on every patient in the sample (age, sex, marital status, employment), their illness (diagnosis, duration and symptoms),

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drugs used and their response, was extracted and coded.

As an antidepressant drug, amitriptyline was used almost exclusively until July 1965, when Triptafen became available. Since then, the majority of the patients have received Triptafen.

The patients were all out-patients; they were treated by five different doctors (Consultant, two Registrars and two Clinical Assistants), all of them understanding and accepting the general outlines of the policy of the unit described.

Criteria of Diagnosis

The diagnosis was agreed in every case by at least two of the doctors. The basic indication for the prescription of the drugs under survey was depression, whether symptom, syndrome, or illness.

Neurotic depressions are grouped with the reactive ones.

Under anxiety reactions have been grouped all those patients in whom the picture is dominated by manifestations of anxiety, with few clinical symptoms of depression, usually of acute onset and present for a relatively short period of time.

The cases of obsessional neurosis included were ones that presented evidence of depression. In the personality disorders treated, the behavioural change was thought to be due to clinically evident depression. The patients with psychosomatic disorder were also depressed.

Drug Administration

Like Hordern *et al.* (1964), we believe that amitriptyline is a predictable antidepressant. If the patient does not respond within two weeks, he will probably not respond at all. Every case was therefore seen within the first two weeks of administration of the drug. The dose we give to a patient initially is always 25 mg. of amitriptyline twice daily, or one tablet of Triptafen twice a day, as it is our experience that the majority of the "responders" will respond to this dose. Only rarely has the dose to be increased to three tablets in the day. Triptafen-Forte (4 mg. of perphenazine) was not used.

The drugs are administered in relation to the diurnal variation of the symptoms, concentrated at the time when the symptomatology is at its worst. When necessary, the drug was concentrated during the late part of the day to use the sedative effect to promote sleep, or to combat such drowsiness as interfered with the patient's working capacity. Administration was recommended before meals.

Discontinuance of the drug was not carried out suddenly, but by reducing the number of tablets to one a day for a week before stopping.

The opinions of the patient and the physician were combined to give an assessment of response. Such assessments were made within two weeks of starting drug therapy and at convenient periods afterwards.

Patients showing no response to the drug after two weeks were given other forms of treatment.

Criteria of Response

Complete remission was considered to have occurred when the patient had returned to his normal self and was free from any symptoms or signs of depression or anxiety and was without any treatment.

Improvement was considered as:

1. Marked reduction or absence of all symptoms but the patient continues to take a maintenance dosage of the drug (many of these patients would later be complete remissions).
2. Remission of main symptoms of depression and anxiety, but persistence of minor symptoms after discontinuing the drug.

Results

A total of 71 patients received amitriptyline, and 42 patients received Triptafen. They were first divided into two groups: the "improved", comprising the complete remissions and the patients improved, and "not improved", including those who failed to respond.

The proportion of patients responding to each drug can be seen in Table I. Forty out of 42 patients improved on Triptafen and 45 out of 71 patients improved on amitriptyline. Statistical analysis of these results indicates that

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TABLE I

Treatment	Improved	Not Improved	Totals
Triptafen ..	40	2	42
Amitriptyline ..	45	26	71
Totals	85	28	113

Triptafen gave significantly better results than amitriptyline ($\chi^2=12\cdot70$ after applying Yates Correction: df=1; $p<0\cdot001$).

In order to assess the possibility of bias in selection, as this is a retrospective study, the distribution of patients to treatment groups with reference to age, sex, diagnosis and duration of illness was investigated.

The analysis of the distribution of the sample by age indicates that groups did not differ by age distribution. ($\chi^2=3\cdot57$: df=4; $p=0\cdot50$-$0\cdot30$).

It can be seen from Table II that about 64 per cent. of the patients who had Triptafen were females, whilst only 45 per cent. of patients who had amitriptyline were females. This is an uneven distribution, which, from a statistical point of view does not quite achieve significance. ($\chi^2=3\cdot25$ after Yates Correction; df=1; $p=0\cdot10$-$0\cdot05$).

Table II

Distribution by Sex in Treatment Groups

Treatment	Sex		Totals
	Male	Female	
Triptafen ..	15	27	42
Amitriptyline ..	39	32	71
Totals	54	59	113

The principal departures from expected values in Table III are the high ratios of Triptafen/amitriptyline in patients with mixed depression (3:1) and involutional depression (6:1). In other diagnoses the ratio varied from 1:2 to 1:5. However, the distribution as a whole does not depart from expected values ($\chi^2=4\cdot78$; df=4; $p=0\cdot50$-$0\cdot30$).

