ORIGINAL RESEARCH

Cost Effectiveness Analysis of Sertraline Versus Amitriptyline in Depression Management in a Psychiatric Hospital in South Southern Nigeria

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To cite this article: Edefo JW and Udezi AW. Cost Effectiveness Analysis of Sertraline Versus Amitriptyline in Depression Management in a Psychiatric Hospital in South Southern Nigeria. Journal of Basic and Social Pharmacy Research, 2020;1(5):34-45.
ISSN: 2705-3245

ABSTRACT

Background: In Nigeria, cost effectiveness data is rare therefore, resources allocated to the management of patients with depression can hardly be said to be optimized.
Objective: The study aimed to determine the cost-effectiveness of sertraline versus amitriptyline in the management of depression.
Methods: It is a prospective study of patients suffering from depression and who are receiving treatment from Psychiatric Hospital, Benin City, Nigeria. Costs were collected with the aid of a data collection sheet, while clinical improvement in depression was assessed by Hospital Anxiety Depression Scale- Depression (HADS-D) subscale instrument. Graph Pad Instat version 3.10 was used for inferential analysis. Markov Chain Monte Carlo model with sensitivity analysis of ± 50% on the effects of the antidepressants was used for pharmacoeconomic evaluation which was conducted from a third-party payers' perspective with the real-world sample bootstrapped to 1000 respondents. Cost-Effectiveness Ratios (CER) was gotten, and Incremental Cost-Effectiveness Ratios (ICER) was calculated.
Results: Females accounted for 60.8 % (84) of the total sample. First scenario of sensitivity analysis of sertraline 50mg versus amitriptyline 50mg gave ICER of NGN10847 which means sertraline will be more cost effective if the cost of making one depression free person in a month is worth more than NGN10847 (USD 27.12) and this amount is enough to treat 10 persons on amitriptyline. The second scenario of the sensitivity analysis gave ICER of -NGN16346 (-USD40.87) meaning that sertraline is more expensive and less effective than amitriptyline.
Conclusion: Sertraline is more effective but from a third payer perspective it is less cost effective than amitriptyline in depression management.

Keywords: Antidepressants, sertraline, amitriptyline, depression, cost effectiveness analysis, pharmacoeconomic analysis

INTRODUCTION

Depression is a mental condition which is mainly characterized with symptoms of low mood, low energy and loss of interest in one's pleasurable activity for at least 2 weeks without any underlying cause[1]. This condition increases the risk for suicidal attempt and suicide in individuals of all ages[2]. Up to 15% of patients with severe major depressive disorders die by suicide[3,4]. Suicide is the third most common cause of death among adolescents and is one of the most devastating events than can happen to a family[2].

Major Depressive Disorders has a prevalence of 5% in the general population and 3.1% in Nigeria[3]. The management of this condition is covered by the government owned social welfare scheme that is National Health Insurance Scheme (NHIS) which is a third-party payer perspective of health services.

The economic burden of managing mental illness per patient in Nigeria of which depression is one of the spectrums of mental illness gave mean direct and indirect cost as USD231 and USD15 respectively[4]. In addition, total direct and indirect costs of depression in the United States were of similar magnitude to those of other major illnesses such as cancer, AIDS and coronary heart disease and recent projections suggested that these total costs will place depression as the second largest medical burden to our global society by 2025[7].

Cost of treatment in pharmacoeconomic analysis can be direct, indirect and/or intangible cost. Direct cost comprised direct medical and non-medical cost. Direct medical cost consists of physician consultation cost, medication cost, laboratory investigations cost.

Third-party payers of health services such as social welfare schemes are responsible for direct medical cost. Depression is among the illnesses covered by insurance and since it is evident that resources are inadequate and data of pharmacoeconomic studies are rare in Nigeria, thus study is apt as it will provide useful information on the cost effectiveness of the two most frequently used antidepressants in psychiatric hospital Benin City for the payers.

Evidence from this study will help third-party payers to know which drug should be first line when developing prescribing guidelines and medication list for physicians who manage patients with depression. The logic is that when a more cost-effective drug is used as first line, the less cost-effective drug may be reserved for those who failed to respond to the first line drug. This will enable more patients to be treated in the presence of limited resources; hence this study was aimed at determining the cost-effectiveness of sertraline versus amitriptyline.

