The prospective, 24-week assessment of cost-efficacy of and compliance to antidepressant medications in a rural setting (PACECAR) study

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ABSTRACT

Background: Anxiety and depression are common mental health disorders that are responsible for considerable societal burden. There are no data on cost-efficacy and medication compliance related to the treatment of these disorders in rural India.

Materials and Methods: All consenting adults (n = 455) diagnosed with generalized anxiety or (unipolar) depressive disorders in Suttur village, Karnataka, were treated with open-label fluoxetine (20–60 mg/day), sertraline (50–150 mg/day), escitalopram (10–20 mg/day), desvenlafaxine (50–150 mg/day), duloxetine (30–90 mg/day), amitriptyline (75–150 mg/day), or clomipramine (75–150 mg/day) in a structured, monotherapy dosing plan. The study was nonrandomized and otherwise naturalistic. Patients were followed up every 4 weeks for 24 weeks. Study discontinuation was defined as medication noncompliance for 3 or more days or withdrawal due to treatment nonresponse.

Results: There was substantial discontinuation (34.5%) in the first 4 weeks; 55.4% had discontinued by 12 weeks. Subsequently, only 11.2% discontinued treatment. Only 33.4% of the subjects tolerated the treatment, responded to it, and remained compliant for 24 weeks. Such successful completion was highest for escitalopram and desvenlafaxine (46%–47%) and lowest for clomipramine and amitriptyline (10%–14%). Adverse events were the most common reason for noncompliance with clomipramine and amitriptyline (45%–46%); the experience of sufficient improvement was the most common reason for noncompliance with the remaining drugs (28%–49%). Whereas the average cost of efficacious treatment for a continuous period of 24 weeks was lowest for fluoxetine, an examination of the cost-efficacy tradeoff suggested maximum advantage for escitalopram, sertraline, and desvenlafaxine. The cost-efficacy profile for amitriptyline and clomipramine was poor.

Conclusions: Reasons for noncompliance vary by drug class and need to be considered when prescribing antidepressant drugs. Escitalopram, sertraline, and desvenlafaxine perhaps have the most favorable 24-week cost-efficacy profile; tricyclics are poorly tolerated. Rural subjects need to be educated that treatment must be continued even after improvement is established.

Key words: Amitriptyline, antidepressant, anxiety, clomipramine, cost-effectiveness, depression, desvenlafaxine, duloxetine, escitalopram, fluoxetine, sertraline

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INTRODUCTION

Anxiety and depressive disorders are widely prevalent and are responsible for a substantial burden of illness among subjects and healthcare providers worldwide. It is projected that, by the year 2020, depression will rise to the second position in illness conditions associated with disease burden, measured in disability-adjusted life years.[1] Escalating costs of treatments, dearth of mental healthcare resources, and restrictions on public health spending have lead to an increasing need for accurate information about the cost-effectiveness of different antidepressant interventions.

New generation antidepressant drugs generally cost more than the older antidepressants and are claimed to be at least as effective, better tolerated, and less likely to result in drug interactions. However, these putative benefits need to be economically quantified to facilitate an effective and efficient allocation of mental healthcare resources. A comprehensive pharmacoeconomic evaluation is therefore required to assess the cost-effectiveness of competing antidepressants.

In recent years, many pharmacoeconomic studies of antidepressant treatments have been conducted worldwide; their findings and hence their usefulness are likely to be country-specific.[2-14] Independent pharmacoeconomic studies, therefore, need to be conducted in India, especially in the medically poorly served rural population. This study was designed to assess the acceptability, tolerability, and cost-effectiveness of different antidepressants in a South Indian rural population.

MATERIALS AND METHODS

Objectives

The Prospective, 24-week Assessment of Cost-Efficacy of and Compliance to Antidepressant medications in a Rural setting (PACECAR) study was conducted in a rural population with a specific view to prospectively examine the rates of discontinuation of different antidepressant drugs across a 24-week period, to assess reasons for noncompliance with different antidepressant drugs, and to study the cost-effectiveness of different antidepressant drugs. Here, cost-effectiveness was operationalized as the average rupee cost incurred per subject who showed clinical response to treatment and who completed 24 weeks of follow-up without discontinuing medication.

