A REVIEW OF CONTROLLED STUDIES WITH NOMIFENSINE, PERFORMED OUTSIDE THE UK

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1 Double-blind controlled comparisons of nomifensine with placebo, imipramine, desipramine, viloxazine, nortriptyline, a combination of amitriptyline and chlordiazepoxide, and diazepam have been carried out in various parts of the world.
2 Dosage ranged from 50–225 mg daily, and treatment lasted from 2–26 weeks.
3 Nomifensine was shown to possess useful antidepressive activity, to counteract inhibition, to restore drive and to relieve anxiety.
4 Adverse reactions were uncommon, particularly anticholinergic effects, and nomifensine was not shown to cause sedation or to interact with alcohol. No withdrawal phenomena were observed after 6 months' treatment.
5 Nomifensine is not suitable for severely agitated patients.

Introduction

It is relatively easy to provide a review of controlled clinical studies with nomifensine, carried out outside the UK, but it is not so easy to make generalizations from such a summary. Jenner (1977) has outlined many of the difficulties encountered in the clinical testing of antidepressants. These are particularly great when carried out in different countries. Most investigators have used the WHO–ICD system for the classification of patients, but whether or not all psychiatrists in such different countries as the USA, Canada, Mexico, Argentina, India, Italy, Switzerland, Norway and Germany understand the same by reactive depressive psychosis (298.0) or neurotic depression (300.4), is doubtful.

We have tried to use only internationally accepted rating scales for the documentation of the psychopathological findings. Apparent or real differences in the results can be explained by the fact that the types of patients subjected to the individual studies were not always comparable. In- and out-patients, and patients with reactive or endogenous depression were all included to obtain data on the effectiveness of nomifensine in the entire field of depression.

Dosage was not constant, but was a function of the type and seriousness of the illness and of the patient's age.

At present, we have completed and evaluated a total of 20 studies against nine established drugs. About 400 patients were treated with nomifensine in controlled trials (Table 1). Further studies are still being carried out, are shortly to be terminated or are being evaluated. The number of patients treated in open trials was about 7,000. The daily dosage of nomifensine ranged from 50–225 mg. The youngest patients were under 20 yr, the oldest more than 90 yr old. The period of treatment varied between 2 weeks and 6 months.

When clinical testing of nomifensine began in 1970, we believed that a substance which did not show sedating properties during pharmacological tests would be best compared with imipramine, nortriptyline and desipramine.

Acebal et al. (1976) carried out a double-blind comparative study against desipramine. Twenty-three patients of the nomifensine group and 20 patients of the desipramine group completed the intended treatment period of 4 weeks. The average daily dose was nomifensine 84 mg and desipramine 76 mg. Assessment was by the Hamilton and Zung Depression Scales at weekly intervals, and the Wittenborn Rating Scale at the beginning and at the end of treatment. The antidepressant effects of both nomifensine and desipramine became evident before the second week of treatment. Between the groups,

Table 1: Number of completed controlled clinical studies

<table>
<thead>
<tr>
<th>Substance</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desipramine</td>
<td>1</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>3</td>
</tr>
<tr>
<td>Imipramine</td>
<td>8</td>
</tr>
<tr>
<td>Chlorimipramine</td>
<td>1</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>3</td>
</tr>
<tr>
<td>Doxepin</td>
<td>1</td>
</tr>
<tr>
<td>Lipamabri (Amitriptyline + Chlordiazepoxide)</td>
<td>1</td>
</tr>
<tr>
<td>Viloxazine</td>
<td>1</td>
</tr>
<tr>
<td>Diazepam</td>
<td>1</td>
</tr>
</tbody>
</table>
there were no significant differences to be found (Figure 1). A moderate anxiolytic effect was found in the nomifensine group, whereas medication had to be discontinued for two patients in the desipramine group, because of its drive enhancing effects.

