

## PATTERNS OF ANTIDEPRESSANT PRESCRIPTIONS : I ACUTE PHASE TREATMENTS

S. CHAKRABARTI & P. KULHARA

### ABSTRACT

*Although depression is an eminently treatable condition, inadequate pharmacotherapy is far too common. Lack of uniform standards of care across different settings characterises psychiatric practice in a developing country like India. But, there have hardly been any attempts at assessing the standards of care being delivered. A case note study was carried out of patients attending a general hospital psychiatric unit with depression, over a one year period, to evaluate the nature and adequacy of antidepressant therapy. Prescribing patterns in 108 cases fulfilling the selection criteria, were examined. The sample consisted mainly of young to middle aged patients, predominantly female, with moderately severe depressive episodes. Antidepressants were prescribed universally with TCAs (mainly Imipramine), followed by Fluoxetine being the most common drugs used. Pharmacotherapy was often found to be 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 patients included in this study, were unclear, and need to be explored further. Inadequate treatment can have a number of adverse consequences, hence some guidelines for minimum standards of care while undertaking antidepressant treatment need to be formulated for India and other developing countries, as none exist at present.*

*Key words: Antidepressant prescriptions, acute phase of depression*

Depressive episodes when accurately diagnosed, respond reasonably well to treatment (Richelson, 1993). Despite this well-known fact, under-treatment of depression is rife, perhaps partly due to difficulties in detecting and accurately diagnosing cases suitable for pharmacotherapy. However, sufficient evidence exists to suggest that a number of correctly diagnosed patients receive inadequate levels of somatotherapy or psychotherapy (Quitkin, 1985). Under-treatment is common in all settings, including psychiatric facilities (Goethe et al., 1988), primary care (Donoghue & Tylee, 1996), and in specialities other than psychiatry (Fauman, 1980). Treatment data gathered during the Collaborative Study of Psychobiology of

Depression (CDS) underlined this by showing that both prior to induction, and while in the study for several years, about one third to half of the patients received low levels of antidepressant treatment (Keller et al., 1986).

The reasons for under-treatment are not exactly clear, but lack of compliance, anticipation of side effects and unawareness of the need to continue treatment even when well, are some of the likely causes on the patient's part. Of more concern, is the tendency of some clinicians to prescribe low doses, or to decrease dose levels when minor side effects occur, and to desist from further efforts at achieving a therapeutic dose (Quitkin, 1985). The consequences of inadequate treatment are not hard to predict and include high

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risks of chronicity, recurrence, and relapse, as well as being labelled 'treatment resistant' (Keller et al., 1986; Keller, 1994).

Hardly any Indian studies have looked at the quality of psychiatric care being delivered, in a country where psychiatric practice is characterised by marked variability across different treatment settings, and a genuine need for establishing uniform standards of care. It was thus decided to examine the nature and adequacy of antidepressant prescribing practices in our unit. The aim was to gather data as a first step towards setting down certain minimum standards required to undertake treatment with antidepressants in India.

### MATERIAL AND METHOD

The study was carried out in the psychiatric unit of a large multi-speciality teaching hospital, the Nehru Hospital of the Postgraduate Institute of Medical Education and Research, Chandigarh.

All patients attending the unit are initially screened by a psychiatrist at the 'Walk-in' clinic level, and drug treatment often started. Subsequently, a detailed evaluation is done by a trainee psychiatrist under supervision of a consultant. Treatment plans are charted out, and patients are then followed-up in the outpatient clinic, unless admitted, or referred elsewhere.

Case notes for the year 1996 were scanned for all cases of depression. Those, which fulfilled the selection criteria, were included for purposes of the study. The data pertaining to antidepressants was then extracted from the notes and entered onto the preset proforma.

Selection criteria : cases were included if they were diagnosed to have either : - a) depressive episodes of mild, moderate, or severe type; with or without somatic symptoms (ICD-10), or b) recurrent depressive disorder with similar current episodes.

Cases were excluded if they had: - a) bipolar depression; b) any comorbid diagnoses; c) psychotic symptoms; d) chronic episodes (> 2 years); e) organic brain syndromes; f)

substance abuse; g) associated physical problems judged to be interfering with antidepressant treatment and h) follow up period less than 6 weeks.

