Research on antidepressants in India

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ABSTRACT

Data suggests that antidepressants are useful in the management of depressive disorders, anxiety disorders, sexual dysfunction, eating disorders, impulse control disorders, enuresis, aggression and some personality disorders. Research focusing on the usefulness of antidepressants in India has more or less followed the trends seen in the West. Most of the studies conducted in India have evaluated various antidepressants in depression. In this article, we review studies conducted in India on various antidepressants. The data suggests that antidepressants have been evaluated mainly in the acute phase treatment and rare studies have evaluated the efficacy in continuation phase treatment.

Key words: Antidepressants, research, India

INTRODUCTION

Antidepressants as a class of drugs are used primarily in the management of depressive disorders and anxiety disorders. However, this class of drugs is also used for the management of sexual dysfunction, eating disorders, impulse control disorders, enuresis, aggression and some personality disorders.

Over the years many classes of antidepressants have become available in India, some of which have stood the test of time and are still in use and some, which are no more marketed or are no more a favorite of clinicians. The research focusing the usefulness of antidepressants in India has more or less followed the trends in the west; however, some of the antidepressants drugs which have been marketed have not been evaluated as thoroughly as others.

Most of the studies done in India have evaluated various antidepressants in depression. There are very few studies which have evaluated antidepressants in conditions other than depressive disorders. In this article, we review studies done in India on various antidepressants. The review shall focus on the research published in Indian Journal of Psychiatry and studies reported in PubMed indexed journals on efficacy, effectiveness, usefulness and tolerability issues of antidepressants in human subjects.

Efficacy/effectiveness in Depression

The trials done to evaluate the efficacy of antidepressants can be divided into studies evaluating an antidepressant (no comparator studies), efficacy of an antidepressant with placebo as a comparator, comparing efficacy of 2 active drugs and those evaluating the efficacy of antidepressants with other modalities of treatment like electro-convulsive therapy or psychological treatment.

Non Comparative Studies

A total of 18 open trials without a comparator group have been conducted to evaluate the efficacy of various antidepressants [Table 1]. Studies done in the 1960s evaluated the efficacy of tricyclic antidepressants. Later studies have evaluated the efficacy of nitroxazepine, centpropazine, amineptine, tianeptine, sertraline and milnacipran. Studies done prior to 1990s have not used any standardized rating scales, most of these also did not mention the diagnostic criteria used for the diagnosis. These studies included subjects diagnosed with various subtypes like reactive depression, endogenous depression, psychoneurotic depression, melancholic depression etc. However, the studies done after 1990s have recruited subjects diagnosed on the basis of DSM or ICD-10 RDC criteria and used standardized rating scales to evaluate the efficacy or effectiveness. The sample sizes of the studies have varied a lot, most of the earlier studies included less than 50 subjects; however, some of the recent studies have included more than 300 subjects. Most of these

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Table 1: Non-comparative studies evaluating efficacy of antidepressants in depressive disorders

| Authors                        | Duration (in weeks) | Sample size/scale/design | Medication(s) | Dose(s) in mg | Outcome                                                                 | Side-effects                                                                 |
|--------------------------------|---------------------|--------------------------|---------------|--------------|--------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Dube and Narendra[1]           | Variable            | N = 11                   | IMN           | 75-225       | • Subjects with endogenous depression showed marked improvement or complete recovery, the psychoneurotic variety showed little and no improvement was seen in schiz group | • Increase in pulse rate, dryness of mouth, hypotension, dilatation of pupils, stomatitis, constipation, excitement and sinking sensation |
| Davis[2]                       | 3-till needed       | N = 30                   | AMT           | 75-150       | • Sixteen subjects became Sx free; 8 subjects were substantially improved; taken together-77% improved, 3 subjects relapsed, when treatment was discontinued | • Dermatitis, constipation, restlessness and panic, dry mouth               |
| Kishore and Murti Rao[3]       | 3-6 months          | N = 10                   | AMT           | 75-150       | • Two lost on follow-up; • One patient improved slightly, 5-completely free of depression, 1-completely free of depression, 1-did not improve (hypochondriasis with sx of depression) | • One patient- severe generalized Pruritus. One patient-dizziness, ataxia, drowsiness, blurring of vision, dryness of mouth, nausea, sweating and pains in the knee joints. One patient- took overdose |
| Master,[4]                     | 4                   | N = 20                   | PTP           | 20-60        | • Effective in treatment of depression                                   | • Dryness of mouth                                                          |
| Kishore and Sharma[5]          | 15                  | N = 16                   | TIMN          | 25-300       | • 8/12 subjects who completed the trial showed response. Superior results were observed in endogenous depression and there was little or no effect on reactive neurotic depression | • Dryness of month, mild drowsiness, dizziness, headache, asthenia         |
| Sharma et al.[6]              | 10                  | N = 78                   | D-IMN         | 75-300       | • D-IMN was found to be effective                                        | • Dryness of mouth, palpitation, agitation, giddiness, constipation         |
| Shah et al.[7]                 | 6                   | N = 104                  | IMN + PRZ     | 75-225       | • Compound proved to be effective in controlling the depression with anxiety | • Commonly reported S/E included dry mouth, tremors, giddiness, constipation, difficulty in visual accommodation |
| Boral and Shah[8]              | 6                   | N = 32; DSM-III, HDR     | AMN           | 100-200      | • AMN was effective as soon as day 7 of treatment and this effect improved continuously throughout the study | • Safe                                                                     |
| Bhatt et al.[9]                | 6                   | N = 10; Pharmacokinetic study DSM-IHR HDRS | NTZ | 75-225      | • The overall reduction in HDRS score was about 50% by 6 weeks. The HDRS score showed a steady reduction between day 14 and 42 when the levels of NTZ and desmethyl metabolites were maintained between 176.5 ng/ml to 251 ng/ml | • No severe A/E reported                                                  |
| Srivastava et al.[10]          | 4                   | N = 42; HDRS, RDC criteria multicentric | CTZ | 40-120       | • Overall 81% of subjects responded • Antidepressant effect was seen in 9 subjects after 1 week, in 28 subjects after 2 weeks and in all 34 subjects after 3 weeks of therapy | • 11 subjects experienced S/E in the form of giddiness, headache, dryness of mouth and weakness |