In three studies which compared nomifensine with nortriptyline, the former was found to be equally effective in two of them and to be better in the remaining one. Tolerance was also found to be better in one study and to be equal in the other two. 'More effective' means that more items of the Hamilton Depression Scale were improved more rapidly with nomifensine (Pöldinger & Gammel, 1976).

The first double-blind study against imipramine was carried out by Angst (1974), with two groups of 15 freshly hospitalized patients. The patients were subjected to physical and psychiatric examinations on days 0, 10, 20 and 30. The psychopathological status was examined and assessed by means of the following methods: (1) global rating of the severity of psychiatric symptoms; (2) AMP system (that is, Arbeitsgemeinschaft für Methodik und Dokumentation in der Psychiatrie); (3) Hamilton Depression Scale. The minimum dose administered was three times 50 mg, whereas the average daily doses on day 10 amounted to 163.3 mg for both drugs.

The analysis of variance of the total score of the Hamilton Depression Scale showed significant improvement for both treatment groups (P<0.01). No differences, however, could be observed between the two groups (Figure 2). The evaluation of 35 items of the AMP scale resulted in different findings. Nomifensine showing here a more rapid onset of action. On the whole, the number of symptoms significantly improved by the day 10, was greater in the nomifensine group than in the imipramine group. The following symptoms, in particular, were improved with nomifensine.

Impaired concentration, impaired memory, slowed down, hemmed in, helplessness, loss of vitality, melancholia/sadness, anxious, inner restlessness, lack of drive and suicidal tendencies.

With imipramine the following were improved: helplessness, melancholia, sadness, hopelessness, sense of insufficiency, suicidal tendencies, difficulties in getting to sleep, decreased appetite.

The initial rapid onset of effect and greater effectiveness of nomifensine, however, did not persist. Both drugs were about equally effective after 20 and 30 d treatment. As far as the autonomic system was concerned, dryness of the mouth and thirst were only increased after imipramine treatment. This was similar to the results reported by Forrest (1977) where no significant differences were found in the total scores of the Hamilton Depression Scale, but with nomifensine, anxiety had already been significantly improved after 1 week.

Rincon (Mexico) investigated the efficacy and tolerance of nomifensine in comparison with imipramine in a long term double-blind study on outpatients. Twenty-four patients in the nomifensine group and 29 patients in the imipramine group completed the 6 months' treatment. The investigator used the Hamilton Depression Scale and the Brief Psychiatric Rating Scale (BPRS) to assess the effects of treatment.

The graphs for the mean values of the total scores of the Hamilton Depression Scale for both groups are shown in Figure 3. The total nomifensine scores were not significantly lower than those of imipramine during weeks 1–5. In week 7, however, the mean total score of the nomifensine group was significantly less than the mean score of the imipramine group.

Table 2 shows those items which significantly improved after a defined period of treatment. More improved with nomifensine during the first 4 weeks than with imipramine.
Figure 3  Double-blind study. Nomifensine compared with imipramine. Mean scores for Hamilton Depression Scale. ◦, Nomifensine (n = 24); ○, imipramine (n = 29).

Figure 4  Double-blind study. Nomifensine compared with imipramine. Mean scores for BPRS. ◦, Nomifensine (n = 24); ○, imipramine (n = 29).

Table 2  Hamilton Depression Scale

<table>
<thead>
<tr>
<th>Week number</th>
<th>Nomifensine</th>
<th>Imipramine</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Feelings of guilt</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Suicide</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Hopelessness</td>
<td>Insomnia (middle)</td>
</tr>
<tr>
<td></td>
<td>Insomnia (middle)</td>
<td>Insomnia (late)</td>
</tr>
<tr>
<td></td>
<td>Helplessness</td>
<td>Helplessness</td>
</tr>
<tr>
<td>4</td>
<td>Anxiety (psychic)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Depression</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypochondriasis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Work and activities</td>
<td></td>
</tr>
</tbody>
</table>

Week from which individual symptom complex shows continuous significant improvement (P < 0.05).