METHODS

Study design / Sampling method

A prospective cohort design of 24 weeks study per patient after the initial contact was employed. Follow-up was done every 4 weeks for up to the 24th week per patient that completed the study. Inclusion criteria were out-patients above 18 years, diagnosed for depression and managed with either sertraline or amitriptyline. Patients who were prescribed the antidepressant for indications other than depression (e.g., neuropathic pain), those who were unable to fill the questionnaire due to their mental illness or any other conditions and respondents who were switched between these drugs were excluded. Written informed consent were gotten from those who participated in the study.

Convenience sampling on the basis of first 4 patients that consented to participate on a random day was used in this study. This sampling technique is a reflection of real-world situation which effectiveness studies aim to achieve. Data collection process spanned within a year.

Study site

The study was conducted at a tertiary Psychiatric Hospital, in Benin City, Nigeria. The health facility is primarily for mental health services. Staff strength includes consultant psychiatrists, resident doctors, 12 pharmacists, 8 intern pharmacists and more than 200 nurses as of 1st September 2020'.

Data collection process

The respondents were allocated into amitriptyline and sertraline treatment group based on the financial strength of the respondents and prescribers' professional judgment. Sertraline and amitriptyline were used in the study because they are the frequently used antidepressants in the health care facility and thus sufficient useful samples can be gotten without much delay.

Socio-demographic factors and medication costs from hospital medication list were collected with the aid of a data collection sheet. The antidepressants prescribed were noted, the doses and its cost were also documented. Validated instruments such as International Classification of Disease (ICD)-10 criteria and Hospital Anxiety Depression Scale-Depression subscale (HADS-D) was used to formulate questionnaire and pretesting of these instruments were done.

Medication cost was used in the study to represent direct medical cost because in the study setting it is the only component of direct medical cost that has high variability in terms of cost as compared to other components that give the same financial burden. For example, same consultation fee for all patients during their hospital visits.
International classification of disease (ICD)-10 criteria was used to diagnose depression, and this was done by consultant psychiatrists in order to exclude those who were not suffering from depression. Clinical improvement in depression was assessed by Hospital Anxiety Depression Scale-Depression (HADS-D) subscale instrument[8,9]. The purpose of HADS-D was to monitor the depressive state of respondents at each follow up in the course of the research.

Medication cost was measured at initial contact and also for each follow- up. At all time, only the cost of the medication that covered till the next 4 weeks was calculated. Outcome (effect) was also measured at every contact based on depression free using the Hospital Anxiety and Depression Scale – Depression subscale (HADS-D) score and the score at each point in time was recorded. Antidepressants of generic brand of both amitriptyline and sertraline were used for the study. The mean medication cost and mean effectiveness of all those on a particular medication were considered as medication cost and effectiveness of that drug.

Data analysis

Data collected were entered, sorted and analyzed using Microsoft Excel for descriptive analysis while inferential analysis was done by Graph Pad instat version 3.10, a statistical software published by Graph Pad software, Inc, California corporation. A p-value of < 0.05 was considered significant.
The effect of antidepressant measured was the number of respondents who were free from depression. A Hospital Anxiety Depression Scale-Depression Subscale (HADS-D) score of below 8 was defined as depression free (normal individuals), a value of 8 - 10 as borderline individuals while above 10 were noted as abnormal patients (depressed patients)[10,11]. Only those who were depression free in this study were considered as free from the depressive symptoms.
Medication cost for patient on particular medications for the first 4 weeks of the study was calculated by multiplying the price of drug of the respondent in a day by 28. This was done for all respondents in the different treatment group. The mean medication cost of all respondents on a particular medication was determined by dividing medication costs of all those on a particular group by the number of respondents in that group and the mean cost was considered as the medication cost for that medication. Cumulative medication cost of drug for a period of time was determined e.g., the cost of taking sertraline for the second 4 weeks of the study was the cost of sertraline for the first 4 weeks plus second 4 weeks. This was done subsequently for other follow-ups till 24th week.

Pharmacoeconomic evaluation

This evaluation was conducted from a third-party payer's perspective which is always interested in the medication cost. It is an entity other than the patient or the healthcare provider that reimburses direct medical costs (expenses). This perspective includes insurance company, governmental agencies and employers. In this study only medication

cost i.e., cost for the purchase of the medication was computed.

The evaluation compared the medication cost and effectiveness of sertraline to that of amitriptyline.

Unit cost of medication in Naira (NGN) was obtained from the hospital price list, while effectiveness (depression free) in this case was assessed by Hospital Anxiety Depression Scale- Depression subscale. No discounting was necessary as medication cost and clinical outcome were measured within the same year.