(Contd...)
### Table 1: Comparison of Multicentric Placebo Controlled Trials

| Authors                     | Duration (in weeks) | Sample size/scale/design | Medication(s) | Dose(s) in mg | Outcome                                                                 | Side-effects                                                                 |
|-----------------------------|---------------------|---------------------------|---------------|---------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Parikh et al.[11]           | 6                   | N = 49; DSM-III, HDRS, HARS, MADRS Dysthymia/MDD | TPN           | 37.5-75       | • There was a significant drop in scores on the HDRS, HARS and MADRS by week 2 which was sustained till week 6 (P < 0.05) | • Common S/E were nausea, giddiness and drowsiness. |
| Channabasavanna and Khanna[22] | 6                   | N = 50; HDRS, MADRS, CGI, ZUNG | AMN           | 200           | • At the end of 6 weeks treatment there was significant reduction in HDRS | • No effect of AMN on heart rate and blood pressure |
| Sonawalla et al.[13]        | 6                   | N = 314; multicentric study outcome measure: Dropout rates MADRS, HARS | TPN           | 37.5          | • Intention to treat analysis showed that 7 subjects (2.3%) discontinued treatment due to S/E | • Well tolerated |
| Mohapatra et al.[14]        | 6 months            | N = 17; Patient of AMI with MDD randomized, single blind | STN Vs Cardiac TAU | 50-200        | • STN significantly better that TAU | • No dropouts due to non-response or S/E |
| Gada[15]                    | 60 day              | N = 320; MDD, HDRS       | TPN           | 37.5          | • Mean HDRS score decreased from 10.9 ± 3.2 at baseline to 6.9 ± 2.7 at day 60 (P < 0.01), with more than half the subjects showing > 50% improvement in HDRS score. Mean compliance with the medication was 91%. | • No patient withdrew due to S/E, which were reported in 23 subjects (7.2%). |
| Pinto et al.[16]            | 8                   | N = 119; MDD, DSM-IV, HDRS, MADRS | ESC           | 10-20         | • By week 8, 76.9% subjects had responded to treatment (≥ 50% reduction in MADRS total score). | • ESC was well tolerated, and only 2 subjects (1.7%) withdrew from the study due to A/E. There were no serious A/Es |
| Margoob et al.[17]          | 6                   | N = 57; DSM-IV, HDRS     | ESC           | 20            | • At the third week of treatment, 12 (63.15%) of Group II (group without functionally dominant genes) had a 50% reduction HRDS score compared to only 4 (10.52%) of the s (group with functionally dominant genes) group (P < 0.001) | • No effect of AMN on heart rate and blood pressure |
| Arora and Kaur[18]          | 6                   | N = 15; post stroke depression DSM-IV, HDRS | MSC           | 100-200       | • 85.71% (12/14) of subjects completing the study were in remission | • Not mentioned |

**Note:** IMN - Imipramine; schiz - Schizophrenia; AMT - Amitriptyline; PTP - Protriptyline; TIMN - Trimipramine; D-IMN - Desmethyl-Imipramine; S/E - Side-effects; PRZ - Promazine; HDRS - Hamilton depression rating scale; AMN - Aminpetine; NTZ - Nitoxazepine; A/E - Adverse effect; RDC - Research Diagnostic Criteria; CTZ - Centropazine; HARS - Hamilton Anxiety Rating Scale; MADRS - Montgomery Asberg Depression Rating Scale; MDD - Major Depressive Disorder; TPN - Tianeptine; CGI - Clinical Global Improvement Scale; ZUNG - Zung Depression Rating Scale; AMI - Acute myocardial infarction; STN - Sertraline; TAU - Cardiac treatment as usual; ESC - Escitalopram; MSC - Milnacipran

**Trials have evaluated the outcome after six weeks. All these trials have shown that various tricyclic antidepressants, nitroxazepine, centropazine, aminpetine, tianepine, sertraline, escitalopram and milnacipran are efficacious in treatment of depression. The trial which evaluated the efficacy of sertraline also showed that treatment of depression with sertraline leads to reduction in cardiac events post myocardial infarction.[13] A recently published trial, which evaluated the efficacy of milnacipran, included subjects who had suffered from stroke.[19] It is also one of the few trials which have included subjects more than 65 years of age. The trial done by Margoob et al.[17] in addition to the efficacy of escitalopram, have also shown that gene polymorphism plays an important role in the treatment response to various antidepressants.**

**Placebo-Controlled Trials**

Six placebo controlled trials have evaluated the efficacy of tricyclic antidepressants in depression [Table 2].[19-24] Four
of these trials have been double blind controlled trials,\cite{19-22} one recruited subjects by consecutive sampling,\cite{23} and one followed cross over design.\cite{24} The duration of these trials has varied from four to eight weeks and these have included 16 to 96 subjects. Of the five trials, one evaluated the efficacy of imipramine in depressive symptoms in schizophrenia\cite{24} and another included subjects with endogenous depression only.\cite{23} Five of these trials showed that amitriptyline, imipramine, protriptyline and trimipramine are better than placebo in the management of depression;\cite{19-23} however, the trial which evaluated the efficacy of imipramine for depressive symptoms in schizophrenia showed negative findings.\cite{24}

**Active Comparator Group Drug Trials of Efficacy**

There have been 18 trials which have compared two antidepressants.\cite{25-41} One trial compared amitriptyline with amitriptyline and trilafurperazine combination\cite{42} and one trial compared amineptine vs. amineptine with benzodiazepine.\cite{43} In another trial nortriptyline was compared with nortriptyline plus fluphenazine [Table 3].\cite{44} The duration of these trials have varied from 10 days to five months; however, most of these have been of four to six weeks duration. Sample size has also varied considerably ranging from 20 to 425 and only four trials have included 100 or more subjects. In terms of study design, 10 trials have followed double blind controlled design; five of these also followed adequate randomization. One trial followed single blind randomized control design and another three trials were open randomized controlled trials. Earlier trials used mixed group of depressive subjects, whereas, recent trials have included subjects with major depressive disorder only. All the trials have used standard doses of antidepressants.

