ANXIETY AND DEPRESSIVE NEUROsis – THEIR RESPONSE TO ANXIOLYTIC AND ANTIDEPRESSANT TREATMENT

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SUMMARY

A total of 90 patients including 30 patients of generalized anxiety disorder and 30 of dysthymic disorder according to DSM III criteria plus 30 patients of mixed anxiety-depressive disorder were given a detailed psychiatric evaluation and four rating scales were made for measuring the level of anxiety and depression at intake and to record their improvement with treatment. Half the subjects in each group were randomly selected for treatment with imipramine and the other half with diazepam. Imipramine and diazepam were found to be equally effective (62.8% vs 62.2%) in reducing anxiety in all subjects. Imipramine was significantly better than diazepam in reducing the level of depression in the depressed group but as effective as diazepam in the other two groups. Imipramine was significantly better for the symptoms of ‘depressed mood’ and ‘retardation’, while diazepam was better in the symptom of ‘fears’. None of the other symptoms was discriminatory.

The nosological distinction between anxiety states and depressive neurosis has long been a subject of controversy, although the use of anxiolytics for the treatment of the former and antidepressants for the latter has been almost taken for granted. In clinical practice patients presenting with symptoms of both anxiety and depression are a common experience and their labelling into one or other category is difficult and mostly arbitrary. Even in patients of anxiety neurosis, depressive mood can be seen both prior to the first anxiety attack or later in the course of the disorder and sometimes the anxiety neurosis even appears to take on a predominantly depressive character (Marks and Lader 1973). On the other hand, in patients suffering from a depressive illness, diffuse anxiety or specific fears are almost always present to some extent (Hamilton 1980). This is supported by the recent reports of Akiskal (1984) who found that anxious depressions are the most common dysphoric mood state and such patients respond well to tricyclic antidepressants. Earlier, the collaborative study on pharmacotherapy of anxiety and depression reported by Lipman et al. (1974) clearly showed that in highly anxious subjects, imipramine produced a significant reduction of both anxiety and depression when compared to chlordiazepoxide or placebo. These effects seemed to run parallel and there is strong evidence to suggest that the observed antianxiety effect of tricyclics is independant of their antidepressant effects (Tyrer 1973, Zitrin 1980, 1983, Sheehan 1980) and more recently Leibowitz (1984) reported acute anxiety and panic attack were the best indicators of phenelzine response in their cohort of anxious depressives, although their utility in the treatment of generalized anxiety disorders appears limited (Klein 1978). Long term followup studies such as those of Leckman et al. (1981) indicate that patients who have an anxiety disorder also have a high incidence of depression, this relationship being particularly strong for panic disorder and depression. The effectiveness of anti-depressants in the treatment of panic disorder (Tyrer 1973, Mountjoy and Roth 1977, McNair and Kahn 1981) and their relative ineffectiveness in the case of generalized anxiety disorders (Marks and Lader 1973) led to the formulation of a broad spectrum of tricyclic antidepressants.
anxiety disorder has led some investigators to suggest that panic may be a form of atypical depression and generalized anxiety disorder is actually a prodromal, incomplete or residual manifestation of other psychiatric disorders lacking validity as a separate diagnostic entity.

From the above it was evident that panic attacks, phobic anxiety and obsessive-compulsive disorder are distinct entities and clinically, genetically and in their response to anti-depressant drugs are distinct from the core 'generalized anxiety disorder'. Further, that almost all the earlier studies on anxiety states have included all types of patients under the broad category of 'Anxiety State' and it undoubtedly influenced the results of the studies. It was therefore decided to study the response to treatment of the pure generalized anxiety disorder to anxiolytic and anti-depressant drugs and compare them with a pure depressive group and a mixed anxious-depressive group.

Aims
1. To study the clinical signs and symptoms in three groups of patients diagnosed according to DSM III criteria as:
   a) Generalised anxiety disorder - Group A.
   b) Mixed anxiety-depressive disorder Group M.
   c) Dysthymic disorder or depressive neurosis-Group D.
2. To study the response to treatment with:
   a) a benzodiazepine anxiolytic-diazepam.
   b) a tricyclic antidepressant-imipramine.