Study setting and design

The study was conducted in Suttur village, Karnataka, after obtaining clearance from the Institutional Ethics Committee of JSS Medical College, Mysore. Suttur is located about 25 km from Mysore. It has approximately 4100 residents, most of whom belong to the Hindu community. It has a Primary Health Centre (PHC) that is run by the Government of Karnataka in collaboration with JSS Medical College.

Suttur is a model village, adopted, and managed by JSS Mahavidyapeeta. The birth and death records, sociodemographic characteristics, and health and other records of all the residents of the village are maintained up-to-date. This study was part of an epidemiological investigation approved and funded by the Indian Council of Medical Research (ICMR, Suttur Study).[15] The study was designed to screen the entire village for anxiety and depression and to prospectively treat identified cases with appropriate, open-label medication for 24 weeks. Informed consent was obtained from all study participants. All treatments were provided free of cost.

Study team

The investigation team comprised a psychiatrist, a psychiatry resident, two female social workers, a data entry operator, and the Suttur PHC staff. The nonpsychiatric members of the team were trained for 2 months on issues related to neuropsychiatric disorders, the art of establishing rapport and communicating with subjects, the objectives of the study, the administration of the study instruments, and other study procedures.

Study instruments

Sociodemographic data were collected using an instrument designed for the purpose. Socioeconomic status was assessed based on the Modified BG Prasad Classification.[16] The MINI International Neuropsychiatric Interview Plus (MINI)[17-19] was used to establish clinical diagnoses. Structured interviews were used to diagnose mental retardation and dementia based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)[20] and International Classification of Diseases, 10th Revision (ICD-10)[21] criteria.

Sample

Eligible consenting adult subjects were screened using the MINI and were recruited if they were diagnosed with major depressive disorder (with or without melancholia), recurrent depressive disorder, generalized anxiety disorder, or mixed anxiety and depression (all ICD-10). Illness severity, as clinically assessed, was required to be at least moderate. Patients with major psychiatric comorbidity were excluded. Patients with current suicidal ideation or history of suicide attempt were also excluded from the study.

Study procedures: General issues

All subjects were interviewed using the MINI Plus. A structured interview, based on ICD-10 and DSM-IV-TR, was used to identify the presence of mental retardation and dementia because neither diagnosis is included in the MINI. The presence of seizure disorder was also screened for.
MINI diagnoses were confirmed by a psychiatrist through a formal psychiatric interview.

This exercise found that approximately 65% of the neuropsychiatric disorders identified were depression and anxiety disorders; the data have already been published. Subjects with these disorders who fulfilled the earlier listed selection criteria were recruited into the present study in which their disorder was treated with free medication belonging to tricyclic antidepressant (TCA; amitriptyline or clomipramine), selective serotonin reuptake inhibitor (SSRI; fluoxetine, sertraline, or escitalopram), or serotonin-norepinephrine reuptake inhibitor (SNRI; desvenlafaxine or duloxetine) classes. Some explanatory notes are provided in Box 1.

The choice of antidepressant was based on what was considered appropriate for the subject, depending on sociodemographic and illness characteristics. The study was thus naturalistic, not randomized. During the 24-week follow-up, each treated subject was visited and evaluated once in 4 weeks. If it was found that the antidepressant had been discontinued, reasons for discontinuation were formally evaluated.

### Study procedures: Treatment issues

Generic brands of antidepressants were obtained from domestic pharmaceutical companies with export operations, to ensure quality. A single brand was used for each antidepressant to avoid cost and other variations across brands.

At baseline (day 0), subjects were educated about the benefits of medication and were dispensed with a month’s supply of their study antidepressant. The dosing strategy is described in Box 2. The antidepressant was chosen by a trained, nonpsychiatric medical professional because it was important to know what outcomes would be under such real-world conditions. As an example, the professional was advised to favor SSRIs and to avoid prescribing TCA to the elderly.

