Accelerated antidepressant response to lithium augmentation of imipramine

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ABSTRACT

Background: Treatment of depressive episode often poses a challenge. Although there are numerous medicines available for its treatment but they all have a lag period of 2–3 weeks before they start showing their result. Aim: The aim of the present study was to test the hypothesis that an initial lithium-tricyclic antidepressant (TCA) combination has a quicker and better antidepressant effect than standard TCA treatment in unipolar depression. Materials and Methods: Twenty unipolar depressed inpatients under lithium-TCA treatment were compared with twenty patients with similar diagnosis treated with TCA-placebo combination. The duration of the study was 4 weeks under double-blind conditions. Results: Initial lithium-TCA treatment reduced depressive symptoms significantly more than TCA alone. The difference was evident from 1st week onward and persisted at 4 weeks. Conclusion: Lithium augmentation of TCA at the outset offers a strategy to reduce the lag period of antidepressant action. The choice can be made for those patients who are likely to benefit from long-term prophylaxis.

Keywords: Lithium, lithium combination, treatment of depression, tricyclic antidepressant

Major depressive disorder is the second leading cause of disability worldwide, and a major contributor to the burden of suicide and ischemic heart disease.[1] The recent epidemiological survey indicates lifetime prevalence of depression in the range of 10%–15%.[2] Its burden on the economy of a nation can be judged from the fact that unipolar major depression ranks second highest in terms of causes of disability. It accounts for 10.7% of total disability for a nation and higher treatment cost.[3–5] Moreover, the sociooccupational distress and the misery caused to depressed patient cannot be quantified in monetary terms. Untreated depression is a leading cause of suicide.[6] It is, therefore, no surprise that references of depressive illness figure prominently in medical literature.

There were no definitive modalities available to counter depression until the serendipitous discovery of tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors in the 1950s that proved to be of seminal importance.[7] First, they demonstrated that major depression was amenable to medical intervention just like other medical conditions such as hypertension and diabetes. Second, they served as roadmaps to improve our understanding of the mechanisms of action. The latter was critical to the era of rational drug development. The approach to pharmacotherapy for depression has remained unchanged over the last several decades; after diagnosis, the clinician initiates his choice

Access this article online

Quick Response Code:
Website: www.industrialpsychiatry.org
DOI: 10.4103/0972-6748.196057

How to cite this article: Saini R, Raju M, Chaudhury S, Srivastava K. Accelerated antidepressant response to lithium augmentation of imipramine. Ind Psychiatry J 2016;25:93-100.
of antidepressant agent and then titrates the drug dose over time until symptoms resolve. However, the goal of achieving accelerated antidepressant response has largely remained elusive. There is a delay of 2–3 weeks in the onset of action of all the available antidepressants. Many patients, who do respond to antidepressant therapy, may lose that response after several months of treatment. Augmentation of antidepressant response with lithium brought the much-needed relief to the harried clinician. Its efficacy in the treatment of bipolar mood disorder and refractory depression sparked further interest in its role in amelioration of many other psychiatric disorders and confirmed that it does have those properties though mechanism of action is different.

Attempts at ensuring faster antidepressant response from the outset have been far and few. Combination therapy is often used to improve efficacy, speed response and to attenuate an adverse effect of initial pharmacotherapy. With advances in psychopharmacology, the emphasis has shifted to focus on receptor-symptom complexes and accordingly newer antidepressants and combinations are being tailor-made to meet the specific requirements. With this information in the background, we attempted to analyze the effect of combining imipramine and lithium from the outset in the treatment of unipolar nonrefractory depression. The study tried to ascertain the efficacy of combined approach toward achieving earlier remission and comparing it with monotherapy alone. A positive response to lithium augmentation at the outset and the correlation of such a response to clinical variables would help in chalking out effective strategies to counter depression.