Markov Chain Monte Carlo model with the aid of Vanguard Studio 5.0 was used for pharmacoeconomic decision analysis. It has two arms namely a Markov chain arm and a Monte Carlo arm. The Markov arm takes care of transitory states that are differentiated by the HADS-D scale when respondents were placed on antidepressant medication. These transitory states are depression (abnormal), borderline and depression free (normal). It takes account separately the number of those with depression, borderline and depression free at every point in time. The information on the number of those who were free from depression was supplied to Monte Carlo arm.

The assumption of the Markov Chain arm is that those who improved from depression to depression free state without being in the borderline were not accounted for but were passed through the borderline state and because the situation was rare and few, it will not significantly affect the result of the model. In case of relapse, the percentage change from that state in the previous month was reduced to prevent negative entry into the model.

Monte Carlo arm of the model takes care of the number of cycles; in this case, 6 cycles were observed in which one cycle represent each follow up which was 4 weeks. This model also gave the cost effectiveness ratios of the different medications considered. The Incremental cost-effectiveness ratios (ICER) is a summary which represent the economic value of sertraline over amitriptyline for 50mg and 100mg and this was determined by getting a ratio of extra cost per extra effectiveness of sertraline over amitriptyline

Sensitivity Analysis

Variation was only considered on the effectiveness of sertraline and amitriptyline and variability level was put at 50 percent while the medication cost component remains constant. Medication cost was not varied because it remained constant during the period of data collection of this study which was within a year.

Research ethical approval

Ethical approval was granted by the Psychiatric hospital Ethics Committee with Reference no: PH/PE 2483/61.

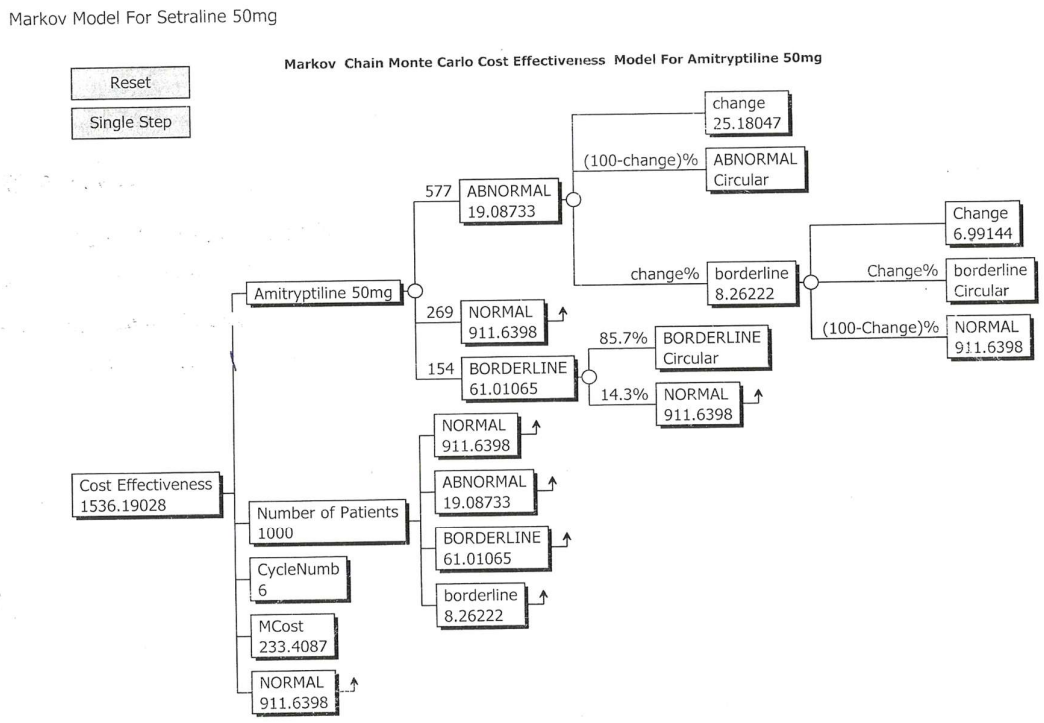

Figure 1: Diagrammatic presentation of Markov chain Monte Carlo model of cost effectiveness evaluation of Sertraline versus Amitriptyline in Psychiatric hospital, Benin City.

RESULTS

Patients who participated in the study were 84 (60.8 %) female, 69 (50 %) married, 9 (6.5%) had no formal education, 29 (21 %) got primary education, while about 32 (23.1%) attained tertiary level of education, see Table 1 below.