A deliberate attempt was thus made to include relatively 'uncomplicated' cases of depression by excluding secondary depressions, chronic episodes, and comorbid conditions. Although this restricted the scope of the study, it was felt that proper judgements about adequacy of treatment could only be made after ruling out these confounding variables.

Criteria for 'adequacy' of antidepressant treatment were derived from standard guidelines and results of original studies. These are included in the appendix.

### RESULTS

Only the results pertaining to acute phase treatments are presented here.

Size of the sample : In all 108 case notes fulfilling the selection criteria were examined.

Selected demographics : Majority of the sample were females (58%), half of them aged between 20-39 years, and a little more than a quarter (26%) in the age range of 40-49 years. Families were divided into those with a monthly income of less than Rs. 3000 per month, and those with incomes at or above this figure. The rationale was that the average cost of some of the more expensive drugs would be about 5% of Rs.3000, thus placing a significant financial burden on families earning less than this. The sample had more families (56%) with incomes of Rs.3000 per month, or more.

Clinical profile :

Treatment setting : Most patients (95%) received treatment on an outpatient basis, perhaps reflecting the less severe nature of their depression. Five patients were admitted, 4 of them for ECT. They were subsequently seen in the outpatient clinic.

Length of follow up : Average length of follow up was 9.5 (s.d. 5.3) months; range 2 - 21 months. Average number of visits during the acute phase of treatment was 6.1 (s.d. 3.5).

## ANTIDEPRESSANT PRESCRIPTIONS : ACUTE PHASE TREATMENTS

**TABLE 1**  
**DIAGNOSTIC DISTRIBUTION OF THE SAMPLE \* †**

<b>1. Depressive episodes (n = 75)</b>	
Mild without somatic symptoms	3
Mild with somatic symptoms	3
Moderate without somatic symptoms	10
Moderate with somatic symptoms	36
Severe without psychotic symptoms	23
<b>2. Recurrent depressive disorder (n = 33)</b>	
Mild without somatic symptoms	2
Moderate without somatic symptoms	8
Moderate with somatic symptoms	15
Severe without psychotic symptoms	8

\* Total number of cases - 108

† ICD - 10 diagnoses

Index episode diagnosis

mild depression - n = 8 (7%)

moderate depression - n = 69 (64%)

severe depression - n = 31 (29%)

**Diagnostic distribution :** The diagnostic break up of the sample is shown in table-1. Moderate depression with or without somatic symptoms was by far the most frequent diagnosis (64%), for the index episode.

**Pre-treatment duration :** The average duration of the index episode prior to seeking treatment was 4.7 (s.d. 4.6) months, with a wide range from 1 week to 18 months. Pre-treatment duration was less than 3 months in 59% of the cases, a further 34% had a duration between 3-12 months. Durations of more than a year were rare (6.5%). Overall, the sample therefore consisted mainly of young to middle aged patients, mostly female, with moderately severe episodes of depression, which were of relatively short durations.

**Treatment profile :**

**Modes of antidepressant treatment :** Only data pertaining to the acute phases of treatment are presented here (table 2).

Sixty nine patients (64%) received only a single antidepressant. Antidepressants were changed once in 26 cases (24%), and in 13 patients (12%) a third or a fourth drug was used. Two antidepressants were used in conjunction in 19 cases (18%). In most of these patients Trazodone was the additional drug, used mainly for its sedative properties, in doses of 25-100 mg at night.

**Dose considerations :**

**TABLE - 2**  
**MODES OF ANTIDEPRESSANT TREATMENT \***

<b>1. TCAs **</b>	
Imipramine	50 (46%)
Dotheipin	18
Amitriptyline	12
Nortriptyline	8
Cloimipramine	2
Doxepin	1
Amineptine	1
<b>2. Fluoxetine</b>	
	47 (44%)
<b>3. Others</b>	
Mianserin	11
Amoxapine	6
Trazodone	1
<b>4. ECT</b>	
	5
<b>5. Lithium +</b>	
	1

\* Although total number of cases was 108, total number of 'treatment episodes' was more, because more than one treatment was used in a proportion of cases.