**MATERIALS AND METHODS**

The study was carried out in a large multispecialty, tertiary care teaching hospital. The project was approved by the Institutional Ethical Committee. Forty consecutive patients conforming to the diagnosis of unipolar depression constituted the study group. The diagnosis was established as per the International Classification of Diseases-10 Diagnostic Criteria for Research criteria. Patients with underlying or comorbid medical condition, psychotropic depression, and those who were already on psychotropic medicines were excluded from the study. Cases having contraindication for imipramine and/or lithium treatment were also excluded from the study. The aim of the study and the method adopted was explained to each patient and his/her cooperation was solicited. Written informed consent was obtained from every patient. Findings of physical examination, mental status evaluation, sociodemographic data were recorded on a specially designed pro forma. All baseline investigations including electrocardiogram and thyroid function were carried out as per standard guidelines. All patients were randomly assigned to one of the two groups: Group A patients were given tablet imipramine and placebo. Group B patients were administered tablet imipramine and tablet lithium carbonate as per schedule given below. The assessment of psychopathology was done by structured interview of the Hamilton Depression/Melancholia Scale designed by Williams. The instrument ensured a high inter-rater reliability. The serial readings were made at 4 weekly intervals starting at day 1.

**Administration of tricyclic antidepressant and lithium**

Imipramine hydrochloride was used for all the patients. The investigator had reviewed the records maintained at this center and found that clinical response was recorded in almost all cases at the dose range of 100–150 mg. Barring unforeseen developments, each patient was to be brought up to dose of 150 mg by day 14. The dose was maintained at that level during the study period. Lithium carbonate was administered in such a way as to achieve a serum lithium concentration in the range of 0.6–0.8 mEq/L by day 7. This range was subject to revision in case of unforeseen circumstances. It was arrived at taking into consideration the findings of earlier studies. Lithium concentration was measured by atomic absorption spectrophotometry. The nursing staff who administered the drugs was blind to the nature of regimen given to the patients. A professional colleague’s help was taken to maintain the double-blind format.

**Statistical analysis**

Students $t$-test was utilized to test the significance of the difference of means of scores at weekly intervals while categorical data were put to Chi-square test, using the Statistical Package for Social Sciences - Version 16.0 (SPSS 16.0. IBM).

**RESULTS**

Demographic and clinical details of depressed patients in both groups did not show any significant differences [Table 1]. The two groups did not differ in duration for their current depressive episode [Table 2]. Most of the patients in both the groups complained of multiple somatic complaints. The patients did not differ in terms of frequency a particular symptom [Table 3]. Depression scores of Group “A” and Group “B” patients at baseline and percentage reduction of scores at weekly intervals is shown in Tables 4 and 5, respectively. Comparison of two Groups in depression ratings at baseline and at weekly intervals [Table 6]. There is no difference between the two groups at baseline, but the difference is significant at the end of $1^{st}$ week, $2^{nd}$ week, $3^{rd}$ week, and $4^{th}$ week.
Mean percentage reductions in depression ratings at weekly intervals for both the groups revealed a larger reduction in depression ratings for Group “B” as compared to Group “A” at end of 1st, 2nd, 3rd, and 4th week [Figure 1]. Difference between the baseline scores and at scores at weekly intervals for Groups A and B is shown in Table 7. There are significant reductions in depression ratings for both groups at 1 week, 2 week, 3 week, and at 4 week intervals. However, the decline in scores is more for Group B as compared to Group A. The mean serum lithium level for the Group achieved was 0.555 (standard deviation: 0.186). The plasma serum levels of lithium correlated with the clinical response positively at 1 week but had no correlation at 4 weeks [Table 8].

Majority (65%) of patients of Group B showed at least 25% improvement in depression ratings by the end of the 1st week. Although the sample size in nonresponder group (i.e., <25% by 1 week) is small, but the trend shows a positive correlation of response with female gender, married status of the patient, absence of an enduring psychosocial problem, and a positive family history for a mood disorder [Table 9].

