

Retrospective cost-utility and budget impact assessments of *Hypericum perforatum* in contrast with Fluoxetine treatment for depression in Karachi, Pakistan

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In this study we have compared two different types of therapies i.e. herbal and allopathic system of therapies for Depression and studied them from the social perspectives. The *Hypericum perforatum* is compared with Fluoxetine [HCL] in terms of cost-utility and financial savings thereby evaluating its influence on annual expenditure of depressive patients that were randomly selected from 178 union councils of the city of Karachi, Pakistan. For both system of therapies a total of 356 patients were selected by stratified random sampling. Taking frequency of depression as '1' annually with discount rate at 3% for calculating the burden-of-illness in terms of disability-adjusted-life-years. The cost-utility and the budget-impact assessments were carried out to assess incremental-cost-effectiveness-ratio, and the budget-impact-per-onset as well as budget-impact-per-year values. In comparison with the Fluoxetine therapy, the *Hypericum perforatum* was found to relieve symptoms in 21.47% less cost; owing 29.23% less disability-adjusted-life-years and 21.45% less budget-impact-per-onset as well as budget-impact-per-year. The annual mean incremental-cost-effectiveness-ratio was found to be at 36.95±270.74 (less than GDP per capita threshold of Rs. 38,173.02). *Hypericum perforatum* provide the optimal utility with less impact on budget of a patient in comparison with the treatment of symptoms of depression with Fluoxetine.

Keywords: *Hypericum perforatum*. Fluoxetine. Burden of illness. Disability-Adjusted-Life-Years. Incremental-Cost-Effectiveness-Ratio.

INTRODUCTION

Depression has been identified as one of the major illnesses, which can curtail the quality of life along with the potential to aggravate hysteria in the day-to-day life. This could lead to suicide attempts that is prevailing these days; therefore, is becoming one of the apprehension of mortality in depression (Supartini, Oishi, Yagi, 2017). According to WHO depression is a psychological disorder that originates from various unspecified reasons. With a prevalence of 28.2% in young population (Oyekcin, Sahim, Aldemir, 2017) and with an annual rise to 113%, this psychological condition has been affecting 4.7% of today's world population (Xu *et al.*, 2017; Wu *et al.*, 2017). Depression is generally characterized as the cerebral impairment categorized by

the absence of a positive demeanor. This represents a clear loss of the presence of enthusiasm and charisma for personal belongings, daily life activities as well as social participation and person becomes introvert. Depression is strongly associated with indications that represents susceptibility to mourning, peevishness and impatience, frequent withdrawals, and aggravation of a very unusual feelings (Wu *et al.*, 2017), particularly the presence of feelings of inferiority and a state of mind for guiltiness (Zhang *et al.*, 2016; Supartini, Oishi, Yagi, 2017). There is loss of libido and the prostration along with the diminished body movements and noticeable nervousness is more recurrent than general anxiety in depression. During the phase of depression, insomnia as well as anorexia has been seen, with very few exceptions. There are also signs of lack of self-confidence, worthlessness, emotional state of powerlessness, and merited sentence in the form of delusion or hallucinations and efforts for harming oneself or any kind of suicide (Supartini, Oishi, Yagi, 2017). The incident of suicide linked to depression

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includes a form of suicide, ‘hara-kiri’, however, it is not the only type of suicide that has been reported in depression (Cheung, Merry, Sundram, 2018). Even some studies suggest that the trivial activities like suicide are not in particularly linked with depression (Cheung, Merry, Sundram, 2018).

Numerous plants have been reported to have such phytochemicals that exhibit therapeutic significance as an antidepressant (Saki, Bahmani, Rafieian-Kopaei, 2014). Among them, one of the most important plants is *Hypericum perforatum* (Bukhari, Dar, 2013; Chrea *et al.*, 2014; Husain *et al.*, 2011; Russo *et al.*, 2014; Saki, Bahmani, Rafieian-Kopaei, 2014; Sarris, 2013; Solomon, Adams, Graves, 2013; Tian *et al.*, 2014). Under various brand names, the herbal medicine *Hypericum perforatum* and an allopathic medicine *Fluoxetine* [HCL] 20mg (Floxac® 20mg Tablets) – a product by The Schazoo Laboratories (Pakistan), are utilized by patients across the globe (Wong, Perry, Bymaster, 2005). Although, there is evidence of several published pharmacoeconomics studies for allopathic medicines throughout the research world, yet there is lack of such research studies on herbal medicines (Huebner *et al.*, 2017) especially in the selected region of the city of Karachi, Pakistan.