Of the 21 trials, 18 have assessed the outcome of depression at the end of trial on Hamilton depression rating scale. Findings from these trials suggest that imipramine is superior to Nialmid,\cite{25} phenelzine,\cite{26} Go 299B,\cite{24} Go 2330\cite{27} and moclobemide\cite{28} in the treatment of depression. Antidepressants like noveril,\cite{29} iprindole,\cite{30} trimipramine,\cite{31} dothiepin\cite{32} and centropazaine\cite{33} have efficacy similar to imipramine. Imipramine has been found to be inferior to sintamil.\cite{34} The study which evaluated amitriptyline and trilafurperazine combination showed that it was no better than amitriptyline alone.\cite{42} Interestingly, the study which used fluphenazine found it to be as efficacious as

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**Table 2: Placebo controlled trials evaluating the efficacy/effectiveness of antidepressants in depressive disorders**

| Authors                  | Duration (in weeks) | Sample size | Medication(s) | Dose(s) in mg | Outcome                                                                 |
|--------------------------|---------------------|-------------|---------------|---------------|-------------------------------------------------------------------------|
| Master et al.\cite{19}   | 12                  | N=60 DBCT   | AMT           | 75-150        | • Only 12 subjects completed the trial<br>• Subjects in the AMT group showed better response compared to placebo |
| Shah et al.\cite{20}    | 4                   | N=56 DBCT   | AMT           | 75-150        | • 62% of subjects in AMT group improved compared to 29% in the PLB group |
| Bassa and Vora\cite{21} | 4                   | N = 96; DBCT | IMN           | 150           | • 60% of IMN subjects showed more than 50% response<br>• No difference between PLB and IMN |
| Teja et al.\cite{22}    | 8                   | N = 65; HDRS Crossover after 4 weeks | PTP          | 10-40         | • On drug treatment -29/46 subjects (63.0%) on PTP were better at 4 weeks with 19.5% rated as recovered, 21.5% were rated as markedly improved, and 21.5% were rated as improved<br>• In the PLB arm only 2(10.5%) of the 19 subjects were rated as improved<br>• The differences between the drug and PLB groups were significant<br>• Drug was better than placebo in all types of depression<br>• More effective in psychotic depressives and involutional melancholia |
| Nandi and Ajmani\cite{23} | 6                   | N = 16; Endogenous Dep, consecutive sample | TIMN         | 100-150       | • Improvement between the 2 groups was not significantly different at the end of week 1 or 2; but it was highly significant at the end of week 4 and the 6 week |
| Dua et al.\cite{24}     | 6                   | N = 18; DBCT, Depressive Sx in schiz RDC, HDRS >17 | CPZ + IMN vs CPZ + PLB | 1200, IMN 75-150 | • Both the groups showed significant reduction in dep. Sx after 6-week trial and the addition of IMN to CPZ therapy did not have any advantageous or deleterious effect. |

DBCT - Double Blind Controlled Trial; AMT - Amitriptyline; PLB - Placebo; S/E - Side-effects; IMN - Imipramine; HDRS - Hamilton Depression Rating Scale; PTP - Protriptyline; TIMN - Trimipramine; schiz- Schizophrenia; RDC - Research Diagnostic Criteria; CPZ - Chlorpromazine
Table 3: Active comparator group drug trials of efficacy/effectiveness of antidepressants in depressive disorders

| Authors          | Duration (in weeks) | Sample size | Medication(s) | Dose(s) in mg | Outcome | Side-effects |
|------------------|---------------------|-------------|---------------|---------------|---------|--------------|
| Chatterjee and Jindal[42] | 3-5 months          | N = 20      | AMT Vs AMT + TFP | AMT 150 AMT 150 + TFP | • 14/20 (70%), showed good response to depressive symptoms, with 8 reporting complete relief of symptoms. Results were better when TFP was added (75% Vs 66) | • TFP reduced the S/E of AMT |
| Neki[33]        | 12                  | N = 200     | IMN Vs NLD Vs PLZ Vs FPZ | IMN 25-200 NLD 25-200 PLZ 15-120 | • IMN was the most effective of antidepressant among the 3 drugs | • IMN produced more S/E than NLD or PLZ |
| Teja and Narang[20] | 4                   | N = 30; HDRS, DBRCT | GO 2998 vs GO 2330 vs IMN | • 77.5% of subjects in IMN group, 55.5 in GO 2998 and 44.4 in GO 2330 groups had more than 50% reduction in HDRS | • S/E appeared most frequently during week 2 or three of trial. | • Maximum S/E were observed with GO 2998 and then with IMN. Go 2330 had the least number of S/E |
| Kumar et al.[37] | NA                  | N = 50      | NVL vs IMN     | NA            | • NVL appears to be a promising and safe treatment for depression | • NVL relatively free of severe S/E |
| Teja and Bhatia[21] | 6                   | N = 59; HDRS, DBRCT | IPL vs IMN     | IPL-180 IMN-150 | • Out of the 59 subjects, 47 completed the 4 weeks period of trial and 12 dropped out (6 each on IPL and IMN) after taking the drugs for a variable period | • Commonest S/E with TIMN were giddiness, weakness, difficulty in walking, drowsiness and dryness of mouth |
| Satiya et al.[31] | 6                   | N = 40; HDRS, DBRCT | TIMN vs IMN    | TIMN-150 IMN-150 | • At 4 weeks, 16 subjects (80%) recovered with TIMN as compared with 14 subjects (70%) with IMN. There was no effect in 4 subjects with TIMN and 6 subjects with IMN and there was no significant difference between the 2 groups | • There was no difference in the frequency of observed clinical side-effects between the two groups of subjects |
| Desouza and Chaudhary[30] | 4                   | N = 64; Modified HDRS, DBRCT | STL vs IMN     | STL-150-250 IMN-150-250 | • 69% of cases treated with STL showed a good response, i.e. reduction in total global score by 50% or more in comparison to only 40.9% of cases treated with IMN responded favorably and this difference was significant | • S/E of severe intensity were seen only with IMN |
| Mahal et al.[44] | 4                   | N = 100; HDRS, DBRCT | FPZ + NTP (20 vs 40) vs NTP (20 vs 40) vs FPZ | FPZ-1 NTP-20-40 | • Only FPZ group showed 63% reduction in HDRS and NTP 20 mg/day group showed 47% reduction in HDRS with other groups falling between the above 2 groups. However, the difference in mean reduction between the treatment groups is not statistically significant | • There were 5 instances of S/E with STL and 13 with IMN |
| Chaturvedi et al.[31] | 4                   | N = 30; DBRCT, HDRS | DTP Vs IMN     | DTP 25-150 IMN 25-150 | • Mean percentage reduction in total HDRS score was more with DTP than with IMN throughout the treatment period, though there was no significant difference between the two treatments in terms of overall response and in the response of target Sx | • Headache, dizziness, body pains and burning sensation were commonly complained of by subjects in all the groups. These complaints were more numerous and intense in those who showed poor response to treatment |