Respondents that completed the study and whose results were used for data analysis were of two groups which comprised: group 1 (36 respondents who were on sertraline 50mg/day versus 47 respondents on amitriptyline 50mg/day); and group 2 (23 respondents were on sertraline 100mg/day versus 32 respondents on amitriptyline 100mg/day). These strengths were used because they are the mostly commonly used strengths of sertraline and amitriptyline in psychiatric hospital as this study attempts to determine the cost-effectiveness of sertraline versus amitriptyline using real-world situation. Respondents were placed on same strength of a particular medication from the start to the end of the study.

Sertraline 50mg is more effective and more expensive than amitriptyline 50mg and sertraline 100mg is more effective and more expensive than amitriptyline 100mg (Table 2)

Table 1: Demographic characteristics of respondents (N= 138)

VARIABLE	FREQUENCY	PERCENTAGE (%)
Sex		
Male	54	39.1
Female	84	60.8
Marital status		
Married	69	50
Widow/widower	13	9.4
Single	55	39.9
Children		
None	45	32.6
1 – 2	19	13.8
3 – 4	21	15.2
5 and above	21	15.2
Age (yrs)		
18 – 30	37	26.8
31 – 40	41	29.7
41 – 50	32	23.2
>50	25	18.1
Education		
No formal education	9	6.5
Primary	29	21
Secondary	62	44.9
Tertiary	32	23.1
Degree of depression at the start of study		
Mild	83	60
Moderate	40	29
Severe	15	11
Occupation		
Government employee	28	20.3
Not employed	17	12.3
Privately owned company	24	17.4
Student	18	13.1
Self employed	51	37
Respondents monthly income (10000 X NGN)		
< 1.1	63	45.7
1.1 – 2.0	20	14.5
2.1 – 3.0	21	15.2
3.1 – 4.0	21	15.2
≤ 4.1	13	9.4

Table 2: Effectiveness and medication cost of amitriptyline and sertraline

Variables	Amitriptyline 50mg (n=47)	Sertraline 50mg (n=36)	P-value
Effects (HADS-D)	593 ± 53	693± 59	<0.001
Cost (NGN) X 1 million	1.042 ± 0.32	8.038 ± 1.02	<0.001
Effects (HADS-D)	Amitriptyline 100mg (n=32)	Sertraline 100mg (n=23)	
Cost (NGN) X 1 million	500 ± 89	781± 111	<0.001
	3.305 ± 0.74	14.324 ± 0.98	<0.001

Key: N=sample size; HADS-D=Hospital Anxiety Depression Scale-Depression

The cost effectiveness analysis without sensitivity test of sertraline 50mg over amitriptyline 50mg revealed ICER of NGN69960 (USD 17.49) at USD1.00 equivalent to N400.00, the cost of an extra depression free is NGN69960 (USD 17.49), meaning that if cost of making one patient free from depression in a month is worth more than NGN69960 (USD 17.49), then sertraline is more cost effective.

The analysis with sensitivity test showed that in the first scenario, ICER of NGN10847 (USD27.12), the cost of an extra depression free is NGN10847 (USD27.12), implying that sertraline is more cost effective than amitriptyline if the cost of making one person free from depression in a month is worth more than NGN10847 (USD27.12) while the second scenario of the analysis revealed ICER of -NGN16346 (-USD40.87), the marginal cost of extra depression is -NGN16346 (-USD40.87), meaning that sertraline is less effective and more expensive than amitriptyline (Table 3).

Cost effectiveness analysis without sensitivity test of sertraline 100mg over amitriptyline 100mg showed ICER of NGN38803 (USD97.01), the marginal cost of extra depression is NGN38803 (USD97.01), implying that sertraline is only cost effective if the cost of making one person living with depression free of the symptoms in a month is worth more than NGN38803 (USD97.01).

However employing sensitivity analysis revealed ICER of NGN13134 (USD32.84), extra cost to extra depression free ratio is NGN13134 (USD32.84), suggesting that at one scenario sertraline will be more cost effective than amitriptyline if the cost of making one patient free from depressive symptoms in a month is more than NGN13134 (USD32.84) while the second scenario gave ICER of -NGN48122 (-USD120.31), extra cost to extra depression free ratio is -NGN48122 (-USD120.31), meaning that sertraline is less effective and more expensive than amitriptyline (Table 4).