Previously, various studies were conducted for determining epidemiology of depression and the pharmacoeconomic benefits associated with the involved therapies. For example, with respect to prevalence of depression in citizens of the United States of America, each one in twelve citizens was found affected by it (Adkins *et al.*, 2012). As stated by the World Health Organization, at the end of the year 2020, the depression would be the next to major causes of Disability Adjusted Life Years (DALYs) expected to be misplaced globally (Al-Qadhi *et al.*, 2014).

In Pakistan, from the year 1957 until 2016, due to the changes in consumer price index, the dynamics of the inflation rate averaged at 7.86% (Pakistan Inflation Rate, 2017). The requirement for national savings is now on the top priority list for Pakistan due to the inflation. Therefore, with respect to the treatment of depression, there was a need to assess two dissimilar therapies from the social perspective. For this, the estimation of cost per DALY and analysis of budget impact of therapies was due for the treatment of depression, i.e. the *Hypericum perforatum* (St. John’s Wort) with *Fluoxetine* [HCL] (Floxac® 20mg Tablets) in terms of the cost utility, the financial savings and reducing the load of depression with the minimum influence on annual budget of a patient in population of the 178 union councils of the city of Karachi, Pakistan.

MATERIAL AND METHODS

The herb ‘*Hypericum perforatum*’ was utilized as a sample while the allopathic medicine *Fluoxetine* [HCL] 20 mg (Floxac® 20mg Tablets) was selected as a control in the study. The ‘*Hypericum perforatum*’ was used as an oral infusion, i.e. in 1 cup; 200mg of ‘*Hypericum perforatum*’ once a day.

Approval of study by ethical review committee

The study was started after an approval of the research project from *Ethical Review Committee, Faculty of Pharmacy and Pharmaceutical Sciences, University of Karachi (Project Approval Protocol, dated: September 18, 2012, ref. no. 0671/Pharm./10(28))*, for data collection of depressed patients. This data collection was confined to the physiological, medical or clinical information, and was constrained for collection of any human biological materials. The methodology of the study was developed in the light of the good research practices of Pharmacoeconomics as provided by the International Society of Pharmacoeconomics and Outcome Research (ISPOR) (Eddy *et al.*, 2012). The methods were validated (Eddy *et al.*, 2012) and replicated for the other two studies of the same series of research, i.e. for common cold and trauma in the 178 union councils of the city of Karachi.

Setting and sample

The required sample size needed for this study was calculated by using the following equation (Pakpour *et al.*, 2011):

$$n = \frac{z^2 p (1 - p)}{d^2}$$

where: n = Sample size; z = Standard normal distribution (1.96); p = Estimated mean of incidence proportion observed for the depression in the city of Karachi (i.e. 0.05); d = Standard error (0.05).

$$n = \frac{(1.96)^2 \times (0.05) \times (1 - 0.05)}{(0.05)^2} \quad (n = 73)$$

Instead of taking least sample size of 73 patients, a relatively large sample size was taken into consideration, i.e. taking one patient from each strata or union councils ($n = 178$) patients each for fluoxetine and *Hypericum perforatum* based therapies. By taking an Average Annual Household Income Per Person (AAHIPP) at Rs. 99,150/-

(Pakistan Statistical Pocket Book 2006, 2006), the 356 patients were selected as stratified random samples from population of 7,755,189 (approx. 7.76 million). The patients were segregated by their age and the process of data collection was completed in accordance with the proportions of each group out of 11 different age groups (i.e. Table I: from 25-75+ years with difference of 5 years in between) as defined by the Pakistan Bureau of Statistics (Pakistan Statistical Pocket Book, 2006). Following formula was used for the sample size based on age groups:

$$\left(\text{Age Group Based Sample Size} \right) = \frac{\left(\text{Percentage of Age Group in Population} \right)}{100} \times \text{Sample Size}$$

Clarity of variables in the study

Study Perspective: The societal perspective was followed for the present study for both the fluoxetine and *Hypericum perforatum* therapies for the depression. *Time Horizon:* The data of the 356 patients sampled for the Fluoxetine and *Hypericum perforatum* therapies were collected for one year (i.e. from March 2015 to February 2016). *Description of decision-analytical model:* A simple decision tree model was used as a guide within the specified time horizon. *Uncertainty:* ‘Standard deviation’ (SD) and ‘Standard Error of Mean’ (SEM) were used as the two main parameters of statistical uncertainty for the study (Table III).