The most common side effect for Group A was dry mouth whereas it was digital tremor for the Group B patients.
Table 5: Depression scores of Group B patients at Baseline and at weekly intervals

| Serial number | Baseline | End of 1st week | Percentage reduction from baseline | End of 2nd week | Percentage reduction from baseline | End of 3rd week | Percentage reduction from baseline | End of 4th week | Percentage reduction from baseline |
|---------------|----------|-----------------|-----------------------------------|-----------------|-----------------------------------|-----------------|-----------------------------------|-----------------|-----------------------------------|
| 1             | 29       | 26              | 10.3                              | 17              | 41.3                              | 7               | 75.8                              | 7               | 75.8                              |
| 2             | 26       | 21              | 19.2                              | 16              | 38.5                              | 14              | 46.1                              | 11              | 57.6                              |
| 3             | 24       | 17              | 29.1                              | 11              | 54.1                              | 13              | 45.8                              | 9               | 62.5                              |
| 4             | 24       | 18              | 25                                | 14              | 41.6                              | 8               | 66.6                              | 9               | 62.5                              |
| 5             | 28       | 23              | 17.8                              | 16              | 46.1                              | 11              | 60.7                              | 8               | 71.4                              |
| 6             | 53       | 43              | 18.8                              | 37              | 24.5                              | 28              | 47.1                              | 24              | 54.7                              |
| 7             | 20       | 19              | 5                                 | 14              | 30                                | 10              | 50                                | 9               | 55                                |
| 8             | 32       | 28              | 12.5                              | 26              | 18.7                              | 22              | 31.2                              | 14              | 56.2                              |
| 9             | 26       | 22              | 15.3                              | 16              | 38.5                              | 10              | 61.5                              | 7               | 73                                |
| 10            | 36       | 32              | 11.1                              | 26              | 27.7                              | 18              | 50                                | 14              | 61.1                              |
| 11            | 32       | 26              | 18.75                             | 23              | 28.1                              | 16              | 50                                | 10              | 68.7                              |
| 12            | 40       | 35              | 12.5                              | 29              | 27.5                              | 22              | 45                                | 19              | 52.5                              |
| 13            | 38       | 30              | 26.66                             | 22              | 42.1                              | 16              | 57.8                              | 10              | 73.6                              |
| 14            | 42       | 37              | 11.9                              | 24              | 42.8                              | 17              | 35.7                              | 11              | 73.8                              |
| 15            | 36       | 30              | 16.66                             | 25              | 30.5                              | 18              | 50                                | 14              | 61.1                              |
| 16            | 32       | 24              | 25                                | 18              | 43.7                              | 16              | 50                                | 23              | 58.8                              |
| 17            | 42       | 36              | 14.28                             | 28              | 33.3                              | 24              | 42.8                              | 23              | 45.2                              |
| 18            | 37       | 40              | -8                                | 34              | 6                                 | 26              | 29.7                              | 19              | 48.6                              |
| 19            | 26       | 22              | 15.3                              | 14              | 46.1                              | 12              | 53.8                              | 8               | 69.2                              |
| 20            | 38       | 33              | 13.1                              | 28              | 26.3                              | 22              | 42.1                              | 15              | 60.5                              |
| Mean          | 33.05    | 28.1            | 16.5                              | 13.2            |                                   |                 |                                   |                 |                                   |
| SD            | 8.0031   | 7.55            | 6.03                              | 5.59            |                                   |                 |                                   |                 |                                   |
| SE            | 1.79     | 1.69            | 1.34                              | 1.25            |                                   |                 |                                   |                 |                                   |

SD – Standard deviation; SE – Standard error
Table 6: Comparison of two Groups in depression ratings at baseline and at weekly intervals (unpaired t-test)

| Time      | Group A | Group B | t  | P       |
|-----------|---------|---------|----|---------|
| Baseline  | Mean    | 33.05   | 31.4| 0.5448  | 0.5891 (NS) |
|           | SD      | 8.0031  | 10.9|         |            |
|           | SE      | 1.78    | 2.44|         |            |
| 1 week    | Mean    | 28.1    | 19.35| 3.8747  | 0.0004 (S) |
|           | SD      | 7.55    | 8.38 |         |            |
|           | SE      | 1.69    | 1.87 |         |            |
| 2 weeks   | Mean    | 21.9    | 12.3 | 3.6895  | 0.0007 (S) |
|           | SD      | 7.24    | 7.63 |         |            |
|           | SE      | 1.62    | 1.66 |         |            |
| 3 weeks   | Mean    | 16.5    | 7.4  | 2.8153  | 0.007 (S)  |
|           | SD      | 6.03    | 5.45 |         |            |
|           | SE      | 1.34    | 1.21 |         |            |
| 4 weeks   | Mean    | 13.2    | 5.1  | 2.2682  | 0.0291 (S) |
|           | SD      | 5.59    | 4.77 |         |            |
|           | SE      | 1.25    | 1.06 |         |            |

