Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 23s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Pharmacoeconomic Evaluation in Generalized Anxiety Disorder: A North India Perspective

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Cite this paper as: Rishi Kapoor Poddar, Piyush Mittal, (2025) Pharmacoeconomic Evaluation in Generalized Anxiety Disorder: A North India Perspective. *Journal of Neonatal Surgery*, 14 (23s), 1096-1102.

ABSTRACT

Background: The most prevalent mental disorder is anxiety disorders. A common type of anxiety disorder is generalized anxiety disorder (GAD). Objectives of the study were to evaluate cost of illness (COI) and cost effectiveness of different pharmacological treatments in patients with GAD.

Methods: This was a single centred prospective observational study. The duration of the study was one year. The inclusion criteria were patients with GAD, both male and female patients, patients within 18-60 years age group, and willingness to participate.

Results: A total of 352 patients were analysed in the study. Escitalopram, venlafaxine XR and paroxetine were the drugs used as the treatment option for GAD patients. Quality-Adjusted Life Year (QALY) gained for paroxetine was found to be highest, followed by venlafaxine XR and escitalopram. Cost effectiveness of escitalopram, venlafaxine XR and paroxetine for GAD were found to be 3395, 4655, and 8554 ₹/QALY gained respectively. The COI attributable to GAD for six months was estimated ₹29945. Indirect costs constituted 70% of total costs whereas pharmacotherapy accounted for 22.5% of the COI. The contribution of absenteeism cost was 45.2% of the COI.

Conclusion: Escitalopram is found to be cost effective compared with venlafaxine XR and paroxetine for the treatment of GAD. GAD shows significant economic burden as COI was significant around thirty thousand Indian rupees.

Keywords: *Pharmacoeconomics, Pharmacoeconomic analysis, Cost effectiveness, Cost of illness, Generalised anxiety disorder*

1. INTRODUCTION

The most prevalent mental disorder is anxiety disorders [1]. A typical type of anxiety disorder is generalized anxiety disorder (GAD) [2]. GAD must be diagnosed based on persistent symptoms for the majority of days for at least six months. Unrealistic or excessive anxiety and stress over various activities or situations are the main characteristics of GAD [3]. Anxiety significantly impairs areas like work, social, and health [4]. The prevalence of anxiety disorders is found to be 2.57% in India for adult population whereas the prevalence of GAD is found to be 0.57% [5]. Decrease in the intensity and duration of the anxiety symptoms while enhancing general functioning are the goals of treatment in the acute management of GAD whereas remission with little to no anxiety symptoms, no functional impairment, and increase in quality of life (QoL) are the long term goals in GAD [6].

The treatment plan is determined by the severity as well as duration of the symptoms, age, medication history, besides coexisting physical plus mental health issues [7]. Patients who feel anxiety symptoms having potential for functional incapacity should use antianxiety medication [8]. The most efficient, safe, and commonly recommended medications for the quick alleviation of acute anxiety symptoms are benzodiazepines [9]. Antidepressants have become the first line therapy in the treatment of chronic anxiety, particularly in coexisting symptoms of depression due to lack of dependence and bearable adverse effect profile [8]. The somatic and autonomic symptoms of GAD are better managed with benzodiazepines than the psychological symptoms such as anxiety and apprehension, which are decreased with antidepressants [9].

Pharmacoeconomics is framed to enlighten decision-makers about the worth of various pharmacotherapies where the costs and effects (clinical, economic, and humanistic) of pharmaceutical products and services are identified, quantified, and compared [10]. In another words, pharmacoeconomic studies compare the costs for providing a pharmaceutical product or service to the health related outcome of the pharmaceutical product or service as shown by an equation in Figure 1 [11].

Health-related quality of life (HRQoL) focuses solely on a patient's nonclinical data, such as functional status, well-being, perception of health, return to work following an illness, and other health outcomes that are directly impacted by health status, while QoL considers all facets of life [10].

Figure 1. Basic Pharmacoeconomic equation

Cost effectiveness analysis (CEA) is the most commonly used method for pharmacoeconomic analysis [12]. Cost of illness (COI) is an another type of economic analysis in which the determination of total economic burden including treatment, losses due to morbidity and mortality of a specific disease is done where direct costs (costs for medical services such as treatment or prevention) as well as indirect costs (costs due to loss of productivity as a result of disease) are generally taken in the analysis [11].