Material and Methods
Ninety consecutive patients presenting with symptoms of anxiety and/or depression in the psychiatry O.P.D. of Rajendra Hospital, Patiala were taken up for the study. These patients were subdivided into 3 groups of 30 patients each, as per the DSM III criteria mentioned above.

Exclusion criteria – all patients with a primary diagnosis of any other psychiatric disorder including panic attacks, phobic and obsessive-compulsive neurosis, psychosis, alcoholism or sociopathy and organic brain disorder. In addition, patients having anxiety or depressive symptoms secondary to other medical illness or drug intake were also excluded.

Each patient was interviewed using a standardized history taking proforma, and then assessed on four instruments i.e. (1) Hamilton's rating scale for anxiety (2) Taylor's manifest anxiety scale (3) Hamilton rating scale for depression and (4) Amritsar depressive inventory. Thus we had two self rating scales to evaluate the subjective emotional state and the two Hamilton scales for objective assessments by the interviewer. Half the subjects in each of the three groups were then randomly assigned either to treatment with imipramine or diazepam. The dose was - imipramine 25 mg or diazepam 5 mg-one tablet three times a day in the first week and increased to 2 tablets three times a day if adequate response was not achieved. Duration of treatment was 4 weeks.

The statistical analysis of data was done by using:
   a) Chi² test of significance.
   b) Analysis of variance by F test.

Results
Socio-Demographic Variables like age, sex, type of onset, precipitating factors and family history of psychiatric illness are given below. All these groups are similar on all these variables, in all respects, there being no significant difference between the groups on any of these variables.
Table 1
Response to treatment with imipramine and diazepam as measured on Hamilton Anxiety Scale

|        | Imipramine | Diazepam |
|--------|------------|----------|
|        | Initial score | Final score | Percent reduction | Initial score | Final score | Percent reduction |
| Group A| 19.5        | 7.3       | 62.5             | 16.5         | 4.9        | 70.4             |
| Group M| 17.5        | 7.5       | 57.1             | 19.7         | 7.1        | 63.9             |
| Group D| 10.8        | 2.8       | 73.4             | 9.7          | 3.8        | 60.9             |

Table 2
Response to treatment with imipramine and diazepam as measured on Hamilton Depression Scale

|        | Imipramine | Diazepam |
|--------|------------|----------|
|        | Initial score | Final score | Percent reduction | Initial score | Final score | Percent reduction |
| Group A| 12.0        | 6.1       | 48.8             | 8.3          | 2.7        | 58.5             |
| Group M| 17.2        | 6.9       | 66.5             | 20.0         | 8.7        | 56.3             |
| Group D| 18.5        | 4.9       | 73.6             | 17.1         | 9.5        | 44.1             |
Response to treatment:

Tables 1 & 2 show the mean, initial and final scores in the three diagnostic Groups A, M and D consisting of 30 patients each on the Hamilton Anxiety Scale, after treatment with imipramine (N = 15) and diazepam (N = 15) separately. The mean score for all 30 subjects in Group A is 18, and 18.6 in Group M and 10.2 in Group D. Thus groups A and M exhibit a similar degree of anxiety which is greater than in group D but this difference is not statistically significant. In Table 2, on the Hamilton depressive scale this pattern is reversed. Groups M and D have high initial scores of 18.6 and 18.0 respectively as compared to score of 10 in the anxiety group.

