A Comparative Study of Antidepressants in the Treatment of Depressive States

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The effect of six antidepressants has been investigated in six groups of twenty patients suffering from depressive states. The over-all response of the six groups, as well as the response of the individual target symptoms of depression according to the Hamilton Rating Scale are reported.

Introduction

Since 1952, the discovery of the mood-elevating effect of MAO inhibitors had opened up a new era in the chemotherapy of the depressive syndrome. Later in 1957 Kuhn demonstrated a similar antidepressive effect of the tricyclic compound imipramine. Ever since, great progress in the development of the pharmacotherapy of depression was noted with the introduction of numerous antidepressive compounds whether of the MAO inhibitor or the tricyclic or tetracyclic group. Each of these compounds has to be investigated to assess whether it possesses new advantages or not.

The aim of this study is two-fold; firstly to compare the therapeutic effect of some antidepressive drugs of the tricyclic or tetracyclic and MAO inhibitor groups; secondly, to delineate the specific therapeutic profile of each of these compounds.

Materials and Methods

The present investigation was undertaken on patients presenting with depressive states not associated with a personality defect, not considered secondary to any other psychiatric illness and not having any obvious organic cause. Patients suffering from glaucoma, prostatism, or a tendency to hypotension or showing evidence of progressive disease were excluded. Patients who had received an antidepressant during the previous two weeks were also excluded.

One hundred and twenty patients fulfilling the previous criteria and who completed the treatment course of four weeks were submitted to the present analysis. Their ages ranged from 20 to 69 years. There were seventy-seven males and forty-three females. On admission to the trial, full details of their present and past history were recorded.

Clinical neuropsychiatric examination was performed in all cases. The severity of the depressive illness was measured by the total one-rater score on the Hamilton Rating Scale (HRS) for depression (Hamilton 1960), before and on the last day of treatment. Patients were subdivided into six therapeutic groups each of twenty patients. Each group was given a single antidepressive drug for four weeks in three divided daily doses. The antidepressive drugs as well as the total daily doses given are shown in Table 1. The trial was an open comparative one with random allocation of treatment.

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Table 1

The antidepressant drugs used and the therapeutic groups

<table>
<thead>
<tr>
<th>Group number</th>
<th>Drug used</th>
<th>Total daily dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chemical name</td>
<td>Trade name</td>
</tr>
<tr>
<td>1</td>
<td>Amitriptyline</td>
<td>Tryptizol</td>
</tr>
<tr>
<td>2</td>
<td>Dibenzepine</td>
<td>Noveril</td>
</tr>
<tr>
<td>3</td>
<td>Doxepin</td>
<td>Sinequan</td>
</tr>
<tr>
<td>4</td>
<td>Maprotiline</td>
<td>Ludiomil</td>
</tr>
<tr>
<td>5</td>
<td>Noxiptyline</td>
<td>Agedal</td>
</tr>
<tr>
<td>6</td>
<td>Nialamide</td>
<td>Niamid</td>
</tr>
</tbody>
</table>

Table 2

Overall response of the six therapeutic groups

<table>
<thead>
<tr>
<th>Group number</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical name</td>
<td>Amitriptyline</td>
<td>Dibenzepine</td>
<td>Doxepin</td>
<td>Maprotiline</td>
<td>Noxiptyline</td>
<td>Nialamide</td>
</tr>
<tr>
<td>Mean total group score before treatment</td>
<td>24·0</td>
<td>23·45</td>
<td>27·4</td>
<td>31·0</td>
<td>30·6</td>
<td>23·95</td>
</tr>
<tr>
<td>Mean total group score after treatment</td>
<td>12·1</td>
<td>11·95</td>
<td>15·05</td>
<td>13·55</td>
<td>15·6</td>
<td>16·85</td>
</tr>
<tr>
<td>Mean reduction in starting scores</td>
<td>11·9</td>
<td>11·5</td>
<td>12·35</td>
<td>17·45</td>
<td>14·0</td>
<td>7·1</td>
</tr>
<tr>
<td>Group percentage improvement</td>
<td>49·58</td>
<td>49·04</td>
<td>45·07</td>
<td>56·29</td>
<td>49·02</td>
<td>29·64</td>
</tr>
<tr>
<td>Significance 't'</td>
<td>6·8</td>
<td>5·0</td>
<td>7·24</td>
<td>6·3</td>
<td>7·27</td>
<td>3·35</td>
</tr>
</tbody>
</table>

The therapeutic efficacy of each of the six antidepressants used was evaluated by:

A. Overall response of each of the six therapeutic groups:

This was achieved by calculating the changes in the total scores of HRS at the beginning of the trial and after four weeks treatment. This was compared in terms of:
1. Mean total group scores.
2. Mean reduction of starting scores.
3. Group percentage improvement.