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### Research on Antidepressants

| Authors                  | Duration (in weeks) | Sample size/scale/design | Medication (s) | Dose (s) in mg | Outcome                                                                 | Side-effects                                                                 |
|--------------------------|--------------------|--------------------------|----------------|----------------|--------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| Mahendru et al.          | 4                  | N = 40; HDRS, ICD-9      | NTZ vs DXN     |                | • There was more than 75% improvement in total HDRS score in 80% of subjects treated with NTZ as compared to 35% subjects receiving DXN  | • None of the subjects on NTZ reported any unwanted or undesirable effects, while one fourth subjects treated with DXN had side-effects like dryness of mouth, giddiness and drowsiness |
|                          |                    |                          |                |                | • NTZ was found more effective in controlling self reproach and guilt feelings, agitation and social withdrawal  |                                                                             |
|                          |                    |                          |                |                | • There was no significant difference between the two groups in terms of reduction in total Hamilton scores |                                                                             |
| Vyas et al.              | 6                  | N = 60; HDRS, SBRCT      | DTP vs IMN     | DTP -50-150 IMN 50-150 | • HDRS scores improved significantly from baseline to the end point (reduced from 22.8 to 11.9)  | • Three subjects receiving DTP and one receiving IMN developed hypomanic/manic features |
|                          |                    |                          |                |                | • The significant improvement on HDRS was evident as early as 2 weeks  |                                                                             |
|                          |                    |                          |                |                | • 21 out of 37 subjects improved (56.8%) to a moderate degree or more, 21.6% of subjects were reported to have slight improvement whereas 21.6% showed no change or worsening in their conditions  |                                                                             |
|                          |                    |                          |                |                | • Did not present the comparison analysis of the 3 groups  |                                                                             |
| Agarwal et al.           | 6                  | N = 40; HDRS, Open trial | AMN vs AMN + BDZ vs BDZ alone | 100-200 | • HDRS scores improved significantly from baseline to the end point (reduced from 22.8 to 11.9)  | • AMN was well tolerated. The S/E reported included dryness of mouth, epigastric pain, constipation, jaundice, headache, insomnia, flushing, and restlessness |
|                          |                    |                          |                |                | • The significant improvement on HDRS was evident as early as 2 weeks  |                                                                             |
|                          |                    |                          |                |                | • 21 out of 37 subjects improved (56.8%) to a moderate degree or more, 21.6% of subjects were reported to have slight improvement whereas 21.6% showed no change or worsening in their conditions  |                                                                             |
|                          |                    |                          |                |                | • Did not present the comparison analysis of the 3 groups  |                                                                             |
| Parikh et al.            | 6                  | N = 67; DSM-IIIR Dysthymia/MDD HDRS, HARS, MADRS | TPN vs AMT     | TPN 37.5-75 AMT 37.5-75 | • Both TPN and AMT led to significant improvement in depression from the 2nd week onwards which was sustained till the end of the study (P < 0.05)  | • Subjects on TPN had significantly fewer anticholinergic S/E than those on AMT |
|                          |                    |                          |                |                | • The antidepressant efficacy of CTZ is similar to IMN  |                                                                             |
| Srivastava et al.        | 6                  | N = 159; HDRS, CGI, DBRCT multicentric study | CTZ vs IMN     | CTZ -40 to 120 IMN -50 to 150 | • MTZ is effective in major depression and its efficacy is equivalent to AMT  | • MTZ was better tolerated than AMT  |
|                          |                    |                          |                |                | • HDRS reduced by 89.91% in the MTZ group and by 54.04% in the AMT group  | • Only six subjects (28.57%) reported S/E, in contrast to 17 (94.45%) subjects in the AMT group |
| Mathur et al.            | 6                  | N = 39; DSM-IV, HDRS, CGI Open RCT | MTZ vs AMT     | MTZ 15-45 AMT 25-150 | • HDRS reduced by 89.91% in the MTZ group and by 54.04% in the AMT group  | • Only six subjects (28.57%) reported S/E, in contrast to 17 (94.45%) subjects in the AMT group |
|                          |                    |                          |                |                | • MTZ is effective in major depression and its efficacy is equivalent to AMT  | • Only six subjects (28.57%) reported S/E, in contrast to 17 (94.45%) subjects in the AMT group |
| Vaya et al.              | 4                  | N = 214; DBRCT multicentric ICD-10, HDRS, CGI | CPM vs ESC vs STN | CPM 20-40 ESC10-20 STN 50-150 | • Response rate (50% reduction in HDRS) at the end of 4 weeks was 90% for ESC, 86% for CPM and 97% for STN  | • MTZ was better tolerated than AMT  |
|                          |                    |                          |                |                | • Remission rate (HDRS < 8) at the end of 4 weeks was 74% for ESC, 65% for CPM and 77% for STN  | • Only six subjects (28.57%) reported S/E, in contrast to 17 (94.45%) subjects in the AMT group |
| Avasthi et al.           | 6                  | N = 60; HDRS, MADRS, open RCT, ICD-10 | MCB vs IMN     | MCB300-600 IMN 75-300 | • IMN better than MCB  | • Subjects who received MCB had a better S/E profile  |
|                          |                    |                          |                |                | • 62% of subjects in MCB group and 84% in the IMN group were classified as responders on HDRS  |                                                                             |
|                          |                    |                          |                |                | • There were 52.38% responders in the MCB group and 73.68% in the IMN group on MADRS  |                                                                             |
| Mathur et al.            | 6                  | N = 40; DSM-IV HDRS, CGI, Open RCT | CPM vs AMT     | CPM 20-60 AMT 75-150 | • The percentage reduction in the mean HDRS score for the CPM group was 72.12%, while that for the AMT group was 67.93% and there was no statistical difference between the two groups  | • 20% of subjects in the CPM group reported S/E whereas 75% of subjects in AMT group reported S/E  |
|                          |                    |                          |                |                | • There was significant reduction in HDRS, MADRS, CGI scores from baseline to endpoint (P < 0.05) in both the groups  |                                                                             |
|                          |                    |                          |                |                | • There was no significant difference between the two groups  |                                                                             |
|                          |                    |                          |                |                | • Response and remission rate was 96% and 69% in DLT group as compared to 92% and 62% in VFN group respectively  |                                                                             |
| Badyal et al.            | 6                  | N = 26; MDD, DSM-IV, open RCT, HDRS, MADRS, CGI | DLT vs VFN     | DLT 20-40 VFN 75-150 | • There was no significant difference in A/E and laboratory investigation in two groups  |                                                                             |