The patients were fairly evenly distributed between treatment groups with regard to the duration of their illness. After pooling the data, analysis showed that no significant departure

TABLE III

Distribution and Responses by Diagnosis in Treatment Groups

Diagnosis	Amitriptyline		Triptafen	
	Improved	Not Improved	Improved	Not Improved
Endogenous depression ..	13 (65%)	7 (35%)	10 (90·9%)	1 (9·1%)
Reactive depression ..	16 (64%)	9 (36%)	10 (90·9%)	1 (9·1%)
Anxiety reaction	9 (69%)	4 (31%)	6 (100%)	—
Other depressions* ..	7 (53·9%)	6 (46·1%)	14 (100%)	—
Totals	45 (63·4%)	26 (36·6%)	40 (95·2%)	2 (4·8%)

* This group includes: mixed (1, 3), involutional (1, 6), and senile depressions (5, 1), obsessional neurosis (1, 1), personality disorders (2, 1), and psychosomatic disorders (3, 2).

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from even distribution was present. ($\chi^2=3\cdot0$; df=3; p=0·50-0·30).

If the data are partitioned by sex and the results tabulated for males and females, the figures in Table IV are obtained.

Both males and females responded significantly better to Triptafen. However, in female patients, Triptafen was far superior to amitriptyline (p=0·01-0·001), whilst in males the superiority of Triptafen was only just significant (p=0·05).

At the time this survey was originally made (February, 1966) a number of patients were still attending the clinic and these might eventually be classified as complete remissions. Table V shows the proportion of complete remissions on each drug, to date, in relation to the total "improved" and the total on the drug. It is interesting to note that there is a higher percentage of complete remissions on Triptafen despite the fact that several patients taking Triptafen had had substantially shorter treatment periods than those taking amitriptyline. We would confidently expect the proportion of complete remissions on Triptafen to increase at subsequent clinic attendances, since the majority of patients attending for the first time towards the end of 1965 were put on Triptafen.

Table VI correlates length of treatment with response; it will be seen that, according to the original criterion of response within two weeks, there were three late responders, two to amitriptyline and one to Triptafen. It also shows that no patient responded after this period, even if the administration of the drug was prolonged (usually due to reluctance of the patient to accept E.C.T.).

In Table VII the length of administration of the drugs in the cases of complete remission are represented for both drugs. When the data contained in the table are analysed it shows that the speed of response to Triptafen is significantly greater than that of amitriptyline ($\chi^2=6\cdot99$; df=2; $0\cdot05>p>0\cdot02$).

Side-Effects

Only six patients reported troublesome side-effects, four on amitriptyline and two on Triptafen. The amitriptyline side-effects (drowsiness, dry mouth, dizziness, muscular weakness, urinary retention) were sufficiently severe in three out of these four patients to make them

TABLE IV

Males				Females		
Totals	Improved	Not Improved		Improved	Not Improved	Totals
15	14	1	Triptafen	26	1	27
39	24	15	Amitriptyline	21	11	32
54	38	16	Totals	47	12	59

TABLE V

Drug	Complete Remission	Improved	Not Improved	Totals
Triptafen	19 (45·2%)	21 (50%)	2 (4·8%)	42 (100%)
Amitriptyline ..	23 (32·4%)	22 (31%)	26 (36·6%)	71 (100%)
Totals	42	43	28	113

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TABLE VI

Triptafen			Amitriptyline	
Improved	Not Improved	Time on Drug	Improved	Not Improved
39	Nil	Under 2 weeks	43	1
1	2	2-4 weeks	2	7
Nil	Nil	Over 4 weeks	Nil	14
Nil	Nil	Drug stopped because of side-effects	Nil	4
40	2	Totals	45	26

TABLE VII

	Up to 6 weeks	7-8 weeks	Over 9 weeks	Totals
Triptafen ..	9	7	3	19
Amitriptyline	4	7	12	23
Totals ..	13	14	15	42

stop taking the drug. One patient on Triptafen experienced loss of libido which was sufficient for him to stop taking his tablets. Another patient on Triptafen reported drowsiness, a burning sensation in the mouth and paraesthesia in the arms—these side-effects were not sufficiently severe to make the patient abandon treatment.

Drug Failures and Subsequent E.C.T.

The two patients who failed to respond to Triptafen subsequently responded well to E.C.T. One was male and one was female.

Of the 26 patients who failed to respond to amitriptyline, 10 subsequently responded to E.C.T., seven men and three women.

DISCUSSION

In the final assessment of the results it should be noted that the selection produced by the general policy of the unit gives a uniform sample, consisting of patients with mainly mild and moderate depression in a reasonably stable social situation.

The findings of this retrospective study (Table I) suggest that the combination of amitriptyline and perphenazine is superior to amitriptyline alone in the treatment of depression, thus confirming the reports of Mattey (1963) and Smith (1963).

This superiority is possibly due to the mixed nature of the affective disorders, anxiety playing a very important part in the whole clinical picture. Ayd (1961) wrote: "Anxiety and depression almost always are intermingled. Anxiety may cause depression as a secondary effect, or it may appear during a primary depression as a secondary effect." This opinion has been reiterated by Coffee (1964), Bennett (1962) and Sargant *et al.* (1966). Recently Rose *et al.* (1965) have taken account of this view in their trial of two antidepressant drugs. "Since many patients with depression also show considerable anxiety or agitation, it is common practice of the authors to give a tranquillizer as well as an antidepressant drug; all patients, therefore, receive promazine hydrochloride 50-100 mg. in addition."