Figure 5  Double-blind study. Nomifensine compared with viloxazine. Mean scores for Hamilton Depression Scale. ◦, Nomifensine (n = 21); ○, viloxazine (n = 29).

Figure 4 shows the results of the BPRS scale. The slopes of the total scores are significantly different at the 5% level and it may therefore be implied that nomifensine improves patients' depression faster than imipramine during the first few weeks. Table 3 shows those items of the BPRS scale which significantly improved after 4 weeks' treatment.

An equivalent number of side-effects were found in both groups during the first 3 weeks of active therapy, but subsequently patients taking nomifensine complained less frequently than the others. The investigator's final double-blind choice of treatment favoured nomifensine.

An equivalent therapeutic effect was also obtained in the other five double-blind studies in which nomifensine was compared with imipramine and tolerability was better in some cases.

During a further comparative controlled study with viloxazine in elderly patients with an average age of 73–74 yr, nomifensine 75 mg daily led to a more

Table 3  BPRS

<table>
<thead>
<tr>
<th>Week number</th>
<th>Nomifensine</th>
<th>Imipramine</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Anxiety</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Guilt feelings</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Blunted affect</td>
<td>Anxiety</td>
</tr>
<tr>
<td></td>
<td>Depressive mood</td>
<td>Guilt feelings</td>
</tr>
<tr>
<td></td>
<td>Excitement</td>
<td>Motor retardation</td>
</tr>
<tr>
<td></td>
<td>Somatic concern</td>
<td>Suspiciousness</td>
</tr>
<tr>
<td></td>
<td>Tension</td>
<td></td>
</tr>
</tbody>
</table>

Week from which each individual symptom complex shows continuous significant improvement (P < 0.05).
significant and greater reduction in the total scores of the Hamilton Depression Scale than did viloxazine 150 mg (Figure 5) (Moizeszowicz & Subira, 1977). Grof (1976) has reported the results of his double-blind study with amitriptyline. The high percentage of somatic and autonomic complaints already before treatment and after a brief placebo wash-out period, is remarkable. His study clearly shows the high incidence of somatic side-effects in depressed patients together with the danger of regarding these as secondary to the therapeutic effects when they are not taken into account before treatment.

During two further controlled studies against amitriptyline, no significant differences between the preparations could be found. Even when a fixed combination of amitriptyline and chlordiazepoxide (using a daily dose of 75 mg A + 15 mg C) was compared with nomifensine 75 mg by itself in patients with involutional depression (Eckmann 1974), no differences were detected.

Andersen (1976) carried out a double-blind study against doxepin. For 5 weeks, he treated two groups of 15 patients suffering from different types of depression. About one-half suffered from endogeneous depression and the other half neurotic depression.

Both drugs were effective, although doxepine acted faster during this trial and led to a greater reduction of the depression scores. In this study the dose of nomifensine averaged 197 mg daily which is unusually high, but side-effects, particularly drowsiness and dizziness, were still more frequent with doxepin than with nomifensine (18/7–16/5).

In this context it is relevant that preliminary investigations by Bergener (Cologne) on a small number of patients, suggest that patients with high serum concentrations of nomifensine respond less well than those with average concentrations.

Earlier, I reported our assumption at the start of our clinical trials, that drugs such as desipramine, nortriptyline or imipramine, would be suitable comparative substances. During our investigations, it has been repeatedly found in both open and controlled studies that even anxiety as a symptom of depression was quickly improved by nomifensine. Such an anxiolytic effect is more often expected of a primarily sedating substance.

It seemed desirable to investigate whether nomifensine was effective in patients suffering from ‘mixed anxiety’ depressions. In such cases, minor tranquilizers of the benzodiazepine type are very frequently prescribed.

Levin (1976) tested nomifensine on anxious depressed patients in a double-blind comparison with diazepam. The study included 40 patients. Thirty-one completed the treatment (18 nomifensine and 13 diazepam). Nine patients dropped out during the second week of treatment for reasons which were not connected with therapy. The treatment period was 4 weeks with a daily dose of nomifensine 75 mg or diazepam 15 mg.