(Contd...)
Nitroxazepine has been shown to be better than doxepin in treatment of depression. The amineptine trial, didn’t present data with regard to comparison in efficacy between the various groups of medications. The studies which have compared various selective serotonin reuptake inhibitors have shown that these are equally effective, except for one which showed that citalopram was better than sertraline. The only trial done on mirtazapine suggests that it is better than amitriptyline. Studies have also shown that citalopram and tianeptine are as efficacious as amitriptyline. The trial by Badyal et al. suggests that duloxetine is as efficacious as venlafaxine in the treatment of major depression. One of the recent multicentric trials have shown that escitalopram is superior to investigational drug LY2216684.

Active Comparator Group (non-pharmacological treatment/ electroconvulsive therapy) Trials of Efficacy/Effectiveness.

One study has compared the usefulness of antidepressants with respect to non pharmacological treatment and two studies have compared antidepressants with electroconvulsive therapy for treatment of depression. Another study compared antidepressants with both electroconvulsive therapy (ECT) and non-pharmacological treatment. One of these studies has shown that pharmacotherapy is more effective and more economical than non-pharmacological treatment. However, one study showed no difference between ECT, antidepressant and Sudarshan kriya in the management of depression over the period of three weeks. The studies which compared ECT with imipramine didn’t find any difference in efficacy between the two; however, Gangadhar et al. reported quicker response with ECT compared to imipramine.

Dosing Studies of Antidepressants

Seven trials have evaluated the different dosing schedules for treatment of depression. These studies suggest that parenteral imipramine is better than oral imipramine and possibly the onset of action is also earlier. Studies have evaluated single dosing versus multiple dosing have shown no difference in efficacy except for one study, which showed that single dose nitroxazepine was better than divided doses.

Prescription Patterns of Antidepressants in Depression

Chakrabarti and Kulhara evaluated the antidepressant prescription pattern in a tertiary care hospital for management...
Side-effects

Duration
N=75
AMT
CDP
IMN
IMN
vs ECT
vs ECT
N= 32; DBRCT, HDRS, Feighner’s criteria, Abrahams criteria for Endogenous dep
N = 30; RCT, MDD, DMS-IV, HDRS, MADRS, CGI, BDI
N= 45; BDI, HDRS

Outcome
• Clinically, drug therapy was found to be more effective and economical.
• However, PPT was effective in relieving the anxiety and depression as well as improving social adjustment. Drug therapy was effective only in the relief of depression.
• Both treatments produced equally significant improvement which was maintained till the end of 6 months.
• ECT produced its effects quicker.
• No significant difference in the two groups on HDRS, MADRS, CGI and BDI.
• No significant difference in 3 groups with regard to reductions in the total scores on BDI and HDRS.
• Remission (HDRS < 7) at the end of the trial - 93%, 73% and 67% in the ECT, IMN and SKY groups, respectively.

Side-effects
• Subjects who received ECT reported lesser subjective S/Es.
• S/E scores at 2 and 4 weeks were lower in ECT group.
• No clinically significant S/Es observed.

of depression during acute and continuation phase. For the evaluation of prescription pattern during the acute phase, case notes of 108 cases fulfilling the ICD-10 criteria of depression or recurrent depression (F32 and F33) were examined. Imipramine was the most commonly prescribed antidepressants followed by Fluoxetine. The authors also observed that pharmacotherapy was often deficient in several areas such as, starting doses, rate of increase in dose, maximum doses used, dose titrations, duration of treatment, change of drugs, recording of side-effects and compliance etc. Results regarding norms for adequate doses and periods of treatment before switching drugs, for the kind of subjects included in this study, were unclear. Regarding the continuation phase treatment, the authors observed that it was deficient in about a third (n = 24; 34 %) of the cases, on either of the two parameters i.e., dose of drugs or duration of treatment and the outcome was poorer in those treated inadequately.

Efficacy/effectiveness in Disorders Other Than Depression Obsessive compulsive disorder/symptoms [Table 6]
One double blind controlled trial has evaluated the efficacy of clomipramine in the treatment of OCD and showed that clomipramine was superior to placebo in the management of OCD.[59] This study also showed that male subjects showed better response than female subjects. Another study evaluated the efficacy of clomipramine in late onset OCD with comorbid Parkinsonism and showed that clomipramine can be used in elderly subjects and in the presence of Parkinsonism.80 A small open label study evaluated the usefulness of neuroleptic and fluoxetine combination for treatment of obsessive compulsive (OC) symptoms occurring during the course of schizophrenia and showed that addition of fluoxetine leads to significant improvement in OC symptoms.81

Insomnia [Table 6]
One study evaluated the efficacy of antidepressants in insomnia and showed that trimipramine was similar to nitrazepam for treatment of insomnia, especially in the presence of anxiety and depression; however, it had poor tolerability as compared to nitrazepam.82