TABLE I - Percentage-wise division of sample size of 178 patients among age groups in depression along with the analysis of age and gender homogeneity between the groups

S. No.	Age Groups (In Years)	% of Total Populace	Actual Sample Size Per Therapy	Fluoxetine Based Therapy			<i>Hypericum perforatum</i> Based Therapy		
				Gender in Age Groups	Age (Maximum No. of Patients)	Gender in Maximum No. of Patients	Gender in Age Groups	Age (Maximum No. of Patients)	Gender in Maximum No. of Patients
1	25 – 29 years	7.37	35	Male: 23 Female: 12	28 years (10 patients)	Male: 8 Female: 2	Male: 15 Female: 20	25 years (10 patients)	Male: 5 Female: 5
2	30 – 34 years	6.22	30	Male: 14 Female: 16	32 years (9 patients)	Male: 4 Female: 5	Male: 14 Female: 16	31 years (8 patients)	Male: 5 Female: 3
3	35 – 39 years	4.77	23	Male: 11 Female: 12	35 years (7 patients)	Male: 4 Female: 3	Male: 10 Female: 13	35 years (8 patients)	Male: 5 Female: 3
4	40 – 44 years	4.45	21	Male: 14 Female: 7	44 years (6 patients)	Male: 4 Female: 2	Male: 11 Female: 10	42, 43, 44 years (15 patients)	Male: 7 Female: 8
5	45 – 49 years	3.53	17	Male: 11 Female: 6	48 years (6 patients)	Male: 6 Female: 0	Male: 6 Female: 11	46 years (5 patients)	Male: 1 Female: 4
6	50 – 54 years	3.21	15	Male: 11 Female: 4	50, 51 years (10 patients)	Male: 7 Female: 3	Male: 8 Female: 7	50 years (4 patients)	Male: 1 Female: 3
7	55 – 59 years	2.15	10	Male: 4 Female: 6	58 years (4 patients)	Male: 3 Female: 1	Male: 7 Female: 3	56, 57 years (4 patients)	Male: 2 Female: 2
8	60 – 64 years	2.04	10	Male: 3 Female: 7	61 years (4 patients)	Male: 0 Female: 4	Male: 5 Female: 5	64 years (5 patients)	Male: 4 Female: 1
9	65 – 69 years	1.20	6	Male: 1 Female: 5	69 years (3 patients)	Male: 1 Female: 2	Male: 4 Female: 2	68 years (2 patients)	Male: 1 Female: 1
10	70 – 74 years	1.09	5	Male: 3 Female: 2	71 years (2 patients)	Male: 2 Female: 0	Male: 3 Female: 2	70 years (2 patients)	Male: 1 Female: 1
11	75 years & up	1.21%	6	Male: 4 Female: 2	75, 87, 88, 89, 90, 95 years (6 patients)	Male: 4 Female: 2	Male: 2 Female: 4	76 years (2 patients)	Male: 0 Female: 2
Total				Male/Female	99/79	Male/Female	85/93		

TABLE II - Theoretical Vs actual savings with the influence of annual inflation accumulated over time

Year	Theoretical Savings (Rs. in Billion)	Actual Savings (Rs. in Billion)
1 st Year	46.82	46.82
2 nd Year	46.82	39.46
3 rd Year	46.82	33.26
4 th Year	46.82	28.03
5 th Year	46.82	23.62
Total	234.10	171.19

Rs.: Pakistani rupees

Survey instrument and data collection

For obtaining the maximum data input from 356 patients selected in the research study, a bilingual layered style interviews, questionnaires and opinion surveys (Groves *et al.*, 2011; Dillman, Smyth, Christian, 2014) were devised, which consists of a blend of open and closed-ended questions. The interviews were rarely used in situations where respondents were unable to feedback to the questionnaires due to diversified reasons. The questionnaires and opinion surveys were available to the respondents in the form of choices between paper-based as well as an online (survey with Limesurvey™

TABLE III - Cost, disability-adjusted life years, burden of illness, incremental cost-effectiveness ratio and budget impact assessments of Fluoxetine and Hypericum perforatum based therapies for depression in 178 union councils of the city of Karachi