Aims of the study are to evaluate the COI and cost effectiveness in patients with GAD on different pharmacological treatments. The study can help in better understanding of pharmacoeconomics in GAD patients in Indian context which is the need of the hour as there are only very few research focused on pharmacoeconomics for GAD in Indian population.

2. MATERIALS AND METHODS

Study Design

This was a prospective observational study and the site of the study was Psychiatry Department, Teerthanker Mahaveer Hospital and Research Centre, Moradabad, India for a period of one year from December 2022 to November 2023.

Study Population

The inclusion criteria were patients with GAD, both male and female patients, patients within 18-60 years age group, and willingness to participate. Patients in pregnancy and lactation, not willingness to participate, and patients on psychotherapy for GAD were exclusion criteria. The study was carried out in compliance with the Helsinki Declaration. Signing an informed consent form was prerequisite to participate in the study for each and every patient.

Sample Size Calculation

Sample size of the prospective observational study was calculated 377 by using Epi-Info software of Centre for Disease Control and Prevention (CDC). However, final target was to add 75 more patients considering the 20% dropout of study participants.

Estimation of COI and ICER

The study involved the enrollment of 421 patients in total. Escitalopram 10-20 mg, venlafaxine XR 75-225 mg, and paroxetine 20-50 mg were the drugs used in the treatment for GAD patients as shown in Figure 2. Direct costs (medication cost, hospitalisation cost, travel cost, food cost) and indirect costs (absenteeism cost, presenteeism cost) were collected at baseline visit, week 2 visit, week 4 visit, week 12 visit, and week 26 visit in the hospital from different sources including medical bills. Presenteeism refers to the issue of employees being at work but not performing fully due to illness or other medical issues [13]. Absenteeism is the absence from work [14]. Questionnaire was asked to the enrolled patients at baseline visit, week 2 visit, week 4 visit, week 12 visit, and week 26 visit in the hospital. HRQoL data were collected for enrolled patients with GAD using the Short Form-12 Health Survey-version 2 (SF-12v2) after sharing them about all study relevant information. Patient satisfactions, functional status as determined by QoL evaluation are examples of humanistic outcomes in pharmacoeconomics [10]. SF-12 consists of Component Summary (PCS-12) and Mental Component Summary (MCS-12) scores. Better health status has the higher score and vice versa [15]. The validated and reliable Hindi version of SF-12v2 questionnaire for India was provided by QualityMetric. Patient-Reported Outcome (PRO) CoRE software was used for scoring of SF-12v2 Questionnaire. Incremental cost effectiveness ratio (ICER) was calculated by the comparison of differences in cost as well as effectiveness for more than one treatment; and effectiveness was represented by Quality-Adjusted Life Year (QALY) [16,17]. QALYs are measure of years lived in healthy life [18].

Statistical Analysis

The data was statistically analyzed using SPSS Statistics version 23. Continuous data were presented as mean±standard deviation (SD), whereas categorical data were expressed as percentage. ANOVA test as statistical method was used to compare the means of groups. Statistical significant was considered at $p<0.05$ for all the tests.