Generalized Anxiety Disorder [Table 6]
One trial included subjects with generalized anxiety disorder, mixed anxiety depression and dysthymia and showed that imipramine was as effective as diazepam for anxiety symptoms and better than diazepam for the depressive symptoms.83

Depressive Symptoms in Schizophrenia [Table 6]
One trial used imipramine in combination of chlorpromazine and compared it with chlorpromazine alone in the treatment of depressive symptoms in schizophrenia and didn’t find any benefit of adding imipramine to chlorpromazine in the treatment of treatment of depressive symptoms in schizophrenia.84

Common Mental Disorders [Table 6]
Two studies have also studied the usefulness of antidepressants in common mental disorders. One study showed that treatment completion rates were higher with fluoxetine than imipramine.85 The trial by Patel et al.86 included subjects with common mental disorders and evaluated the outcome at one year. It can be considered the longest study which has evaluated the effectiveness of antidepressant in Indian subjects.
Table 5: Dosing studies of antidepressants

| Authors                  | Duration (in weeks) | Sample size/ scale/design | Medication (s) | Dose (s) in mg | Outcome                                                                 | Side-effects                                                                 |
|-------------------------|---------------------|----------------------------|----------------|----------------|-------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Chatterjee and Dayal    | 6-12                | N = 80                     | IMN IM         | 25-100         | • Parenteral IMN more effective                                         | • Most common S/E: Dryness of the mouth, severe constipation and tremors   |
| DeSouza et al.          | 2 weeks             | N = 3; HDRS DBCT           | Parental NTZ   | 75-150         | • Pattern of reduction in the mean HDRS is similar to both the groups   | • Intra muscular NTZ was well tolerated                                    |
| Sharma and Nandkumar    | 4 weeks             | N = 20                     | DTP (OD dose   | 75-150         | • 2 subjects receiving divided doses showed marked improvement,        | • S/E reported: Giddiness, restlessness, palpitation, breathlessness, chest pain, visual black out, perspiration |
| Shah et al.             | 6 weeks             | N = 28; HDRS DBCT          | DTP (Single    | 225            | • 64.28% in the single dose and 71.42% in the divided dose group had >50% reduction in HDRS | • S/E more common with single dose                                         |
| Singh et al.            | 4-6                 | N = 57                     | NTZ (single     | 75-150         | • At both 4 and 6 weeks, OD dose better than divided doses              | • Common S/E reported were dryness of mouth and constipation               |
| Sharma and Hegde        | 4 weeks             | N = 43; HDRS DBCT          | DXN (Single     | 75-150         | • 94% in the OD dose and 81% in the divided dose group had >50% reduction in HDRS | • No significant difference in S/E profile between single and divided doses |
| Sharma                  | 4 weeks             | N = 30                     | DTP (Single     | 75             | • No significant difference between the groups in terms of reduction in mean Hamilton scores | • S/E reported were mild and did not require discontinuation of medication |
| Malhotra and Santosh    | 4 weeks             | N = 16; DSM - IIIR DBRCT  | IMN Loading     | 75             | • IMN hydrochloride can relieve depression almost completely within 72 hrs, if given in high bolus doses | • No difference in S/E reported between the 2 dosing schedules            |

IMN - Imipramine; IM - Intra muscular; S/E - Side-effects; HDRS - Hamilton depression rating scale; NTZ - Nitroxazepine; DTP - Dothiepin; DBCT - Double blind controlled trial; DXN - Doxepin

Sexual Dysfunction [Table 6]