Patients were instructed to tick the calendar dates on which they took their medication; compliance was also assessed through pill counts. The definition of noncompliance was stringent; subjects who had skipped treatment for 3 or more days were considered to have discontinued medication and were removed from the study and referred to tertiary care after brief counseling. Reasons for noncompliance were ascertained under five headings: sufficient treatment response, absence of treatment response, experience of adverse effects, concerns about becoming dependant on the medication, and poor motivation to take medication. Only the most important reason for noncompliance was recorded.

At the first 4-weekly visit, if clinical improvement was considered adequate, the same dose of medication was continued; if not, the medication dose was doubled. If clinical improvement was inadequate at the week 8 visit, the maximum dose of the study medication was advised [Box 2].

At subsequent 4-weekly visits, subjects with adequate improvement were continued on the same dose. Dose escalations were permitted at these visits, if clinical required, subject to the maximum dose [Box 2]. If a subject already on the maximum study dose failed to show adequate improvement, s/he was withdrawn; efficacy of second-line management was not an objective of the current study.

### Statistical methods

As this was an observational study with no prespecified hypotheses, only descriptive statistics are furnished.

### RESULTS

#### General sample characteristics

The overall sample comprised 2608 consenting adults. One-third of the sample fell in the 18–25 (17.10%) and...
31–40 (16.20%) year categories. The gender distribution was almost equal. More subjects were married (62%) than single (38%). A quarter of the sample (25.2%) comprised students and 55.1% were literate. Nearly one-third of subjects (30.1%) were residing in joint families, nearly two-thirds (60.5%) were in a nuclear family, and the rest were residing alone. The sample was mostly ‘upper lower’, class (32.5%) or ‘lower middle’, class (43.2%). The prevalence of chronic medical comorbidity (diabetes mellitus, 2.4%; hypertension, 2.2%) and alcohol use (6.9%) was low.

**Study sample characteristics**

The study sample comprised 455 adults diagnosed with generalized anxiety disorder (9.7%), mixed anxiety and depression (13.0%), major depressive disorder without melancholia (31.2%), major depressive disorder with melancholia (14.9%), and recurrent depressive disorder (31.2%). The modal age group was 51–60 years (21.8% of the sample). Two-thirds (64.6%) of the sample was female, 88.6% of subjects were married, 80.2% were illiterate, and 50.5% were homemakers. Most of the sample belonged to the “lower middle” class and “upper lower” class; 19.1% had a chronic medical illness, and 11% consumed alcohol.

**Antidepressant treatment**

The SSRIs as class were prescribed to nearly half of the sample (48.1%); the SNRIs to 28.4%, and the TCA to 23.5%. In decreasing order of frequency, the antidepressants prescribed were escitalopram (20.4%), sertraline (17.8%), desvenlafaxine (16.7%), amitriptyline (12.7%), duloxetine (11.6%), clomipramine (10.8%), and fluoxetine (9.9%).

**Course of treatment: Discontinuation**

About one-third (34.5%) of the sample discontinued treatment within the first 4 weeks, itself. These proportions were 23%–32% for escitalopram, sertraline, desvenlafaxine, and duloxetine, and 44%–51% for fluoxetine, amitriptyline, and clomipramine. More than half of the sample (55.4%) had discontinued by the midway (12 week) mark. The sample attenuated by only 11.2% between weeks 12 and 24 [Table 1].

Only 33.4% of the subjects completed 24 weeks of antidepressant treatment; that is, tolerated the treatment, responded to it, and remained compliant for 24 weeks. These completion proportions, in decreasing order of success, were 47.3% for escitalopram, 46.1% for desvenlafaxine, 37.0% for sertraline, 34.0% for duloxetine, 26.7% for fluoxetine, 13.8% for amitriptyline, and 10.2% for clomipramine [Table 1].