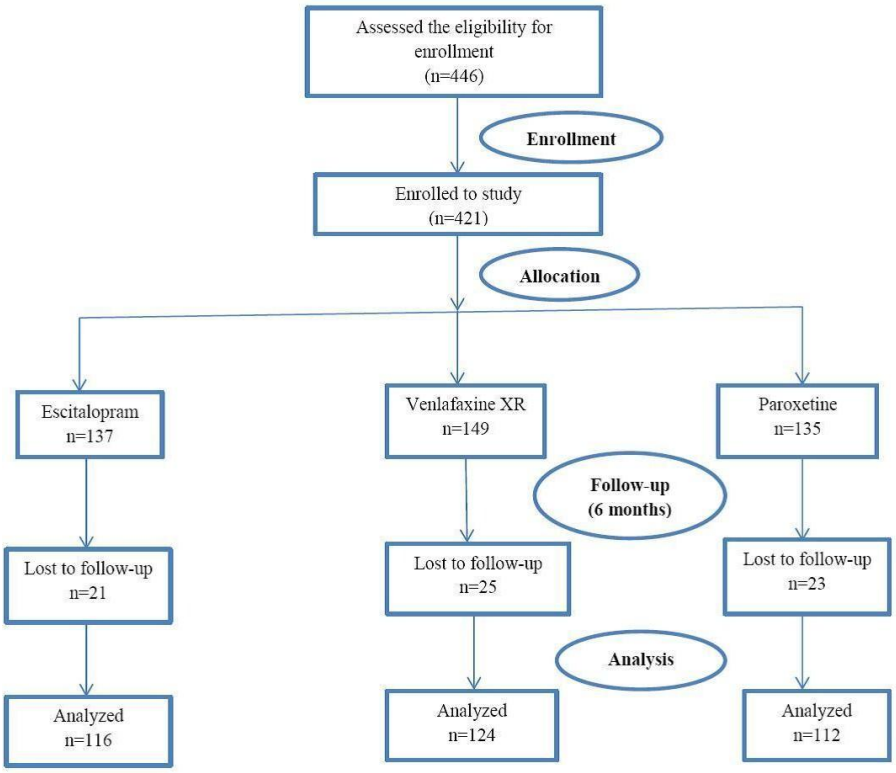

Figure 2. Schematic diagram of subjects

3. RESULTS

Socio-demographic Details

A total of 421 patients were enrolled in the study owing to fulfillment of enrollment criteria from screening of 446 patients. However, a total of 352 patients were analysed for the results due to loss of patients in post treatment follow-up. All 352 patients responded to SF-12v2 at baseline in hospital. Table 1 summarizes the sociodemographic characteristics of the patients with different pharmacological treatment groups at baseline visit in the hospital. The mean age was found to be around 31 years at the time of entry in the study.

Table 1. Baseline socio-demographic characteristics in treatment groups

Characteristics		Escitalopram	Venlafaxine XR	Paroxetine
Age (years), mean±SD		31.4±14.29	32.2±15.46	30.1±14.29
Gender n (%)	Male	51 (43.97)	54 (43.55)	49 (43.75)
	Female	65 (56.03)	70 (56.45)	63 (56.25)
Education level n (%)	Primary	26 (22.41)	27 (21.77)	26 (23.21)
	Secondary	18 (15.52)	20 (16.13)	19 (16.96)
	Intermediate	33 (28.45)	37 (29.84)	32 (28.57)
	University	39 (33.62)	40 (32.26)	35 (31.25)
Marital status n (%)	Married	52 (44.83)	56 (45.16)	51 (45.53)
	Unmarried	49 (42.24)	54 (43.55)	48 (42.86)
	Widowed	11 (9.48)	12 (9.68)	8 (7.14)

	Divorced	4 (3.45)	2 (1.61)	5 (4.46)
Employment status n (%)	Employed	24 (20.69)	25 (20.16)	22 (19.64)
	Unemployed	92 (79.31)	99 (79.84)	90 (80.36)

Evaluation of Pharmacoeconomics

Table 2 presents the results of treatment costs in all the pharmacological treatment groups at baseline, week 2, week 4, week 12, and 26 week. The average treatment costs were estimated to be ₹968, ₹1420, and ₹2954 for escitalopram, venlafaxine XR, and paroxetine respectively for a six months (26 weeks) pharmacotherapy of GAD. At every observation point of time, the paroxetine group's treatment costs were higher than those of the escitalopram and venlafaxine XR groups, beginning from initial treatment.

Table 2. Comparison of treatment costs among treatment groups

Time	Escitalopram	Venlafaxine XR	Paroxetine
Week 0	₹233	₹322	₹654
Week 2	₹141	₹207	₹431
Week 4	₹141	₹207	₹431
Week 12	₹564	₹828	₹1723
Week 26	₹968	₹1420	₹2954

Physical Component Summary (PCS-12) and Mental Component Summary (MCS-12) scores reported from SF-12 of pharmacological treatment groups at different time are included in Table 3. The difference in QoL scores among three treatment groups was not significant before the treatment ($p>0.086$). After two weeks of treatment, SF-12 scores improved in all the three groups. Furthermore, study found significant difference in SF-12 scores within each group before and after treatment ($p<0.031$). The study revealed higher SF-12 scores in the paroxetine group compared to the escitalopram group and venlafaxine XR group.