The improvement after drug treatment is given in terms of percentage reduction of scores at the end of 4 weeks treatment. The improvement after treatment with imipramine is almost the same in all 3 groups being 62.5%, 57.1% and 73.4% in Group A, M and D respectively. This suggests that imipramine reduces the anxiety level by approximately 2/3rd in all patients more so in the depressed group. Treatment with diazepam also brings about similar degree of improvement, the figures being 70.4%, 63.9% and 60.9% for Groups A, M and D respectively. In this case the response is slightly better in the generalised anxiety group. An analysis of variance was carried out and yielded the following F values:

a) Between drugs = 0.008 - Not significant
b) Between groups = 0.329 - Not significant

Table 3 shows the initial and final scores and percentage reduction of scores after treatment as measured on the Taylors manifest anxiety scale. The mean initial scores in all three groups is almost the same. The improvement on both imipramine and diazepam treatment shows a better response in group A followed by group M and lesser in group D. Analysis of variance gave the following F values:

a) Between drugs = 0.63 - Not significant
b) Between groups = 10.60 - Significant at 0.01 level.

On the Amritsar Depressive Inventory (table 4) the initial scores are distinctly higher in groups D and M as compared to group A (20.3, 19.9 and 9.0 respectively), this test thus clearly distinguishes the D and M groups as being in the depressed range while A group score is in the not depressed range. Furthermore, on treatment with imipramine group D shows the best improvement (74.1%) as compared to M and A groups (63.8 and 38.6% respectively). Analysis of variance gives the following values of F:

A groups Analysis of variance gives the following values of F:

a) Between drugs = 3.8 - Not significant
b) Between groups = 9.98 - Significant at 0.01 level.

Table 5 shows the percentage improvement in each symptom of the Hamilton
Table 3
Response to treatment with imipramine and diazepam as measured on Taylor manifest anxiety scale

|           | Imipramine | Diazepam |
|-----------|------------|----------|
| Initial  | Final      | Percent  | Initial | Final      | Percent  |
| score    | score      | reduction| score   | score      | reduction|
| Group A  | 13.6       | 5.6 58.8 | 14.1    | 5.7 57.6   |
| Group M  | 16.6       | 7.4 57.2 | 17.1    | 9.0 44.7   |
| Group D  | 11.1       | 6.7 41.5 | 11.6    | 7.0 35.3   |

Table 4
Response to treatment with imipramine and diazepam as measured on Amritsar Depressive Inventory

|           | Imipramine | Diazepam |
|-----------|------------|----------|
| Initial  | Final      | Percent  | Initial | Final      | Percent  |
| score    | score      | reduction| score   | score      | reduction|
| Group A  | 8.7        | 3.7 58.1 | 9.4     | 4.1 55.9   |
| Group M  | 18.8       | 6.8 63.8 | 21.0    | 10.3 50.9  |
| Group D  | 19.7       | 5.1 74.1 | 21.0    | 12.8 38.6  |

Anxiety Scale after treatment with imipramine and diazepam separately for the total sample. It is observed that there is a statistically significant (p < 0.01) improvement in the symptom of 'depressed mood' on treatment with imipramine as compared to diazepam, whereas imipramine in the symptom of 'Fears' (p < 0.01). The overall improvement in the three groups on the two drugs was also evaluated by analysis of variance using a 2 x 3 design. The F ratio between drugs was found to be - 0.008 (not significant) and for between patient groups was 0.239 (not significant).

Table 6 shows the percentage improvement in each symptom of the Hamilton Depression Scale. Since there were no patients with symptoms of loss of insight or loss of weight, these symptoms have not been included in the table. It is seen that imipramine is effective in improving the symptom of depression to the extent of 66% in both the Anxiety and Depressive groups and to the extent of 55% in M group. Interestingly diazepam also is effective in reducing the level of depression by 25% in the D group and 46% in the M group, but not effective in the Anxiety group. This difference is statistically significant at 0.01 level. The only other symptom in which imipramine is significantly better than diazepam is in the symptom of psychomotor retardation, and in relieving delayed insomnia especially in the depressed group but it fails to reach statistical significance. On the other hand diazepam was more effective than imipramine in relieving the symptom of agitation in all three groups to the extent of 85, 80 and 50 per cent in the three groups whereas imipramine was effective to the extent of 100% in A group and 57% in M group and no effect in D group. By using analysis of variance we get:

a) between drugs $F = 0.80$ - Not significant
b) between groups $F = 0.01$ - Not significant
### Table 5