B. Response of individual target symptoms of depression according to HRS:

From the HRS, seven target symptoms were chosen, namely: depressed mood, insomnia, retardation, agitation, psychic anxiety, general somatic symptoms and hypochondriasis and their response to the antidepressants was calculated and compared. Two indices were used to compare improvement of each of these target symptoms in each of the six therapeutic groups:
1. The mean absolute reduction in initial scores.
2. The percentage improvement of initial scores.

All the results were subjected to statistical analysis using the 't' test at $p = 0.01$.

Results

A. Overall response of the six therapeutic groups:
The mean total group scores before and after treatment, mean reduction in starting scores as well as the group percentage improvement of total scores for each of the six antidepressive drugs are summarized in Table 2. Analysis of this Table shows that the highest amelioration was obtained in group 4 (maprotiline), followed by group 1 (amitriptyline), group 5 (noxiptyline) and group 2 (dibenzepine). The latter three groups show a nearly equal degree of improvement. Lesser improvement of total HRS scores is shown by group 3 (doxepin); and the least response is shown in group 6 (nialamide). However, the improvement of mean total scores in all the six groups was statistically significant. Figure 1 illustrates the percentage improvement of total scores in each of the therapeutic groups.

B. Response of individual target symptoms of depression according to HRS:
The mean absolute reduction in initial scores as well as the percentage improvement of initial scores of individual target symptoms in each of the six groups is summarized in Table 3. The response of each individual symptom is compared in the six groups as follows:

1. Depressed mood:
The response of depressed mood to antidepressants is superior in group 5 (noxiptyline) and group 4 (maprotiline) followed by group 1 (amitriptyline), group 2 (dibenzepine) and then group 3 (doxepin) (Figure 2). The least response obtained was in group 6 (nialamide).

2. Insomnia:
(a) Initial Insomnia:
Whereas group 4 (maprotiline), group 3 (doxepin) and group 1 (amitriptyline) proved to be most effective in overcoming initial insomnia, group 2 (dibenzepine) and group 6 (nialamide) failed in this respect. Group 5 (noxiptyline) had an intermediate action (Figure 3).
Table 3

Response of individual target depressive symptoms of Hamilton Rating Scale in each of the six therapeutic groups

<table>
<thead>
<tr>
<th>Target symptoms</th>
<th>Group 1 (Amitriptyline)</th>
<th>Group 2 (Dibenzepine)</th>
<th>Group 3 (Doxepin)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$M_1$</td>
<td>$M_2$</td>
<td>C</td>
</tr>
<tr>
<td>1. Depressed mood</td>
<td>2.65</td>
<td>1.15</td>
<td>1.5</td>
</tr>
<tr>
<td>2. Insomnia:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Initial</td>
<td>0.8</td>
<td>0.3</td>
<td>0.5</td>
</tr>
<tr>
<td>(b) Middle</td>
<td>0.7</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>(c) Delayed</td>
<td>0.65</td>
<td>0.25</td>
<td>0.4</td>
</tr>
<tr>
<td>3. Retardation</td>
<td>0.8</td>
<td>0.95</td>
<td>0.15</td>
</tr>
<tr>
<td>4. Agitation</td>
<td>0.95</td>
<td>0.2</td>
<td>0.75</td>
</tr>
<tr>
<td>5. Psychiatric anxiety</td>
<td>2.75</td>
<td>0.95</td>
<td>1.8</td>
</tr>
<tr>
<td>6. General somatic symptoms</td>
<td>1.1</td>
<td>0.45</td>
<td>0.65</td>
</tr>
<tr>
<td>7. Hypochondriasis</td>
<td>1.05</td>
<td>0.8</td>
<td>0.25</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Target symptoms</th>
<th>Group 4 (Maprotiline)</th>
<th>Group 5 (Naxipsiline)</th>
<th>Group 6 (Nialamide)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$M_1$</td>
<td>$M_2$</td>
<td>C</td>
</tr>
<tr>
<td>1. Depressed mood</td>
<td>3.4</td>
<td>1.35</td>
<td>2.05</td>
</tr>
<tr>
<td>2. Insomnia:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Initial</td>
<td>1.9</td>
<td>0.55</td>
<td>1.35</td>
</tr>
<tr>
<td>(b) Middle</td>
<td>1.2</td>
<td>0.55</td>
<td>0.65</td>
</tr>
<tr>
<td>(c) Delayed</td>
<td>1.05</td>
<td>0.45</td>
<td>0.6</td>
</tr>
<tr>
<td>3. Retardation</td>
<td>1.75</td>
<td>0.7</td>
<td>1.05</td>
</tr>
<tr>
<td>4. Agitation</td>
<td>1.6</td>
<td>0.55</td>
<td>1.05</td>
</tr>
<tr>
<td>5. Psychiatric anxiety</td>
<td>2.65</td>
<td>1.1</td>
<td>1.55</td>
</tr>
<tr>
<td>6. General somatic symptoms</td>
<td>1.25</td>
<td>0.5</td>
<td>0.75</td>
</tr>
<tr>
<td>7. Hypochondriasis</td>
<td>1.95</td>
<td>0.85</td>
<td>1.1</td>
</tr>
</tbody>
</table>