- All cases received antidepressants.

\*\* 92 patients (85%) received a TCA at some point during their treatment.

+ Lithium was used primarily to treat a hypomanic switch.

**Starting and maximum doses :** A total of 144 episodes of treatment with antidepressants were analysed. The starting and maximum doses were recorded for each episode, (table - 3).

**'Rate of hike' :** The time taken to attain maximum doses was less than 3 weeks in most (n=81; 56%) of the treatment episodes, but in 21% (n=30) it took 3-6 weeks, and in 23% (n=33) even longer. In 57 episodes (40%) antidepressants were started at their maximum doses.

**'Dose titration' :** From the data available a judgement was also made whether doses were adjusted during the course of treatment depending upon response, or emergence of side effects. The proportion in which such 'dose titrations' were made (n = 79; 55%) exceeded those in which such attempts were absent (n = 65; 45%), but only by a small margin.

**Duration of treatment :** Antidepressants were prescribed at maximum doses for more than 6 weeks in about three quarters (73%) of the treatment episodes. Thus, even after excluding episodes where the dose had to be reduced because of side effects or patient drop out, a substantial proportion (21%) had received maximum doses for less than 6 weeks.

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TABLE - 3  
STARTING AND MAXIMUM DOSES OF ANTIDEPRESSANTS

1. TCAs*	IMI. (n = 43)	DOT. (n = 17)	ATN. (n = 9)	NT. (n = 10)	CLOIMI. (n = 2)	DOX. (n = 1)	TOTAL # (n = 82)
<b>Starting doses (mg/day)</b>							
25 - 50	6	3	5	-	-	-	14 (17%)
75	21	12	3	4	1	1	42 (51%)
> 100	16	2	1	6	1	-	26 (32%)
<b>Maximum doses (mg/day)</b>							
< 150	16	7	7	4	2	1	37 (45%)
150	14	6	1	4	-	-	25 (30%)
> 150	13	4	1	2	-	-	20 (24%)
<b>2. Fluoxetine (n = 47)</b>							
<b>Starting doses (mg/day)</b>				<b>Maximum doses (mg/day)</b>			
20	34 (72%)			20	16 (34%)		
40	13 (28%)			40	25 (53%)		
				60	6 (13%)		
<b>3. Mianserin (n = 9)</b>							
<b>Starting doses (mg/day)</b>				<b>Maximum doses (mg/day)</b>			
10 - 30	8			10 - 30	5		
> 30	1			> 30	4		
<b>4. Amoxapine (n = 6)</b>							
<b>Starting doses (mg/day)</b>				<b>Maximum doses (mg/day)</b>			
< 100	2			< 100	2		
> 100	4			> 100	4		

\* - All TCA doses in imipramine equivalents

# - This is the no. of treatment episodes, different from the no. of cases; some episodes have not been included in this analysis

IMI - Imipramine; DOT - Dotheipin; ATN - Amitriptyline; NT - Nortriptyline;  
CLOIMI - Clomipramine; DOX - Doxepin

**Response considerations :** Data regarding the type of response, time to remission, and dose-response relationships is shown in table - 4. Since no structured assessments were used judgements about response had to be made somewhat arbitrarily. If the notes indicated that the patient was 'euthymic' or 'asymptomatic' on two occasions a month apart, the episode was judged to have remitted. Assessments of improvement in mental state were also made from the notes.

**Change of antidepressant :** In the 39 cases where drugs had been switched, all antidepressant treatment episodes were analysed on two parameters, viz. reasons for change and adequacy of treatment. In a quarter of the sample reasons for change of drug were not clear. After excluding changes due to side effects or cost, antidepressants were found to be used in inadequate doses, or for inadequate periods, on most occasions (67%), before they were

changed. ECT was only used in one such case and augmentation with lithium was non-existent.

**Recording of side effects and compliance :**

Compliance with treatment was not recorded at all in 64% cases, in 34% it was recorded for less than half of the follow-up visits. The recording of side effects was not done in 58% of the cases. In about a third (36%) of these cases side effects were recorded on less than half the occasions.