Improvement in each symptom of Hamilton Anxiety Scale

| Symptom                        | Imipramine | Diazepam |
|--------------------------------|------------|----------|
|                                | AMD        | A        | Mean   | M | D | Mean |
| Anxious mood                   | 61.1       | 55.3     | 66.7   | 61.0 | 72.5 | 56.3 | 56.3 | 63.0 |
| Tension                        | 62.8       | 59.4     | 60.0   | 60.7 | 68.6 | 60.0 | 50.0 | 59.5 |
| Fears                          | 50.0       | 25.0     | 0.0    | 37.5 | 100.0 | 0.0 | 60.7 | 83.3 |
| Insomnia                       | 59.4       | 60.0     | 84.0   | 67.8 | 85.0 | 77.1 | 73.7 | 73.6 |
| Intellectual                   | 75.0       | 35.3     | 78.6   | 62.9 | 100.0 | 45.4 | 42.8 | 62.7 |
| Depressed mood                 | 85.7       | 65.0     | 72.7   | 74.5 | 37.5 | 51.7 | 24.3 | 37.8 |
| General somatic (muscular)     | 38.9       | 37.5     | 66.6   | 47.7 | 66.7 | 57.1 | 54.5 | 59.4 |
| General somatic (sensory)      | 56.0       | 68.7     | 75.0   | 66.6 | 63.0 | 65.1 | 50.0 | 59.4 |
| Cardiovascular                 | 77.3       | 64.2     | 83.3   | 74.9 | 68.0 | 80.8 | 100.0 | 82.9 |
| Respiratory                    | 75.0       | 71.4     | 100.0  | 82.1 | 64.3 | 83.3 | 100.0 | 82.9 |
| Gastrointestinal               | 61.1       | 60.0     | 57.1   | 59.4 | 68.7 | 48.1 | 71.4 | 62.7 |
| Genitourinary                  | 66.7       | 57.1     | 0.0    | 41.3 | 66.7 | 75.0 | 25.0 | 55.6 |
| Autonomic                      | 36.8       | 36.8     | 71.4   | 48.3 | 65.2 | 56.0 | 80.0 | 67.1 |
| Behaviour at interview         | 44.0       | 39.0     | 80.0   | 54.3 | 67.5 | 76.0 | 70.6 | 71.4 |
| **Mean**                       | **63.4**   | **53.8** | **71.2** | **62.8** | **68.6** | **62.8** | **55.3** | **62.2** |

### Table 6

Improvement in each symptom of Hamilton Depressive Scale

| Symptom                        | Imipramine | Diazepam |
|--------------------------------|------------|----------|
|                                | AMD        | A        | Mean   | M | D | Mean |
| Depression mood                | 66.6       | 55.2     | 66.7   | 62.0 | 0.0 | 47.7 | 25.0 | 23.7 |
| Depression guilt               | 0.0        | 100.0    | 57.1   | 78.5 | 100.0 | 100.0 | 100.0 | 100.0 |
| Depression suicide             | 0.0        | 55.6     | 87.5   | 47.7 | 0.0 | 54.3 | 38.5 | 31.0 |
| Insomnia (initial)             | 64.8       | 58.8     | 70.0   | 64.5 | 66.7 | 87.5 | 83.3 | 79.2 |
| Insomnia (middle)              | 12.5       | 100.0    | 81.8   | 64.8 | 88.9 | 73.1 | 87.5 | 83.2 |
| Insomnia (delayed)             | 60.0       | 57.9     | 84.6   | 67.5 | 66.7 | 82.6 | 50.0 | 66.4 |
| Work and interests             | 50.0       | 57.9     | 63.3   | 57.1 | 28.6 | 51.8 | 31.4 | 37.3 |
| Retardation                    | 50.0       | 100.0    | 85.7   | 78.6 | 0.0 | 57.1 | 40.0 | 32.4 |
| Agitation                      | 100.0      | 57.1     | 0.0    | 52.4 | 85.7 | 80.0 | 50.0 | 71.9 |
| Anxiety (psychic)              | 60.7       | 48.6     | 67.8   | 59.0 | 70.0 | 45.9 | 43.7 | 53.2 |
| Somatic symptoms (G. 1)        | 33.3       | 72.7     | 47.3   | 51.1 | 60.0 | 52.3 | 42.5 | 51.6 |
| Somatic symptoms (Gen)         | 61.9       | 34.2     | 70.8   | 54.6 | 53.8 | 28.6 | 28.1 | 36.5 |
| Somatic symptoms (G. U)        | 25.0       | 50.0     | 66.7   | 47.2 | 50.0 | 20.0 | 60.0 | 43.3 |
| Hypochondriasis                | 50.0       | 50.0     | 75.0   | 58.3 | 50.0 | 47.1 | 100.0 | 65.7 |
| **Mean**                       | **55.2**   | **58.8** | **70.9** | **61.6** | **60.3** | **54.8** | **45.3** | **56.3** |
Discussion