The following scales were used: Zung Depression Scale; Hamilton Anxiety Scale; Hamilton Depression Scale; Taylor Manifest Anxiety Scale (TMAS); and Eysenck’s Personality Inventory. Results are shown in Table 4. Both depression scales showed no significant differences between the groups. The TMAS showed a significant decrease of the total scores only in the nomifensine group.

To summarize the various studies already referred to and also consider the results of open studies, nomifensine is an effective antidepressant with a quick onset of action, acting on all symptoms of depressive illness. It acts on inhibitions as well as anxiety, eliminating them as symptoms of depression and promoting the patient’s readiness to make social contact and increasing his activity. Nomifensine does not sedate, does not produce fatigue during the day and does not augment the effect of alcohol. Even after long-term treatment of up to 6 months and more, there were no withdrawal phenomena observed to indicate that it was habit-forming. The results of the

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Double-blind study of nomifensine compared with diazepam</th>
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<tbody>
<tr>
<td></td>
<td>Nomifensine (n = 18)</td>
</tr>
<tr>
<td></td>
<td>Before</td>
</tr>
<tr>
<td></td>
<td>Hamilton Anxiety Scale</td>
</tr>
<tr>
<td>Total</td>
<td>26.94 ± 2.33</td>
</tr>
<tr>
<td>Psychic</td>
<td>14.00 ± 0.86</td>
</tr>
<tr>
<td>Somatic</td>
<td>12.83 ± 1.68</td>
</tr>
<tr>
<td></td>
<td>58.00 ± 2.00</td>
</tr>
<tr>
<td></td>
<td>31.68 ± 1.47</td>
</tr>
</tbody>
</table>

Mean values ± s.d. of scores.
comparative investigations with desipramine, nortriptyline, viloxazine, imipramine, amitriptyline and the combination of the latter with chlordiazepoxide, always showed at least a therapeutically comparable effect. This suggest a wide therapeutic spectrum of activity. On the basis of its ability to restore drive, it is unsuitable for the treatment of severely agitated patients but a combination with tranquilizers is possible with no problems of incompatibility. As far as secondary effects are concerned, some sleep disturbance and internal restlessness were observed in 4-6% of cases. Pharmacologically, nomifensine does not have any central anticholinergic effects.

Malsch (1976) was able to show in 30 patients with reactive depression that single doses of nomifensine 75 mg, in comparison with placebo, did not affect the secretion of saliva, whereas the combination of amitriptyline and chlordiazepoxide reduced it significantly. Dry mouth, therefore, hardly ever occurred as a secondary effect. Neither animal experiments, investigations on human volunteers nor in the clinical trials have to date provided any indication of cardiotonic effects, or of any action on blood pressure.

Nomifensine seems to be not only an effective, but also a relatively safe, antidepressant.

References


Discussion

DR ANDERSON (Norway) said that Dr Habermann had quoted his (Dr Anderson's) work with nomifensine and doxepine and had stated that both drugs were shown to be effective. The design of the investigation had been to determine whether after 5 weeks' administration of either drug improvement was measurable on the Hamilton Depression Scale. Analysis of the total group of depressed patients and the two subgroups' neurotic depression and endogenous depression was made. In the total group, in both subgroups, and at the 1% significance level, doxepine was shown to be effective. On the other hand, neither the improvement in the total group nor in either subgroups with nomifensine reached significance. Dr Anderson believed that the value of an antidepressive can be measured best in endogenous depression. With doxepine the Hamilton Depression Scale score fell from an average of 21 to 7 points. With nomifensine, it fell less impressively from 20 to 15. The average daily dose of nomifensine was high (197 mg), and this might explain the results. On the other hand, adverse effects were very small and less with nomifensine. Doxepine caused more sedation.