**Cost of the drug :** Among the demographic parameters only family income emerged as a significant determinant of drug choice. Fluoxetine was prescribed as a first choice antidepressant in 14 families from a higher income bracket (Rs.3000 per month or more), as opposed to only 7 patients with family incomes less than this, who prescribed were this drug to start with. On the other hand more patients from lower than higher income families received Imipramine (19 v/s 12). These differences were significant ( $X^2 = 3.91, df=1, p < 0.05$ ).

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TABLE 4  
RESPONSE PATTERNS # & TIME TO REMISSION #

	TCAs	FLX.	Others	Total
<b>Response</b>				
Number +	(82)	(47)	(15)	(144)
Remitted	37	21	5	63 (43%)
Improved	22	11	7	40 (28%)
No response	23	15	3	41 (28.5%)
<b>Time to remission</b>				
Number ++	(37)	(21)	(5)	(63)
0-6 weeks	14	6	5	25 (40%)
6-12 weeks	11	7	-	18 (29%)
> 12 weeks	12	8	-	20 (32%)
<b>Dose v/s response</b>				
<b>TCAs*</b>				
(n = 82)	< 150 mg/day		> 150 mg/day	
Remitted or improved	29		33	
No response	13		7	
<b>Fluoxetine**</b>				
(n = 47)	20 mg/day		40-60 mg/day	
Remitted or improved	9		23	
No response	6		9	

# Response is to maximum doses of antidepressants & time to remission is the time taken for the depressive episode to remit after maximum doses have been achieved

+ Number of treatment episodes; ++ Number of treatment episodes which ended in remission

- FLX. - Fluoxetine; - Others - include Mianserin & Amoxapine

\*  $\chi^2 = 2.01$ ; df = 1; NS

\*\*  $\chi^2 = 0.66$ ; df = 1; NS

## DISCUSSION

A number of confounding variables make it difficult to interpret and draw conclusions from such retrospective studies. Indicators of outcome are usually crude as structured assessments are not used routinely. Records can be incomplete, often not accurately reflecting the setting in which treatment decisions were taken. Some information is simply not available. To avert some of these problems it was decided to focus mainly on data that was relatively unambiguous e.g. type of drug used, dose and duration of treatment etc. Further, the sample was deliberately chosen to exclude confounders such as diagnosis (psychotic or bipolar depression), comorbidity (dysthymia, physical illness, substance abuse), and chronicity, which could have influenced treatment decisions. This,

despite restricting the scope of the study lends more credence to its findings.

The results show that antidepressants were used universally. Though TCAs (mainly Imipramine) were used most frequently, the number of Fluoxetine prescriptions was almost similar to Imipramine. This parallels national trends and represents a tremendous increase in prescriptions since the drug was first introduced in India in the early nineties (Andrade, 1997). This is perhaps a good indicator of the safety, efficacy, and acceptability of Fluoxetine, the only SSRI available in India, till recently.

Cost of the drug (not age or sex of the patient) was found to be a significant determinant of its choice. Imipramine is less expensive than Fluoxetine, and is dispensed by the hospital pharmacy free of cost. Thus, it was not surprising that patients prescribed Fluoxetine mostly came from a higher income bracket, while the reverse was true for Imipramine. The slight higher income bias of the sample must, however, be noted.

The practice of antidepressant therapy was deficient in several respects. Although drugs were usually started in low doses and gradually increased over a period of two to three weeks as recommended (Laurence & Bennet, 1992), in a substantial proportion starting doses were either too high, or the rate of hike too slow. Moreover, there were many instances of starting treatment with the maximum dose. Dose adjustments are necessary during the course of therapy, depending on response and emergence of side effects. However, such dose titrations were neglected in about half of the treatment episodes.