$M_1$ = Mean score before treatment  $M_2$ = Mean score after treatment  C = Change of mean initial score  %C = Percentage change of mean initial score  t = Significance
(b) MIDDLE INSOMNIA:
The best results were obtained with group 3 (doxepin) then group 1 (amitriptyline) and group 5 (nortriptyline) (Figure 3). Less improvement was shown in the case of group 4 (maprotiline), and least amelioration in group 2 (dibenzepine) and group 6 (nialamide) respectively.

3. Retardation:
A good response was obtained with group 2 (dibenzepine) (Figure 4), less improvement with group 5 (nortriptyline), group 4 (maprotiline) and group 6 (nialamide) respectively. Failure and even aggravation of this symptom was shown with group 1 (amitriptyline) and group 3 (doxepin).

(c) DELAYED INSOMNIA:
Most improvement was achieved with group 3 (doxepin), group 1 (amitriptyline) and group 4 (maprotiline) respectively, and was poor with group 6 (nialamide). Group 5 (nortriptyline) and group 2 (dibenzepine) had an intermediate action (Figure 3). Thus of the antidepressant drugs tested, doxepin followed by amitriptyline had generally the most effective soporific effect. Maprotiline and nortriptyline came next in efficiency; the former being more effective in controlling initial insomnia, while the latter was superior in middle insomnia.

4. Agitation:
The best control was achieved by group 1 (amitriptyline), group 4 (maprotiline), followed by group 5 (nortriptyline) and group 3 (doxepin) respectively (Figure 5). Failure of response was shown in group 2 (dibenzepine) and aggravation of this symptom with group 6 (nialamide).

5. Psychic anxiety:
This was best controlled by group 3 (doxepin) followed by group 1 (amitriptyline) and group 4 (maprotiline) (Figure 6). A poor result was
obtained with group 6 (nialamide) whereas intermediate improvement was shown with group 5 (noxiptyline) and group 2 (dibenzerpine).

6. General somatic symptoms:
Good control was noted with group 2 (dibenzerpine) (Figure 7). Lesser improvement was shown with group 4 (maprotiline), group 1 (amitriptyline), group 3 (doxepin) and group 5 (noxiptyline) respectively. The response was poor with group 6 (nialamide).

7. Hypochondriasis:
Notable control was achieved by group 4 (maprotiline) followed by group 5 (noxiptyline), whereas other drugs showed far less response (Figure 8).

Discussion
Amitriptyline was shown to exert a significant therapeutic effect on agitation, psychic anxiety, insomnia, and depressed mood respectively. This agrees with Freed (1960), Harder (1962) and Allam (1971), who concluded that amitriptyline possesses an anxiolytic and a sedative activity in addition to its antidepressive effect. Moreover, it had a significant beneficial therapeutic effect upon general somatic symptoms rated by HRS (Diamond 1964 and Aly Hassan 1973).

Noxiptyline exerted a significant therapeutic response particularly upon depressed mood, retardation, agitation, general somatic symptoms and insomnia respectively. Though these findings agree with Aly Hassan (1973), Petrilowitsch (1968) stressed only the mood-elevating and drive-stimulating effect of noxiptyline. However the additional sedative effect of noxiptyline is clearly demonstrated in the present work. Thus this compound can be considered as having a combined drive-stimulating as well as a sedative effect in addition to its potent antidepressive property.