Table 3. SF-12 scores of treatment groups before and after treatment

Time	Escitalopram		Venlafaxine XR		Paroxetine	
	PCS-12	MCS-12	PCS-12	MCS-12	PCS-12	MCS-12
Week 0	47.38±6.21	36.23±5.54	46.46±5.84	35.75±5.86	48.06±6.31	37.12±5.51
Week 2	48.41±6.04	39.47±6.57	48.35±7.32	40.07±5.21	49.56±5.64	41.46±5.72
Week 4	49.72±5.05	42.54±5.33	49.74±6.01	43.28±6.65	50.37±7.82	44.12±6.43
Week 12	51.37±7.96	49.65±5.58	51.48±6.61	48.42±6.92	52.18±6.45	49.86±6.11
Week 26	54.85±5.67	56.89±6.82	53.86±7.68	55.31±5.54	55.03±6.04	57.53±5.74

Table 4 shows average costs and QALYs evaluated in pharmacoeconomic analysis for three pharmacotherapy variables. Medication cost for paroxetine was found to be highest, followed by venlafaxine XR and escitalopram, whereas QALY gained for paroxetine was found to be highest, followed by venlafaxine XR and escitalopram.

Table 4. Cost and effectiveness of treatment groups

Variable	Escitalopram	Venlafaxine XR	Paroxetine	p
Total drug cost	₹2047	₹2984	₹6193	0.028
QALY gained (Effectiveness)	0.603	0.641	0.724	0.043
Cost/Effectiveness	3395	4655	8554	0.037

Comparing various treatment programs shows that some of the more effective ones are also having more economic value; hence, patient spending rises in tandem with treatment effectiveness. For this reason, the cost of each treatment unit should be taken into account. Furthermore, ICER (ΔC/ΔE) or the cost per additional unit of effectiveness is taken into account in CEA presented in Table 5.

Compared to escitalopram XR (0.603 QALY gained) and venlafaxine XR (0.724 QALY gained), the estimated mean QALY gained with paroxetine therapy were 0.121 and 0.083 respectively for a six months pharmacotherapy. The incremental cost for paroxetine versus escitalopram, paroxetine versus venlafaxine XR, and venlafaxine XR versus escitalopram were ₹4146, ₹3209, and ₹937 respectively. The resulting ICER for paroxetine versus escitalopram was ₹34264 per QALY gained while only pharmacotherapy being considered (Table 5). Similarly, ICER was found to be ₹38663 per QALY gained for paroxetine versus venlafaxine XR and ₹24658 per QALY gained for venlafaxine XR versus escitalopram.

Table 5. Cost-effectiveness analysis

Incremental outcomes	Paroxetine versus Escitalopram	Paroxetine versus Venlafaxine XR	Venlafaxine XR versus Escitalopram
Incremental cost (₹)	4146 (6193-2047)	3209 (6193-2984)	937 (2984-2047)
Incremental QALY	0.121 (0.724-0.603)	0.083 (0.724-0.641)	0.038 (0.641-0.603)
ICER (₹per QALY gained)	34264	38663	24658

Table 6 provides direct costs and indirect costs where average total direct costs were ₹8980 while average total indirect costs were ₹20965. In this study, indirect costs constituted 70% of total costs. According to the estimates, the average value of COI per patient attributable to GAD for six months was ₹29945. Pharmacotherapy accounted for 22.5% of the COI, whereas absenteeism cost added 45.2% to the COI for six months.

Table 6. Average costs per patient with GAD

Type of cost	Component	Cost (₹)
Direct costs	Medication cost	6752
	Hospitalisation cost	653
	Travel cost	832
	Food cost	743
	Total direct cost	8980
Indirect costs	Absenteeism cost	13544
	Presenteeism cost	7421
	Total indirect cost	20965
Cost of illness	Total direct cost plus total indirect cost	29945

4. DISCUSSION

Patients with moderate to severe GAD who did not have any psychiatric comorbidity were enrolled in the study. About 80% of enrolled patients were present at the end of the study. Escitalopram was used to treat 33.69% of the relevant analyzed population under the present therapy choice, venlafaxine XR for 34.75%, and paroxetine for 31.56%. In this study, the expected clinical and economic outcomes of treating GAD were estimated using CEA, which could guide therapy choices for GAD patients. The current study's findings highlight the effectiveness of citalopram, venlafaxine, and paroxetine in treating GAD. The difference in 6-month treatment costs for paroxetine, venlafaxine XR, and escitalopram, divided by the difference between QALY gained in two treatments at 6 months, was used to evaluate CEA. Nevertheless, superior outcomes

in terms of increased quality of life gain as measured by QALY gain accompanied the incremental cost, making the incremental cost per QALY gained reasonable. According to findings of economic analysis, an important determinant of cost effectiveness for pharmacotherapy of GAD is the cost of acquiring the drug.