It is evident from Tables 1 and 3 which show the improvement on the Hamilton Anxiety Scale and the Taylor Manifest Anxiety Scale respectively, that imipramine is as effective as diazepam in reduction of anxiety as measured on these two scales, Diazepam being slightly more effective in the anxiety group and imipramine more effective in the depressive group with the mixed anxiety depressive group falling in between. On the two depressive scales we find that imipramine is clearly more effective than Diazepam in reducing the level of depression as measured on the Hamilton Depression Scale in the depressive groups. Diazepam seems to be more effective in reducing depression in the anxiety groups as compared to imipramine.

It is thus apparent that contrary to expectations, there does not seem to be a clear cut difference in the pure anxiety group, the mixed anxiety depression group and the pure depression group in their selectiveness of response to either imipramine and diazepam. Both drugs seem to be moderately effective in all groups, with antidepressants being slightly better in the depressed group and anxiolytics in the anxiety group. Our findings confirm the earlier reports of the efficiency of tricyclic antidepressants in the treatment of anxiety and that anxiety and depression are invariably both present even though the cases may be diagnosed as primary anxiety neurosis or depressive neurosis (Marks and Lader 1973, Clancey et al 1978, Hamilton 1980) and tends to support the suggestion of Akiskal (1984) that mixed anxiety depressions are the most common dysphoric mood state and that they respond well to tricyclic antidepressants.

However, most earlier studies have taken anxiety states as a whole and have reported that within this, panic anxiety only seems to respond to tricyclic antidepressants which have been considered to be relatively ineffective in the treatment of generalised anxiety disorder (Tyrer 1973, Mountjoy and Roth 1977, and McNair and Kahn 1981). However, our findings clearly show that tricyclic antidepressants are also effective in the treatment of generalized anxiety disorder and almost as effective as diazepam. In none of the four rating scales used was there a significant difference in effectiveness between the two drugs.

Considering individual symptoms the only two symptoms in which imipramine was found to be significantly more effective than diazepam were 'Depressed Mood' and 'Psychomotor retardation', while diazepam was significantly more effective as compared to imipramine in the symptom of 'Fears'. None of the other symptoms were discriminatory. In fact the mean overall percentage improvement on imipramine Vs diazepam as measured on the Hamilton Anxiety Scale was found to be 62.8% and 62.2% respectively, whereas on the Hamilton Depressive Scale the overall percentage improvement on imipramine Vs diazepam was 61.3% and 56.5% respectively. The findings of the present study thus establish the effectiveness of tricyclic antidepressants in the treatment of generalized anxiety disorder and at the same time cast doubt on the validity of the clinical differentiation of anxiety neurosis and depressive neurosis both phenomenologically and from the point of view of predicting treatment response, the mixed-anxious depressive group appears closer to the 'anxiety' group on scales that measure anxiety, and on the other hand are closer to the 'depressive' group on scales that measure depression and hence clinically would be liable to be arbitrarily assigned either of the two diagnosis depending on the whims of the investigator and since they constitute a large percentage of patients diagnosed as anxiety or depressive neurosis, this highlights the inadequacy of the existing system of classification in this area.
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