Dibenzepine was superior in alleviating retardation, general somatic symptoms and depressed mood respectively. Thus it has an
energizing property in addition to its mood-elevating effect. Similar results were recorded by Fouks et al. (1966), who further claimed that this compound quickens the mental processes and flow of ideas. Moreover, dibenzepine proved in this study to be beneficial in controlling psychic anxiety.

Doxepin exerted its maximum therapeutic effect on psychic anxiety followed by insomnia (all forms), general somatic symptoms, agitation and lastly depressed mood. It can thus be considered as a potent anxiolytic and calming drug with a relatively lesser antidepressive effect. These results are in agreement with those of Krakowski (1968) and Gomez-Martinez (1969).

Maprotiline produced a significant therapeutic response on agitation, depressed mood, insomnia (all forms), retardation and psychic anxiety as well as on general somatic symptoms. This agrees with Kuhn (1972), and Guz (1972) who stressed the beneficial therapeutic value of this compound on depressive states and its clearly identifiable anxiolytic as well as drive-enhancing properties. On the other hand, Angst et al. (1972) reported that maprotiline acts chiefly on the somatic symptoms of depression (loss of appetite and sleep disorders) as well as on mood, whereas its influence on enhancing drive is rather less evident. Balestrieri et al. (1971) concluded, after a controlled study, that maprotiline was an effective, powerful and well tolerated antidepressant drug, both in endogenous and in neurotic depression. Further confirmation of this therapeutic effect has been demonstrated by Welner (1972), Pinto et al. (1972) and Levin (1974). Murphy & Forrest (1975) comparing the response of amitriptyline and maprotiline, in a dose of 150 mg daily, concluded that both drugs had an equally effective therapeutic action.

Nialamide failed to exert a significant improvement on many of the target symptoms except depressed mood and retardation; so it can be considered as a mild antidepressive drug having an additional drive-enhancing property. Similar findings have been reported by Khvibivitski & Nuller (1968).
In the present investigation analysis of the symptom-response to the six therapeutic groups tried would suggest their categorization into the following therapeutic profiles:

1. Antidepressants with predominant anxiolytic and sedative properties in addition to their mood-elevating features. These are represented by amitriptyline and doxepin. The former has a relatively mood-elevating property, while the latter possesses more potent anxiolytic and sedative effects. Thus these two compounds are recommended for agitated depressive states.

2. Antidepressants with predominant energizing and drive-enhancing properties in association with their mood-elevating action. This group is represented by dibenzepine and to a much lesser extent by nialamide. They are recommended in retarded depressive states.

3. Antidepressants with an intermediate action having a broad-spectrum anxiolytic and sedative effect in addition to their energizing and mood-elevating activity. This group is represented by maprotiline and noxiptyline; the former having a relatively potent sedative and anxiolytic effect. These drugs can be used in various types of depressive state as they have a broad spectrum action on all depressive target symptoms.

Conclusion
The effect of six antidepressive drugs of either (a) the tricyclic group (amitriptyline, dibenzepine, doxepin, noxiptyline) and tetracyclic (maprotiline), or (b) MAO inhibitor group (nialamide), has been investigated in six groups of patients, each consisting of twenty patients suffering from depressive states. The over-all response of the six groups as well as the response of the individual target symptoms of depression according to the HRS were reported. It has been found that these drugs can be classified into three groups:

1. Antidepressants with predominant anxiolytic and sedative properties; represented by amitriptyline and doxepin. The former has a superior mood-elevating property while the latter possesses more anxiolytic and sedative effects.

2. Antidepressants with predominant energizing and drive-stimulating effects; represented by dibenzepine and to a much lesser extent by nialamide.

3. Antidepressants having an intermediate broad spectrum action producing both anxiolytic and energizing effects, represented by maprotiline and noxiptyline; the former being more potent as an anxiolytic and the latter having a greater mood-elevating property.

Acknowledgement
The authors are grateful to Wander, Bayer, Pfizer and Ciba-Geigy Scientific Office in Cairo for the supply of the drugs used in this trial.

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Errata

The Journal of International Medical Research, Volume 4 No. 1 (1976) pages 15–22, authors J S Borer, MD, M B Comerford, MB, BS and E Sowton, MD, FRCP have the following corrections on page 20:-

for (Pest) read (Rest) in time scale on both graphs

for ● HIGH DOSE METOPROLOL read ● LOW DOSE METOPROLOL in the legend for both graphs