NS – Not significant; S – Significant; SD – Standard deviation; SE – Standard error

Table 7: Difference between the baseline scores and at scores at weekly intervals for Groups A and B (Student’s paired t-test)

| Time           | Group A | Group B | t  | P       |
|----------------|---------|---------|----|---------|
| Baseline to 1 week | 8.1859  | <0.05 (S) | 6.9664 | <0.01 (S) |
| Baseline to 2 weeks  | 13.8400 | <0.01 (S) | 9.5569 | <0.001 (S) |
| Baseline to 3 weeks  | 16.4007 | <0.01 (S) | 9.8109 | <0.0001 (S) |
| Baseline to 4 weeks  | 16.0319 | <0.001 (S) | 10.2738 | <0.0001 (S) |

5 – Significant

Table 8: Mean serum lithium levels and percentage response at 1 week and at 4 weeks for Group B patients

| Time at which mean serum lithium level was measured | Mean serum lithium level at week 1 | Percentage reduction of symptoms at week 1 | Percentage reduction of symptoms at week 4 |
|--------------------------------------------------|-----------------------------------|---------------------------------------------|--------------------------------------------|
| Mean                                             | 0.555                             | 38.37                                       | 83.75                                      |
| SD                                               | 0.186                             | 18.6                                        | 16.4                                       |
| $R^*$                                            | 0.60                              | 0.19                                        | 0.14                                       |
| PE                                               | 0.096                             | 0.14                                        |                                             |

$R^*$ Pearson’s correlation coefficient by direct method; PE – Probable error; SD – Standard deviation

Other side effects encountered were constipation, postural hypotension, foul taste, blurred vision, urinary problems, palpitations, and impotence. Manic switch for 2 patients in Group A and dysarthria and arrhythmia in one patient each for Group B were exclusively group specific [Table 10].

DISCUSSION

The last century was often termed as the century of anxiety. In contrast, 21st century can perhaps be described as the age of depression as evidenced by the fact that it is one of the most common scourges causing distress and disability. Although remarkable advances in somatic and psychological interventions have brought in salutary change, but patients are still obliged to endure the anathema at least for a few weeks until the administered drugs start to take effect. Ongoing research holds promise of rationalizing and optimizing drug therapies so as to provide maximum benefit to the patient. The current study was a step in this direction wherein an attempt was made to curtail the lag period of TCA response by the addition of lithium from the outset and comparing it with the same TCA monotherapy in a double-blinded randomized controlled study.

The mean age of the sample is around 37 years [Table 1]. The means are comparable to a similar study where mean age was about 39 years (39.5 for imipramine and 38.5 for imipramine + lithium group). A total of five patients in Group A and 1 patient of Group B [Table 1] shared a positive family of a mood disorder. A total of 6 patients of Group A and 5 patients of Group B [Table 1] had a history of mental or neurological illness. However, none of the patients had a concurrent medical or surgical illness and were not on any psychotropic medications (exclusion criteria). The trial was extended to include unipolar, recurrent depression as well as dysthymic patients [Table 1] against an earlier study where they restricted the sample...
to only bipolar depressed with melancholic features. Duration of the index depressive episode was identical for both the groups [Table 2]. The symptom profile for patients of both the groups at baseline [Table 3] is in agreement with a similar study,[25] which suggests higher prevalence of somatic rather than cognitive symptoms in depressed subjects of this country.

In the current study, patients receiving lithium and imipramine combination responded more rapidly and completely than the imipramine-placebo groups [Tables 4 and Figure 1]. The differences in response between the two groups at the end of 1st week, 2nd week, 3rd week, and 4th week were both statistically significant and clinically meaningful. The mean percentage change in depression ratings [Figure 1] after 1 week (38.37%) for the lithium + imipramine group was higher than the imipramine + placebo group (14.97%). Although the difference between the two groups [Table 6] was not significant at baseline ($t = 0.5891, P > 0.05$), but it was significant at week 1 ($t = 3.8747, P < 0.01$), week 2 ($t = 3.6895, P < 0.01$), week 3 ($t = 2.8153, P < 0.01$), and at week 4 ($t = 2.2682, P < 0.05$). The important clinical relevance in the finding is that the combination proves its superiority over monotherapy in that it brought a faster onset of action which persisted during the duration of the study. The mean percentage reduction at 4 weeks [Figure 1] of depression ratings was higher (96.2%) for Group B (imipramine + lithium combination) than that of 60.5% for Group A (imipramine + placebo combination) implying that the combination brought a more complete remission. The findings are supported by a similar study[26] who found better efficacy at 6 weeks rather than at 4 weeks.