In our series this effect of the combination of drugs on anxiety is confirmed by the response obtained in the group of anxiety reactions, where the improvement rate is particularly high. Although other diagnostic categories also responded better to the mixed drug, the results, owing to the small numbers, can only be

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considered as valid for the three main clinical sub-groups described (Table III) endogenous depression, reactive depression and anxiety reaction.

The all-pervading nature of the anxiety seems to point to the artificiality of the classification of depression. In our series both drugs appeared to be as effective in reactive as in endogenous depression, the response rate in both groups being similar to the overall response rates (approximately 90 per cent. for Triptafen and approximately 65 per cent. for amitriptyline). Our findings differ from those of Burt *et al.* (1962) and more recently Rose *et al.* (1965) who have found amitriptyline to be more effective in endogenous depression. Conversely Browne *et al.* (1963) obtained better results with amitriptyline in reactive depression.

There are differences between the results for men and women. In the sample studied, the sex composition differs. The ratio of females who received amitriptyline-perphenazine is greater than that of those who received amytriptyline alone (Table II). Although this difference does not reach statistical significance ($p=0\cdot10$-$0\cdot05$) it is important, as it could represent a bias in the selection, produced by observing the better response of females to the combination. Table IV shows this difference of response, which is statistically significant. Of the patients on amitriptyline alone, women accounted for 45 per cent. of the total sample and 29·5 per cent. of the patients considered improved; for the amitriptyline-perphenazine group the ratios were 64 per cent. and 61·7 per cent. respectively.

This difference of response in relation to sex is interesting. As already discussed, the combination of drugs seems more effective where anxiety is prominent. In so far as anxiety, anxiety-provoking factors and emotional sensitivity are generally more apparent in the female, this may be the reason for their better response.

A further point to note is the fact that the results reported were obtained using relatively small doses of both drugs. The generally recommended minimal dose of amitriptyline is 75 mg. daily and of Triptafen 75 mg. of amitriptyline and 6 mg. of perphenazine daily, this being usually increased. The maximum dose used in this study was, however, 50 mg. of amitriptyline and 4 mg. of perphenazine. Nevertheless, the results are almost identical to those reported for both drugs with higher doses. We think that there may be several factors contributing to these results. The drugs used are potent psychopharmacological agents which not only have a basic central depressant action, which produces a certain amount of disruptive effect on the integrative psychic processes, but also produce a series of side-effects, mainly due to autonomic nervous system activity. The low dosage used reduced the unwanted reactions in both spheres. This reduction, without detriment to the antidepressant-antianxiety properties, was achieved and enhanced by careful consideration of the time of administration. Thus, the drugs were given in relation to the diurnal variation of the symptoms of the individual patients and also in relation to his social and work commitments, rather than at fixed regular intervals. This avoided a blanket effect during the hours of the wakeful state.

Although the preceding considerations appear to us to be the most important, psychotherapeutic measures also play a part. The following, we consider, may have been important: Firstly, the effects, side-effects and expected length of drug administration were carefully explained to every patient. Secondly, a clear picture was given of the general prognosis and possible alternative forms of therapy. Thirdly, all patients were reassured and given a better idea of the nature of their illness, thus diminishing fear and anxiety. Finally, all were encouraged to continue with their normal activities; this was welcomed in the great majority of cases.

Abreactive and analytical psychotherapy did not seem to play a major part. Most patients responded within the first two weeks of starting drug therapy, and psychotherapy was minimal during this period in which they would only be seen on average twice.

Summary

A retrospective study was carried out on 113 patients with mild or moderate forms of depressive illness treated with either amitriptyline alone or a mixture of amitriptyline and

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perphenazine (Triptafen). The dose used was 50 mg. of amitriptyline daily for the first group and 50 mg. of amitriptyline and 4 mg. of perphenazine daily for the second. The drugs were administered orally in two doses in relation with the diurnal variation of the symptomatology.

Age, sex and duration of illness did not differ to a significant degree from the expected values or even distribution of the samples.

The analysis of the data contained in the hospital records of these patients shows the combination of drugs (Triptafen) to be more effective than amitriptyline alone. The possible reasons for this are discussed, with the suggestion that the combined drug is more effective where anxiety is prominent. This effectiveness is more marked in females.

The low dosage administered seems to be sufficient to produce a satisfactory response and remission. The efficiency of this low dosage regime is discussed and possible contributing factors described.

The majority of the patients not responding within two weeks did not do so on prolongation of therapy, a good index of the drug's effectiveness.

The total duration of administration of the drug to obtain a complete remission was significantly shorter for Triptafen than for amitriptyline, the limit being about twelve weeks.

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