**Course of treatment: Reasons for discontinuation**

Noncompliance with medication was responsible for the bulk of the study treatment discontinuation, and the figures for noncompliance versus total discontinuation were 31 out of 33 for fluoxetine, 41 out of 49 for escitalopram, 44 out of 51 for sertraline, 39 out of 44 for desvenlafaxine, 32 out of 35 for duloxetine, 48 out of 50 for amitriptyline, and 40 out of 44 for clomipramine. The range for noncompliance as a reason for discontinuation was 84%–96%.

**Course of treatment: Reasons for noncompliance**

Adverse effects were an important reason for noncompliance (in 45%–46%) only with the TCA; this figure was low (3%–10%) with the other drugs. Nonresponse was an infrequent reason for noncompliance (5%–18%). With the exception of the TCA, the experience of sufficient improvement was the leading reason for noncompliance (28%–49%) [Table 2].

**Cost of treatment**

The unit cost of each medication is presented in Box 3, and the average cost of medication in responders who completed 24 weeks of treatment is presented for each drug in Box 4. Whereas fluoxetine was the least expensive, escitalopram, sertraline, and desvenlafaxine were associated with reasonable cost-efficacy. The overall cost of treatment for the entire sample was estimated at approximately Rs. 4.57 lakhs.

**DISCUSSION**

**Discontinuation of antidepressant treatment**

Salient findings from our study are presented in Box 5. In keeping with our findings of early antidepressant

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**Table 1: Antidepressant drug discontinuation by time**

| Treatment        | Started treatment | Discontinued treatment between week 0 and 4, n (% | Discontinued treatment between week 4 and 8, n (%) | Discontinued treatment between week 8 and 12, n (%) | Switched to/switched between with other medication at week 12, n (%) | Discontinued treatment between week 12 and 16, n (%) | Discontinued treatment between week 16 and 20, n (%) | Discontinued treatment between week 16 and 24, n (%) | Completed 24 weeks of medication, n (%) |
|------------------|-------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Fluoxetine       | 45                | 20 (44.4)                                      | 4 (8.9)                                       | 4 (8.9)                                       | 2 (4.4)                                       | 0                                             | 2 (4.4)                                       | 1 (2.2)                                       | 12 (26.7)                                     |
| Escitalopram     | 93                | 21 (22.6)                                      | 9 (9.7)                                       | 9 (9.7)                                       | 8 (8.6)                                       | 1 (1.1)                                       | 1 (1.1)                                       | 0                                             | 44 (47.3)                                     |
| Sertraline       | 81                | 24 (29.6)                                      | 7 (8.6)                                       | 7 (8.6)                                       | 7 (8.6)                                       | 3 (3.7)                                       | 1 (1.2)                                       | 2 (2.5)                                       | 30 (37.0)                                     |
| Desvenlafaxine   | 76                | 21 (27.6)                                      | 7 (9.2)                                       | 8 (10.5)                                      | 2 (2.6)                                       | 1 (1.3)                                       | 2 (2.6)                                       | 0                                             | 35 (46.1)                                     |
| Duloxetine       | 53                | 17 (32.1)                                      | 5 (9.4)                                       | 6 (11.3)                                      | 3 (5.7)                                       | 2 (3.8)                                       | 2 (3.8)                                       | 0                                             | 18 (34.0)                                     |
| Amitriptyline    | 58                | 29 (50.0)                                      | 9 (15.5)                                      | 8 (13.8)                                      | 2 (3.5)                                       | 0                                             | 0                                             | 2 (3.5)                                       | 8 (13.8)                                     |
| Clomipramine     | 49                | 25 (51.0)                                      | 6 (12.2)                                      | 6 (12.2)                                      | 4 (8.2)                                       | 2 (4.1)                                       | 1 (2.1)                                       | 0                                             | 5 (10.2)                                     |
| Total            | 455               | 157 (34.5)                                     | 47 (10.3)                                     | 48 (10.5)                                     | 28 (6.2)                                      | 9 (2.0)                                       | 9 (2.0)                                       | 5 (1.1)                                       | 152 (33.4)                                   |

*Numbers in the cells are n (%)*
discontinuation, the Medical Expenditure Panel Survey also found that most subjects discontinued antidepressant therapy during the first 30 days and that only 27.6% of subjects continued treatment for > 90 days. A 6-month follow-up study conducted in a PHC found that 53% of subjects discontinued antidepressant medication within 6 months.