The principal hypothesized mechanism of action of imipramine is its ability to inhibit reuptake of both serotonin and noradrenaline. The exact mechanism of action of lithium remains a mystery though recent research points toward its salubrious effect in stabilizing ionic and molecular transmission. Lithium is also known to produce striking enhancements in some aspects of serotonergic functions, which is also caused by Imipramine. Although the exact pharmacodynamics and pharmacokinetics were not the principal foci of this study, it appears that the superior response to the combination may have been obtained because of two separate actions

| Variable                                | Response | $F$-exact test ($P$) |
|-----------------------------------------|----------|----------------------|
| Age (years)                             | $>25\%$ (n=14) | $<25\%$ (n=6) | $>0.05$* |
| Mean                                    | 38.38    | 36.9                 |
| SD                                      | 8.12     | 8.87                 |
| Gender                                  |          |                      |
| Males                                   | 12       | 6                    | $<0.05$ |
| Females                                 | 2        | 0                    |
| Occupation                              |          |                      |
| Civilians                               | 3        | 4                    | $>0.05$ |
| Soldiers                                | 11       | 2                    |
| Marital status                          |          |                      |
| Married                                 | 13       | 2                    | $<0.05$ |
| Unmarried or widowed                    | 1        | 4                    |
| Education                               |          |                      |
| Below 10                                | 4        | 3                    | $>0.05$ |
| $>10                                     | 10       | 3                    |
| Interpersonal relations                  |          |                      |
| Cordial                                 | 9        | 4                    | $>0.05$ |
| Strained                                | 5        | 2                    |
| Psychosocial problem                    |          |                      |
| Yes                                     | 11       | 6                    | $<0.05$ |
| No                                      | 3        | 0                    |
| History of mental or neurological illness|          |                      |
| Yes                                     | 4        | 1                    | $>0.05$ |
| No                                      | 10       | 5                    |
| Family history of mood disorder         |          |                      |
| Yes                                     | 1        | 0                    | $<0.05$ |
| No                                      | 13       | 6                    |
| Duration of index episode, weeks except dysthymics |          |                      |
| Mean                                    | 8.5      | 8                    | $>0.05$* |
| SD                                      | 3.6      | 2.9                  |
| Type of depression                      |          |                      |
| Unipolar                                | 9        | 6                    | $>0.05$ |
| Recurrent                               | 3        | 0                    |
| Dysthymia                               | 1        | 1                    |

* $t$-test for difference between the two means has been used. SD – Standard deviation

and completely than the imipramine-placebo groups [Tables 4, 5 and Figure 1]. The differences in response between the two groups at the end of 1st week, 2nd week, 3rd week, and 4th week were both statistically significant and clinically meaningful. The mean percentage change in depression ratings [Figure 1] after 1 week (38.37%) for the lithium + imipramine group was higher than the imipramine + placebo group (14.97%). Although the difference between the two groups [Table 6] was not significant at baseline ($t = 0.5891, P > 0.05$), but it was significant at week 1 ($t = 3.8747, P < 0.01$), week 2 ($t = 3.6895, P < 0.01$), week 3 ($t = 2.8153, P < 0.01$), and at week 4 ($t = 2.2682, P < 0.05$). The important clinical relevance in the finding is that the combination proves its superiority over monotherapy in that it brought a faster onset of action which persisted during the duration of the study. The mean percentage reduction at 4 weeks [Figure 1] of depression ratings was higher (96.2%) for Group B (imipramine + lithium combination) than that of 60.5% for Group A (imipramine + placebo combination) implying that the combination brought a more complete remission. The findings are supported by a similar study[26] who found better efficacy at 6 weeks rather than at 4 weeks.