Table 3: Cost effectiveness analysis of Sertraline 50mg versus Amitriptyline 50mg using Markov Chain Monte Carlo model from third party payer's perspective of bootstrapped sample size of 1000

Category	Strategy	N	Drug cost X NGN I Million	I C	Effect (HADS-D)	I E	ICER
No Sensitivity Analysis							
Undominated	Sertraline	1000	8.038		693	100	69960
Undominated	Amitriptyline	1000	1.042	6.996	593		
Sensitivity Ser +50%, Ami -50%, 1st scenario							
Undominated	Sertraline	1000	8.038		1040	645	10847
Undominated	Amitriptyline	1000	1.042	6.996	395		
Sensitivity Ser -50%, Ami +50%, 2nd scenario							
Dominated	Sertraline	1000	8.038	6.996	462	-428	-16346
Dominant	Amitriptyline	1000	1.042		890		

Key: Ser = Sertraline; Ami = Amitriptyline; N=sample size; IC = Incremental cost; IE = Incremental effect; ICER = Incremental Cost Effectiveness Ratio.

Table 4: Cost effectiveness analysis of Sertraline 100mg versus Amitriptyline 100mg using Markov Chain Monte Carlo model from third party payer's perspective of bootstrapped sample size of 1000

Category	Strategy	N	Drug cost X NGN I Million	I C	Effect	I E	ICER
No Sensitivity Analysis							
Undominated	Sertraline	1000	14.324	11.02	781	281	38803
Undominated	Amitriptyline	1000	3.305		500		
Sensitivity Ser +50%, Ami -50%, 1st scenario							
Undominated	Sertraline	1000	14.324	11.02	1172	839	13134
Undominated	Amitriptyline	1000	3.305		333		
Sensitivity Ser +50%, Ami -50%, 2nd scenario							
Dominated	Sertraline	1000	14.324	11.02	521	-229	-48122
Dominant	Amitriptyline	1000	3.305		750		

Key: Ser = Sertraline; Ami = Amitriptyline; N=sample size; IC = Incremental cost; IE = Incremental effect; ICER = Incremental Cost Effectiveness Ratio.

The Incremental Cost Effectiveness Ratio (ICER) of sertraline 50mg over amitriptyline 50mg in relation to the mean cost of Amitriptyline (MCA) showed that in first scenario the marginal cost effectiveness of sertraline 50mg over amitriptyline 50mg will be able to treat at least 10 persons who are on amitriptyline while the second scenario revealed that the financial losses of choosing sertraline over amitriptyline can treat 16 persons who are on amitriptyline (Table 5) .

Table 5: Comparing the ICER of Sertraline 50 mg over Amitriptyline 50mg with mean cost of Amitriptyline

ICER	Mean cost of Ami (NGN)	Ratio of ICER to MCA	Comments
No Sensitivity Analysis			
69960	1042	67	Marginal cost effectiveness will treat 67 persons on Ami
Sensitivity Ser +50%, Ami -50%, 1st scenario			
10847	1042	10	Marginal cost effectiveness will treat 10 persons on Ami
Sensitivity Ser -50%, Ami +50%, 2nd scenario			
-16346	1042	-16	Sertraline is less cost effective

Key: Ser = Sertraline; Ami = Amitriptyline; ICER = Incremental Cost Effectiveness Ratio; MCA = Mean Cost of Amitriptyline.

Comparing the Incremental Cost Effectiveness Ratio (ICER) of sertraline 100mg over amitriptyline 100mg to the mean cost of Amitriptyline (MCA) revealed that first scenario, the marginal cost effectiveness of sertraline 100mg over amitriptyline 100mg will be able to treat at least 4 persons who are on amitriptyline while the second scenario revealed that the financial losses of choosing sertraline over amitriptyline can treat 15 persons who are on amitriptyline (Table 6).

Table 6: Comparing the ICER of Sertraline 100 mg over Amitriptyline 100mg with mean cost of Amitriptyline

ICER	Mean cost of Ami (MCA)	Ratio of ICER to MCA	Comments
No Sensitivity Analysis			
38803	3305	12	Marginal cost effectiveness will treat 12 persons on Ami
Sensitivity Ser +50%, Ami -50%, 1st scenario			
13134	3305	4	Marginal cost effectiveness will treat 4 persons on Ami
Sensitivity Ser -50%, Ami +50%, 2nd scenario			
-48122	3305	-15	Sertraline less cost effective

Key: Ser = Sertraline; Ami = Amitriptyline; ICER = Incremental Cost Effectiveness Ratio; MCA = Mean Cost of Amitriptyline.