We found that sample attenuation in the first 4 weeks was highest among subjects prescribed TCA. A primary care study in the UK obtained similar results: subjects prescribed tricyclic were more likely to switch treatment in the first few weeks. A follow-up study found that only 20% of subjects who had been prescribed first-generation antidepressants filled four or more prescriptions in the following 6 months, compared to 34% of subjects who had been prescribed newer antidepressants. In another 6-month antidepressant follow-up study, discontinuation rates were higher for TCA than for SSRIs. It therefore seems fairly clear that, in rural India, as in other parts of the world, TCA are accepted less well than the newer antidepressants.

**Reasons for antidepressant discontinuation**

Noncompliance was the most important reason for antidepressant discontinuation, and with the exception of the TCA, clinical improvement was the most important reason for noncompliance [Box 5]. This was an unexpected finding given that all subjects were counseled about depression and antidepressant treatment at the time of diagnosis and treatment initiation, and that the importance of treatment would have been subliminally emphasized and reemphasized by the consenting process and the 4-weekly home visits. Nevertheless, across different drugs, 28%–49% of subjects stopped medications once they felt better. This is a matter that will need special attention in clinical care and in the future studies in rural subjects with anxiety or depression. However, other authors have also reported this finding. In one primary care study that examined antidepressant compliance, 53% of subjects were found to have discontinued antidepressant treatment by the end of 6 months, and the most common reason given was that they were “feeling better.”

The high dropout rate due to adverse effects among the TCA but not the SSRIs [Box 5] is supported by a meta-analysis of randomized controlled trials which found that SSRIs have a significant and clinically important advantage over TCAs with respect to tolerability. A pilot study in Goa reported that the discontinuation rate for imipramine was much higher as compared with other antidepressant drugs, and the most common reason for discontinuation was the experience of adverse effects. Among the TCA, dothiepin is generally considered to be well tolerated. However, Thompson et al. showed a 15% advantage in compliance for fluoxetine relative to dothiepin in a primary care population.

**Antidepressant treatment: Cost-efficacy**

Pharmacoeconomics cannot be judged from the unit cost of medication. Different subjects need different doses, and the doses are escalated or reduced at different times. Therefore, the cost of treatment is best averaged across subjects and across time; this is what we did. Furthermore, computing cost of treatment is a meaningless exercise if the treatment is not tolerated or does not work; therefore, persistence with treatment into at least the intermediate term requires to be simultaneously considered. With these issues in mind, we found that escitalopram, sertraline, and desvenlafaxine had the best 24-week cost-efficacy for rural subjects with anxiety and depression. These findings can inform public mental health strategies that seek to improve health outcomes with the best utilization of resources. Importantly, we show that whereas older antidepressants are considered by many to be cheaper, their short- and intermediate-term cost-efficacy is questionable.

Other studies support our data. One report suggested that, in spite of the higher unit cost, newer antidepressants may be more cost-effective than the older TCA as they may be better tolerated and therefore more effective in preventing treatment failure. A systematic review of articles examining the cost-efficacy evaluation of interventions for depression also concluded that SSRIs and the newer antidepressants venlafaxine, mirtazapine, and nefazodone appear cost-effective relative to older antidepressants. A cost-effectiveness study conducted in Germany, Italy, Netherlands, Poland, Spain, Sweden, Switzerland, United Kingdom, United States, and Venezuela showed that initiating treatment for major depressive