Better QoL was associated in patients treated with paroxetine compared to escitalopram and venlafaxine XR. The incremental cost per QALY gained was ₹24658 in venlafaxine XR versus escitalopram and ₹34264 in paroxetine versus escitalopram. Overall, it was found that Indian patients with GAD had substantially worse HRQoL, as evidenced by their lower SF-12 Health Survey version 2 scores, especially MCS. GAD was linked to significantly poorer HRQoL scores, and it had a negative impact on patients' functioning and day-to-day lives. In the study, the average total medication cost for paroxetine was the highest whereas it was the lowest for escitalopram for a period of 6 months. Unit cost of escitalopram, venlafaxine XR, and paroxetine were ₹100.8, ₹147.9 and ₹307.75 respectively in pharmacoeconomic analysis. According to the results of this study, paroxetine had greater effectiveness than escitalopram and venlafaxine XR in term of QALY gained. Jingjing Zhang *et al*, reported that in outpatients treated for GAD, venlafaxine is found to be cost effective compared with citalopram. When comparing QOL score, venlafaxine group was shown to be considerably more than citalopram group ($p<0.05$). The efficacy of venlafaxine was found to be greater than that of citalopram [19]. These findings are inconsistent with previous study where Michael Iskedjian *et al*, reported that escitalopram is better than paroxetine in term of cost effectiveness for the treatment of GAD. Compared to paroxetine, escitalopram was related with a higher number of symptom-free days (SFDs) (86.4 versus 77.0). The costs for escitalopram and paroxetine arms were Canadian $724 and Canadian $663 respectively. As a result, the ICER for escitalopram versus paroxetine was found to be Canadian $6.56/SFD (Canadian $2362/symptom free year) [20].

Tine Rikke Jørgensen *et al*, reported that in a study conducted in United Kingdom, escitalopram seems to be better than paroxetine in term of cost effectiveness when treating GAD. Patients who received escitalopram had considerably lesser discontinuation rates due to adverse events and 14.4% higher first-line treatment success than those who received paroxetine. Patients treated with escitalopram had total expected nine month costs of 1408 pounds sterling (2560 USD), lesser than patients treated with paroxetine [21]. Escitalopram treatment is cheaper due to low buying unit cost compared to paroxetine and venlafaxine XR.

Indirect costs constituted a larger component of the total costs because of work impairment (absenteeism and presenteeism). It is important to note that indirect costs had an impact that was more than twice as large as direct costs. Finding of a study by Joan Rovira *et al*, showed that indirect costs constituted more than twice (75 %) as that of total cost [22]. This evaluation highlights absenteeism as the biggest contributor in COI out of all the variables. Basil G. Bereza *et al*, reported that the lifetime cost of illness was found to be $31,213 in a study conducted in Canada wherein cost of absenteeism contributed 96% of COI [23]. Anxiety disorders result in lost productivity and place a significant financial strain on healthcare resources. Joan Rovira *et al*, reported that a study conducted in Spanish primary healthcare settings for GAD patients showed significant treatment cost along with costs due to loss of productivity. Total yearly costs were found to be higher in GAD than controls without GAD (€7,739 versus €2,609). The mean costs were reported to be €5,139 including 75 % of total cost as indirect costs. The improvement in quality of life was associated with lower cost [22].

Limitation of the study is drug utilization data which is totally based on the information provided by the patient itself which might not be completely accurate as compliance may vary among the GAD patients. Consultation cost is not included as consultation fee was exempted in the hospital serving as the study centre. Cost associated with management of adverse drug reactions is also not considered in the evaluation.

5. CONCLUSION

GAD shows significant economic burden as six month cost of illness per patient was around thirty thousand Indian rupees. Cost of absenteeism is double than the cost of pharmacotherapy in patients with GAD. Escitalopram is found to be cost effective compared with venlafaxine XR and paroxetine.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical Approval

The protocol was approved by Teerthanker Mahaveer University Institutional Ethics Committee (TMU-IEC), Moradabad (Registration Number TMU/IEC/2021-22/66).

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