The principal hypothesized mechanism of action of imipramine is its ability to inhibit reuptake of both serotonin and noradrenaline. The exact mechanism of action of lithium remains a mystery though recent research points toward its salubrious effect in stabilizing ionic and molecular transmission.[15,26] Lithium is also known to produce striking enhancements in some aspects of serotonergic functions, which is also caused by Imipramine. Although the exact pharmacodynamics and pharmacokinetics were not the principal foci of this study, it appears that the superior response to the combination may have been obtained because of two separate actions

| Side effects                      | Group A (%) | Group B (%) |
|-----------------------------------|-------------|-------------|
| Dry mouth                        | 19 (85)     | 14 (55)     |
| Constipation                      | 12 (60)     | 9 (45)      |
| Postural hypotension              | 13 (65)     | 12 (60)     |
| Bitter/metabolic taste            | 14 (70)     | 11 (55)     |
| Blurred vision                    | 5 (25)      | 6 (30)      |
| Urinary hesitancy/polyurea        | 8 (40)      | 12 (60)     |
| Impotence/decreased libido        | 8 (40)      | 10 (50)     |
| Palpitations                      | 7 (35)      | 10 (50)     |
| Digital tremor                    | 6 (30)      | 20 (100)    |
| Dysarthria                        | 0           | 2 (10)      |
| Arrhythmia (conduction block)     | 0           | 1 (5)       |
| Muscle twitch                     | 1 (5)       | 1 (5)       |
| Manic switch                      | 2 (10)      | 0           |
concomitantly by imipramine (in monoamine enhancement at the synaptic cleft) and lithium (in altering intra-neuronal signal pathways) at molecular level.

The strategy is not new to medical profession and is an accepted norm in the treatment of malignancies and chronic infections such as tuberculosis and HIV. Lithium is not known to interfere with pharmacokinetics of imipramine, and the combination has been described to be a safe and effective one. At the outset, it was not known as to what degree patients would be tolerating the combination, and the emergence of side effects (in the form of coarse digital tremor) at the predefined serum levels of 0.6–0.9 mEq/L was underestimated. Emergence of this side effect in the combination group warranted a more cautious approach and serum lithium targets were revised from 0.6–0.9 mEq/L to 0.4–0.8 mEq/L. The strategy helped in restricting the tremor to only a mild form, which was acceptable to the patients. The use of other antitremor agents such as clonazepam or propranol was of course considered but was not required as tremors reached acceptable levels by just lowering the mean serum lithium levels. That the therapeutic effect was obtained with this much concentration is supported by earlier studies, which suggest that lower concentrations may be as effective as higher concentration for augmentation purpose. Moreover, correlation studies at 1 week and at 4 weeks [Table 8] suggest a mildly significant positive correlation at 1 week and an insignificant correlation at 4 weeks. This study did not address whether augmentation should be continued beyond 4 weeks. Lithium was administered for 4 weeks because the intent was to augment imipramine and interest was in early response. How far is the combination likely to be beneficial beyond 4 weeks is subject to further evaluation. However, existing research supports its use, and it may be an alternative in difficult cases.

On further analysis, it is seen that 14 out of 20 patients in Group B (i.e. 70%) showed a higher than 25% response in depression ratings by the end of 1st week [Table 9]. A search was made to study the variables associated with difference in response of more than 25% and that of <25%. The variables of age, occupation, educational status, interpersonal relations, past history of mental or neurological illness, depression typology, or duration of index depressive episode did not significantly influence the outcome though the variables of gender (of being females), married status, absence of enduring psychosocial problem, and a positive family history for a mood disorder predicted a better response. It appears fairly reasonable to presume at this stage that the response to lithium plus imipramine combination was quicker and superior than tricyclic monotherapy alone and it was seen across majority of depressed subjects. The limiting factor of the study was small sample size and a narrow spectrum of depressive disorders which were studied. However, more research in this direction with larger sample is suggested.

CONCLUSIONS

Concurrent administration of lithium and imipramine from the outset produced quicker antidepressant response in unipolar depression and the effect was evident in 70% of the patients by the end of the 1st week. However, larger sample and more studies are needed to confirm these findings.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.
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