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**Table 2: Reasons for noncompliance**

| Reason for Discontinuation | Poor motivation, n (%) | Adverse effects, n (%) | Concern about addiction to medications, n (%) | Experience of sufficient improvement, n (%) | Unsatisfactory improvement, n (%) | Total |
|---------------------------|------------------------|------------------------|-----------------------------------------------|-------------------------------------------|---------------------------------|-------|
| Fluoxetine                | 8 (25.8)               | 3 (9.7)                | 8 (25.8)                                      | 8 (25.8)                                  | 4 (12.9)                        | 31    |
| Escitalopram              | 8 (19.5)               | 2 (4.9)                | 10 (24.4)                                     | 14 (34.1)                                 | 7 (17.1)                        | 41    |
| Sertraline                | 9 (20.5)               | 3 (6.8)                | 10 (22.7)                                     | 14 (31.8)                                 | 8 (18.2)                        | 44    |
| Desvenlafaxine            | 4 (10.3)               | 1 (2.6)                | 10 (25.6)                                     | 19 (48.7)                                 | 5 (12.8)                        | 39    |
| Duloxetine                | 7 (21.9)               | 1 (3.1)                | 10 (31.2)                                     | 9 (28.1)                                  | 5 (15.6)                        | 32    |
| Amitriptyline             | 8 (16.7)               | 22 (45.8)              | 6 (12.5)                                      | 8 (16.7)                                  | 4 (8.3)                         | 48    |
| Clomipramine              | 7 (17.5)               | 18 (45.0)              | 7 (17.5)                                      | 6 (15.0)                                  | 2 (5.0)                         | 40    |
| Total                     | 51 (18.5)              | 50 (18.2)              | 61 (22.2)                                     | 78 (28.4)                                 | 35 (12.7)                       | 275   |

*Numbers in the cells are n (%)
disorder with venlafaxine yielded a lower expected cost compared to the SSRIs and TCAs in all countries except Poland in the insubject setting, and Italy and Poland in the outsubject settings.\[29\]

**Limitations**

This was an exploratory study; we did not prespecify hypotheses and therefore did not perform inferential statistical analyses of the data. Next, our definition of noncompliance was perhaps more stringent than is common in literature: we assumed that if subjects did not take their medications for 3 or more consecutive days, deliberate discontinuation would be a more likely explanation than forgetting to take the pills. It is possible that some of the subjects might have voluntarily resumed their medications, later. However, the fact of deliberate discontinuation was a matter of concern, and we wished to capture its occurrence.

Neither subjects nor the treating team were blind to the treatments prescribed. However, this was intended to be a naturalistic study that reflected real-world practice. Further, the end-points that we studied were reasonably objective and unlikely to be influenced by rater biases, if any.

For internal reasons, we were unable to separately analyze the data in subjects with anxiety vs depression. It is possible that the depressive disorders, which tend to be more serious, might have shown different patterns of treatment adherence.

Our conclusions are limited to the drugs that we studied. For practical reasons, we could not study the entire range of antidepressants available in the Indian market. We therefore chose drugs that were representative of the major antidepressant classes, and in particular, drugs that are popular in clinical practice. Because all the brands of antidepressants that we used were generic brands, variations across other generic brands could be expected to be small, and so the conclusions that we drew for the brands that we studied could justifiably be applied to all generic brands of the same drug.

We supplied the study medications free. The results may have been different had patients to pay for their own medications. However, in governmental set-ups, medications are usually provided free. Finally, treatment was chosen and delivered by psychiatrists and by a specially constituted and trained research team. We cannot be certain that outcomes would be similar or as good were treatment to be delivered by primary healthcare doctors who do not have special training in psychiatry. However, such training can certainly be provided.

**CONCLUSIONS**

In rural India, subjects with anxiety and depression commonly discontinue antidepressant treatments in the 1st month; fewer than half of the treated subjects persist with treatment for >12 weeks. Noncompliance is the most common cause of discontinuation, and experience of improvement is the most common reason for noncompliance. TCA drugs are associated with a high risk of dropout due to adverse events; in contrast, monotherapy with escitalopram, sertraline, or desvenlafaxine shows good 24-week cost efficacy. We suggest that these 3 antidepressants can be prioritized for treating anxiety and depressive disorders in rural India, and that attention be paid to ensuring that subjects do not stop treatment when they feel better.

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Conflicts of interest

There are no conflicts of interest.

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