Adequacy of antidepressant treatment is usually defined in terms of the dosage of medication used and the duration of treatment. General consensus suggests that an adequate dose of an antidepressant is 150 mg/day Imipramine equivalents or more (Quitkin, 1985; Clinical Resource and Audit Group, 1993), although doses higher than this have also been recommended (Goethe et al., 1988). In this study, maximum doses of TCAs were less than 150 mg/day in 45% of the treatment episodes. Doses of

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Fluoxetine appeared adequate, although creating dose equivalencies is difficult, especially for SSRIs where dose-response relationships are less clear (Schatzberg, 1995). A surprising finding was that although the commonly recommended dose of Fluoxetine is 20 mg/day, two-thirds of the patients on this drug had received doses in the range of 40–60 mg/day.

Why were antidepressants, especially TCAs, used in such inadequate doses? The reasons are not clear, though one could be the differing dose requirement of this particular population, which perhaps belonged to the milder end of the spectrum. Moreover, a number of studies have now demonstrated that Asians usually require lower doses of psychotropics to achieve similar degrees of response (Kuruville, 1996). Two aspects of the data are worth noting in this regard. Firstly, despite such 'inadequate doses', 72% of the episodes had a favourable outcome, comparing well with response rates reported in literature (Richelson, 1993). Further, for TCAs the number of treatment responsive episodes were not significantly different between the two dose conditions, i.e. less than or greater than 150 mg/day of Imipramine equivalents. The number of favourable outcomes was more with higher doses (40-60 mg/day) of Fluoxetine, but these differences were also not significant. Without reading too much into the results, it is possible to conclude that further dose-response studies are needed in this population to determine what constitutes an adequate dose of a particular antidepressant.

How long should antidepressants be used before a decision is made to switch drugs because of non-response? Opinions are divided with some authors suggesting that six to eight weeks is adequate (Szabadi & Bradshaw, 1995) and others proposing periods of 12 weeks or longer (Potale & Gogates, 1994). The problem becomes more complex if there is only partial response to treatment. About three fourths of this sample had received treatment for more than 6 weeks. However, only 38% of the sample remitted within 6 weeks of attaining the maximum dose, 29% took up to 12 weeks, and

32% even longer, to remit. This data thus suggests that a substantial proportion of cases on antidepressants take longer than 6 weeks to remit. Although definite conclusions are again not possible it seems preferable to persist with one drug for longer than 6 weeks, especially in cases of partial response.

Cases, which required one or several changes in drugs also, revealed some flaws in the current prescribing practices. Although non-response was recorded as the main reason for switching antidepressants, drugs were often used in inadequate doses, or for inadequate periods of time, before a change was made. Changes from one agent to another of the same family (e.g. from Dotheipin to Imipramine) were made in over a quarter (28%) of such cases, which goes against the standard practice of using a drug from a different group in such instances (American Psychiatric Association Work Group on Major Depressive Disorders, 1993). Since these cases would be considered difficult to treat or be labelled 'treatment-refractory', these findings lend further support for the belief that, more often than not, such problems are a result of inadequate treatment (Quitkin, 1985).

Side effects often determine the choice of a particular agent (Mcpherson & Robson, 1994), and several studies suggest that about half the patients become non-compliant at some point during treatment (Clinical Resource and Audit Group, 1993). Given these facts, the scant attention paid to noting down side effects, or compliance with treatment, also raises some concern.

The trend towards under-treatment of depression highlighted by this study is depressingly familiar. It was not possible to explore the reasons for these deficiencies in practice, which is a major limitation of this study. Nevertheless, the results suggest that the norms regarding adequate doses and periods of treatment before switching drugs, could be different for such patient populations. There is thus a need for further prospective studies to determine the minimum standards of care for drug treatment of depression across various settings in our country.

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The sample was fairly representative of the bulk of depressed patients being treated in general hospital psychiatric units in this country. Since these units form the backbone of psychiatric services in India (Venkoba-Rao, 1986), the results would probably be applicable to a large number of patients using the psychiatric facilities. However, the findings cannot be generalised to other settings such as primary care, or mental hospitals, and the size of the sample is perhaps too small to make any definite predictions about the treatment being received by depressed patients in all general hospital units. Future studies, which address these issues, will hopefully provide the foundations of rational and uniform standards of care, with regard to antidepressant treatment in India.

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