Various sexual side-effects of antidepressants have been utilized for the management of sexual dysfunction. In a recently published open trial Dhikav et al.[67] compared fluoxetine with yoga for the management of premature ejaculation. The study included 68 subjects, of whom 38 were in the yoga group and 30 subjects in the fluoxetine group. All 38 subjects (25-65.7% 5 good, 13-34.2% 5 fair) of yoga group and 25 out of 30 of the fluoxetine group (82.3%) had statistically significant improvement in premature ejaculation and the
| Authors                  | Duration Sample size | Medication Dose | Outcome                                                                 | Side-effects                                                                 |
|-------------------------|----------------------|-----------------|---------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Ananth et al.⑩⑩        | 12                   | N = 27          | CLN Vs PLB                                                                | • At termination, statistically significant improvement (52.8%) in YBOCS score in the drug group and 10% in the PLB group. |
|                         |                      |                 |                                                                           | • Improvement in the CLN group at 4, 8 and 12 weeks of treatment and the difference between the two groups was statistically significant. |
|                         |                      |                 |                                                                           | • Male subjects improved better than the females (78% vs. 51%), and the difference was statistically significant. |
| Agarwal and Agarwal⑩⑩  | 12                   | N = 7           | Neuroleptic + FLX 40-80                                                   | • Five subjects showed response in both OC and psychotic symptoms, 2 showed no response. |
|                         |                      |                 |                                                                           | • At 12 weeks, there was a significant improvement on YBOCS. |
|                         |                      |                 |                                                                           | • Total scores on PANSS also showed a significant reduction, it was significant on all the three subscales of PANSS. |
|                         |                      |                 |                                                                           | • Significant reduction in CGI severity scores. |
|                         |                      |                 |                                                                           | • On CGI 1 patient showed very much improvement, 3 - much improvement, 1- minimal improvement, 2 - no change. |
|                         |                      |                 |                                                                           | • 5 out of 10 subjects showed 100% improvement, 3 showed 75% improvement, 1 showed 50% improvement and 1 showed 40% improvement in YBOCS. |
| Agarwal et al.⑩⑩        | 32                   | N = 10; Late onset OCD (>40 years) with Parkinsonism; YBOCS | CLN IMN-150/1200 CPZ up to 80 IMN 75-150 CPZ + IMN 200 CLN + PLB | • None had worsening of psychotic Sx. |
|                         |                      |                 |                                                                           | • Dryness of mouth seen only in TIMN group. |
|                         |                      |                 |                                                                           | • Not mentioned. |
| Vyas and Purohit⑩⑩      | 10 days              | N = 61          | TIMN vs NZM                                                               | • Treatment completion rates were higher with FLX and least with the IMN 150 mg/day. |
|                         |                      |                 |                                                                           | • IMN and DPM were found to be equally effective (62.8% vs 62.2%) in reducing anxiety in all subjects. IMN was significantly better than DPM in reducing the level of depression in the depressed group but as effective as DPM in the other two groups. |
|                         |                      |                 |                                                                           | • IMN was significantly better for the symptoms of ‘depressed mood’ and ‘retardation’, while DPM was better for Sx of ‘fears’. |
| Singh et al.⑩⑩          | 4                    | N = 90          | IMN vs DPM                                                                | • Psychiatric outcome was significantly better with FLX than with PLB at 2 months, but not over the 2-12 month period. |
|                         |                      |                 |                                                                           | • AD were significantly more cost effective than PLB in the short term and long term (P < 0.05). |
|                         |                      |                 |                                                                           | • Psychological treatment was not more effective than PLB for any outcome during either period. |
|                         |                      |                 |                                                                           | • All 38 subjects (25-65.7% = good, 13-34.2% = fair) belonging to yoga and 25 out of 30 of the FLX group (82.3%) showed statistically significant improvement in PME. |
|                         |                      |                 |                                                                           | • Commonly reported S/E of FLX- nausea, insomnia, vomiting, anxiety. |
| Dua et al.⑩⑩            | 6                    | N = 18          | CPZ + IMN vs CPZ + PLB 1200 IMN 75-150 CPZ upto 1200 CPZ, CPZ + PLB         | • Anticholinergic SEs and giddiness were common in the IMN group; headaches and restlessness were common in the FLX group. |
|                         |                      |                 |                                                                           | • IMN treated group did not exhibit more S/E than the group receiving PLB. |
| Pereira and Patel⑩⑩     | 7                    | N = 61          | FLX vs IMN                                                                | • Both the groups showed significant improvement after the 6-week trial and the addition of IMN to CPZ therapy did not have any advantageous or deleterious effect. |
|                         |                      |                 |                                                                           | • Treatment completion rates were higher with FLX and least with the IMN 150 mg/day. |
| Patel et al.⑩⑩          | 12 months            | N = 450         | FLX vs PLB                                                                | • Psychiatric outcome was significantly better with FLX than with PLB at 2 months, but not over the 2-12 month period. |
|                         | (treatment for 6 months) |                 |                                                                           | • AD were significantly more cost effective than PLB in the short term and long term (P < 0.05). |
|                         |                      |                 |                                                                           | • Psychological treatment was not more effective than PLB for any outcome during either period. |
|                         |                      |                 |                                                                           | • All 38 subjects (25-65.7% = good, 13-34.2% = fair) belonging to yoga and 25 out of 30 of the FLX group (82.3%) showed statistically significant improvement in PME. |
|                         |                      |                 |                                                                           | • Commonly reported S/E of FLX- nausea, insomnia, vomiting, anxiety. |

YBOCS - Yale Brown Obsessive Compulsive Scale; DBCT - Double Blind Controlled Trial; CLN - Clomipramine; PLB - Placebo; PANSS - Positive and Negative Syndrome Scale; CGI - Clinical Global Improvement Scale; OC - Obsessive Compulsive; Schiz - Schizophrenia; OCD - Obsessive compulsive disorder; FLX - Fluoxetine; TIMN - Trimipramine; NZM - Nitrazepam; GAD - Generalized anxiety disorder; MAD - Mixed anxiety and depression; HDRS - Hamilton Depression Rating Scale; HARS - Hamilton Anxiety Rating Scale; IMN - Imipramine; DPM - Diazepam; DBCT - Double Blind Controlled Trial; Schiz - Schizophrenia; RDC - Research Diagnostic Criteria; CPZ - Chlorpromazine; CMD - Common Mental Disorders; PME - Premature ejaculation.
difference between the two groups was statistically significant too. In an open clinical study, Prusty and Rath (2000)[68] found clomipramine effective in nocturnal enuresis. In another open trial, Prusty et al. (2003)[69] found clomipramine 5 mg along with Sildenafil 50 mg was successful in preventing premature ejaculation of 18 men who had erectile dysfunction also.

**Childhood Onset Disorders** [Table 7]
Two studies have evaluated imipramine for management of enuresis in children.[70,71] In one of these trials,[71] in addition to enuresis, children had other behavioral abnormalities too. These studies have shown that imipramine is useful for management of enuresis and also for behavioral problems like obstinacy and temper tantrums. It was further seen that compared to subjects with mental retardation, the response to imipramine was better in children with average intelligence.

**Usefulness in other conditions** [Table 8]
Besides the above studies, case series and case reports have also shown usefulness of antidepressants in the management of trichotillomania with trichobezoar,[72] Atypical bulimia Nervosa,[73] Skin Picking,[74] Persistent developmental stuttering,[75] primary hypersomnia,[76] cognitive functioning in

### Table 7: Studies evaluating the efficacy of imipramine in childhood onset disorders

| Authors | Duration (in weeks) | Sample size/ scale/design | Dose (s) in mg | Outcome |
|---------|---------------------|---------------------------|----------------|---------|
| Chatterjee and Khandpur[70] | 6-8 | N=22 open label, (5-14 years) enuresis | 25-100 | • Good response (<1 week) - 4 cases  
• Delayed response (2-4 weeks) -14 cases  
• No response - 2 cases  
• Abandoned - 2 (1-S/E; 1- otherwise) |
| Mahendru et al. 1970[71] | 12 | N=75 open label, behaviorally disturbed children age - 4 to 15 years | 20-50 | • 58 of the 75 completed the trial  
• At 4 weeks - 46% of enuretic subjects recovered completely, 21% partially and 32% had no improvement  
• At 12 weeks - complete recovery - 68%; partial - 8%; no recovery - 24%  
• Recovery more in subjects with mild enuresis at the beginning  
• At 12 weeks - in obstinacy and temper - 53% favorable response; 47% - no improvement  
• Better response in intellectually average group (73%); compared to mentally retarded children (52%) |