DISCUSSION

Demographic distribution of the study revealed more female than male, age group 20- 40 years suffered more from depression and about two-third of those diagnosed of depression were of mild form. This is in consonant with studies which posited that females are generally more depressed than males[14,16] and another work in Nigeria[14] which revealed that being in the age group of 20 - 40 years old increases the risk of depression.

Sertraline 50mg is more effective than amitriptyline 50mg by making more than two-thirds of the respondents on this medication free from depression while the same strength of amitriptyline 50mg made slightly above half of the respondent free from depression. For 100mg of sertraline about three-quarter of the respondents were made free from depression while amitriptyline 100mg made half of the respondents' depression free. This higher effect of sertraline than that of amitriptyline in the management of depression as seen in this study is in agreement with a double blind, placebo-controlled study of sertraline versus amitriptyline in the treatment of depression. The study found that sertraline has ability to resolve depression faster because of its ability to cause more improvement in quality of life of patients[15].

Despite the fact that sertraline 50mg has higher effect than amitriptyline 50mg; the cost of purchasing sertraline is higher as it will cost an average of NGN8038 (USD20.10) to be on sertraline for 6 months while that of amitriptyline will cost NGN1042 (USD2.61) for the same period of time, thus considering this situation where sertraline is more effective and more expensive which was also seen when comparing sertraline 100mg with amitriptyline 100mg hence the need for Incremental Cost Effectiveness Ratio (ICER) of sertraline over amitriptyline was determine in order to know to what amount an extra depression will be worth if sertraline is considered instead of amitriptyline consequently giving us an idea of which of the antidepressants is more cost effective

Cost effectiveness analysis carried out on the antidepressants employed in the study revealed that on one arm of the sensitivity analysis, sertraline 50mg will be more cost effective than amitriptyline 50mg if the cost of making one person free from schizophrenia is worth more than NGN10847 (USD 27.12) and this amount is enough to place 10 persons suffering from depression on amitriptyline 50mg for 24 weeks. In the second arm of the sensitivity analysis, the financial losses of -NGN16346 (-USD40.87) - of sertraline 50mg over amitriptyline 50mg can be used to place about 16 patients on amitriptyline implying that sertraline 50mg is less effective and more expensive than amitriptyline 50mg.

The same pattern was also seen when comparing sertraline 100mg and amitriptyline 100mg which revealed that in the first scenario of the analysis, sertraline 100mg will be more cost-effective if the cost of making one person suffering from depression free from depressive symptoms is worth more than NGN13134 (USD32.84) and this amount is enough to treat 4 persons suffering from depression with amitriptyline 100mg for 24 weeks. On the second scenario of the test, the financial loss of -NGN48122 (-USD120.31) of sertraline 100mg over amitriptyline 100mg is sufficient to place about 15 persons on amitriptyline thus sertraline 100mg is less effective and more expensive than amitriptyline 100mg.

Similar study done using health service or institutional perspective[16]revealed that for values of an additional depression free month of using sertraline instead of amitriptyline was over £200 (NGN100,000), £1.00 was equivalent to NGN500.00[16].

In a resource limited country like Nigeria, a third-party payer of health services and medications will easily choose amitriptyline over sertraline in the

management of depression meaning amitriptyline is more cost effective than sertraline in the management of depression from their view point.

Limitation of the study and Areas for further research

We adopted a third-party payer's perspective for the pharmacoeconomic evaluation, and it is possible that the result might have differed if we had used another viewpoint such as societal or patient perspective.

A cost-utility study should also be done in order to compare the Quality of life Adjusted Life Years (QALY) and to make a more categorical statement about cost-utility of sertraline as compared to amitriptyline in this local setting.

Weaknesses of the study are the assumption that medication cost should represent direct medical cost as well as not employing therapeutic dose equivalent of antidepressants.

CONCLUSION

Sertraline is more effective than amitriptyline but from third party payer's perspective, sertraline is less cost effective compared to amitriptyline.

The third party payer of health services such as National Health Insurance Scheme (NHIS) should adopt amitriptyline as first line antidepressant for the management of depression and reserved sertraline for second line antidepressant for those who cannot tolerate the side effects of amitriptyline.

ACKNOWLEDGEMENTS

Our gratitude goes to the management of Federal Neuropsychiatric Hospital (FNPH), Benin City for their roles they played in granting approval for this research to be done. Big thanks to Dr Ediae Ikponwonsa Cliff, the Head of Pharmacy Department and all pharmacists at FNPH Benin City, Nigeria. Our appreciation goes to Vanguard Corporation, United States of America, who constructed the model with the aid of Vanguard Studio 5.0 and donated it in an academic partnership which was used in this study.

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