### Table 8: Usefulness of antidepressants (findings from case reports/case series/descriptive studies)

| Antidepressant | Condition |
|----------------|-----------|
| Fluoxetine | Trichotillomania with trichobezoar[72]  
Atypical bulimia Nervosa[71]  
Skin Picking[74]  
Persistent developmental stuttering[75]  
Primary hypersomnia[76] | |
| Dothiepin | Improves cognitive functioning in depression[77] |
| Paroxetine | Proctalgia fugax with dysthymia[78]  
Palmar-plantar hyperhidrosis[79] | |
| Tranylcypromine | Severe resistant depression[80] |
| Zemelidine | Obsessive Compulsive disorder[81] |
| Sertraline | Chronic tension type headache[82]; Sertraline led to significant reduction (P > 0.05) in mean analgesic intake per week; however, there was no difference in reduction of headache index and percentage reduction in frequency of headache was not significant in sertraline group compared to placebo Late onset pedophilia[83]; | |
| Escitalopram | Transvestic fetishism[84] |
| Fluoxetine, Sertraline | Trichotillomania in children and adolescent[85]; Clozapine induced sialorrhea[86]; |
| Amitriptyline | |

### Table 9: Side-effects of antidepressants

| Side-effects | Antidepressant implicated |
|--------------|--------------------------|
| Antidepressant Induced/ associated hypomania/mania | • Venlafaxine 150 mg/day[87,88]  
• Escitalopram 20 mg/day[89,90]  
• Clomipramine 150 mg/day[88,90]  
• Tricyclic induced mania[91]  
• Fluoxetine 60 mg/day[92]  
• Sertraline 50 mg/day[93,94]  
• Citalopram[95] | |
| Antidepressant associated hyponatremia/SIADH | • Citalopram 10 mg/day in elderly subjects[97]  
• Escitalopram 10-15 mg/day in elderly subjects[98]  
• Sertraline[99]  
• Fluoxetine induced akathisia 20mg/day[100]  
• Fluoxetine 80 mg/day and amitriptyline 150 mg/day[101]  
| | |
| Antidepressant associated extrapyramidal Symptoms | • Clomipramine 50 mg/day[101]  
• Imipramine 150 mg/day (on withdrawal)[102]  
• Buproprion 300 mg/day[103] | |
| Acute colonic (pseudo) obstruction (Ogilvie syndrome) | • Venlafaxine 150 mg/day[104]  
• Fluoxetine 20 mg/day[105]  
• Dothiepin 25 mg/day[106]  
| | |
| Seizures | • Fluoxetine 40 mg/day[107]  
• Imipramine 150 mg/day[108]  
| | |
| Galactorrhea | • Fluoxetine 20 mg/day[109]  
• Mirtazapine[110]  
• Paroxetine 25 mg/day[111]  
| | |
| Mania due to antidepressant withdrawal | • Imipramine 150 mg/day[112]  
| | |
| Upper Gastrointestinal Bleeding | • Sertraline 100 mg/day[113]  
• Duloxetine 40 mg/day[114]  
| | |
| Bleeding gums | • Paroxetine 560 mg/day[115]  
• Sertraline, trazodone and trazodonol[116]  
| | |
| Safety in overdose | • Lithium carbonate, amiodipine,phenytoin, sertraline, trazodone and escitalopram[117] | |
| Serotonin syndrome | • Sertraline[118]  
• Fluoxetine 20 mg/day[119] | |
| Facial Paresthesia/facial numbness and dysmorphic symptoms | • Escitalopram[120] | |
| Behavioral activation and Suicidality | | | |
depression, proctalgia fugax with dysthymia, palmar-plantar hyperhidrosis, severe resistant depression etc. One open label study also evaluated the usefulness of sertraline in chronic tension type headache and showed that sertraline leads to significant reduction in mean analgesic intake per week, but there is no difference in reduction of headache index and frequency of headache.

Tolerability of Antidepressants

As is evident from Tables 1 to 6, tricyclic antidepressants are poorly tolerated compared to the newer antidepressants. Additionally, there are multiple case reports implicating various antidepressants for induction of hypomania/mania, hyponatremia/Syndrome of inappropriate antidiuretic hormone secretion (SIADH), extrapyramidal symptoms, acute colonic (pseudo) obstruction (Ogilvie syndrome), psychosis, hypertension, vascular headache, torsades de pointes, alopecia, cardiogenic shock, seizures, galactorrhoea, mania on withdrawal of antidepressants, upper gastrointestinal bleeding, bleeding gums, serotonin syndrome etc [Table 9].

Antidepressant Withdrawal/Dependence

One case report presented tricyclic withdrawal syndrome with amitriptyline 300 mg/day and another was described by Jhiwal and Chakrabarti with Venlafaxine. Dependence syndrome has been described with dothiepin 450 mg/day.

Safety in Overdose

In a case report, Gupta et al. described a patient who could tolerate paroxetine 560 mg/day.

Conclusion and Future Directions

Many studies have evaluated the efficacy of antidepressants in depression and have shown that most of the currently marketed antidepressants are useful. In addition, studies also suggest usefulness of antidepressants in generalized anxiety disorder, dysthymia and common mental disorders. Many of the recent studies have been of good design and have followed double blind randomized controlled design and had reasonable sample size. Further, several studies have been carried out at multiple sites throughout the country. The available data also suggest that antidepressants are more cost-effective than other modalities of treatment for depression.

In addition, there is some evidence to suggest the usefulness of clomipramine in OCD and that of fluoxetine in management of OC symptoms in schizophrenia. However, some major limitations of the research have been that almost all the data available in relation to treatment of depression pertains to acute phase treatment and rarely studies have evaluated the continuation phase treatment. There is also lack of data with regard to the efficacy and effectiveness in the maintenance phase treatment. Surprisingly, no study has evaluated the efficacy/effectiveness of SSRIs in the management of OCD.

There is a need to conduct studies to evaluate the usefulness of antidepressants in the management of panic disorder and depression in medically ill subjects. Studies are also required to evaluate the efficacy of SSRIs in the management of OCD, and to study the usefulness of polypharmacy in the management of depression and other disorders. Studies are few and sparse and there is a need for multi-centric studies in such a vast country.

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