Analysis	Related Therapy	Sex	N	Minimum	Maximum	Mean	Std. Error of Mean	Std. Deviation	Variance
COI (in Rs.)	COI _F		178	56,662.00	138,503.00	96,147.17	1,323.67	17,659.92	311,872,663.46
		Male	100	56,662.00	138,312.00	94,733.34	1,775.56	17,755.58	315,260,737.72
		Female	78	65,149.00	138,503.00	97,959.78	1,979.52	17,482.64	305,642,636.35
	COI _H		178	45,903.00	100,553.00	75,501.19	914.74	12,204.15	148,941,386.36
		Male	85	53,601.00	98,321.00	75,262.28	1,168.06	10,768.95	115,970,178.01
		Female	93	45,903.00	100,553.00	75,719.55	1,393.39	13,437.39	180,563,528.51
DALY (in Years)	DALY _F		178	1,893.64	3,821.57	2,805.15	34.11	455.05	207,070.06
		Male	100	1,893.64	3,805.16	2,794.18	45.11	451.14	203,529.12
		Female	78	1,965.89	3,821.57	2,819.21	52.37	462.55	213,955.31
	DALY _H		178	1,561.49	3,515.60	2,368.86	30.56	407.71	166,230.34
		Male	85	1,600.24	3,485.66	2,371.99	44.29	408.34	166,739.18
		Female	93	1,561.49	3,515.60	2,365.99	42.45	409.34	167,555.19
COI/DALY (in Rs. per Year)	COI _F /DALY _F		178	17.45	62.92	35.23	0.67	8.99	80.77
		Male	100	17.45	57.75	34.83	0.88	8.83	78.06
		Female	78	20.66	62.92	35.73	1.04	9.21	84.84
	COI _H /DALY _H		178	16.50	59.31	32.80	0.58	7.79	60.76
		Male	85	16.50	57.57	32.56	0.75	6.92	47.96
		Female	93	16.94	59.31	33.03	0.89	8.54	73.00
DALY Per 1000 Population (in Years)	DALY _F /1000		178	18,428.90	63,923.40	36,474.07	809.81	10,804.20	116,730,693.58
		Male	100	18,428.90	61,885.95	36,422.15	1,076.71	10,767.11	115,930,753.01
		Female	78	18,723.14	63,923.40	36,540.64	1,236.55	10,920.95	119,267,181.03
	DALY _H /1000		178	30,431.83	222,815.24	89,753.35	3,004.16	40,080.56	1,606,450,989.98
		Male	85	30,431.83	222,815.24	89,188.20	4,306.78	39,706.56	1,576,610,705.46
		Female	93	34,587.92	198,201.51	90,269.89	4,212.87	40,627.49	1,650,593,078.48
BIPO or BIPY (in Rs.)	BIPO _F or BIPY _F		178	57.15	139.69	96.97	1.34	17.81	317.24
		Male	100	57.15	139.50	95.55	1.79	17.91	320.68
		Female	78	65.71	139.69	98.80	2.00	17.63	310.91
	BIPO _H or BIPY _H		178	46.30	101.42	76.15	0.92	12.31	151.51
		Male	85	54.06	99.16	75.91	1.18	10.86	117.97
		Female	93	46.30	101.42	76.37	1.41	13.55	183.68
ICER			178	(2,428.55)	1,037.71	36.95	20.29	270.74	73,300.02
			Valid N (listwise)	178					

Rs.: Pakistani Rupees; COI: Cost of illness; DALY: Disability adjusted life years; COI/DALY: Cost per disability adjusted life year; BIPO: Budget impact per onset; BIPY: Budget impact per year; ICER: Incremental cost effectiveness ratio

and surveymonkey.com). Surveys were the only mode of data collection that were more convenient to gather information. They were found relatively cheap and respondent-friendly than the interviews as surveys can be completed and submitted with patient's own ease and will.

Utilization of database for data collection and preliminary calculations

Since there were no database available for the herbal and allopathic therapies chosen in relevance with the scope of the study, therefore, the fresh data were collected from 356 patients from 178 union councils in the city of Karachi. The information gathered from either interviews, questionnaires or opinion surveys were distributed into two categories. The first category of data deal with epidemiological data including incidences as well as old cases to calculate the prevalence of depression. The second category of data deal with the addresses of patients including their towns and union councils, their genders and age, the monthly household income, fees of physicians/herbal practitioners, the cost of medicines and transport, the loss of income and the loss due to pain experienced in the condition of depression. All the data input was used to calculate: the disability adjusted life years (DALY), an incremental cost effectiveness ratio (ICER), budget impact per onset (BIPO), budget impact per onset differences (BIPOD), budget impact per year (BIPY), budget impact per year differences (BIPYD) and the actual savings.

Data analysis

The data were gathered gradually and calculated into meaningful and required pharmacoeconomic evaluations (cost utility analysis and the budget impact analysis) via software, i.e. with Microsoft Excel 2016. The detailed statistical analysis was performed along with graph generation with the help of IBM® SPSS version 23. For the Cost utility analysis and Budget impact analysis we divided the process in different stages for better understanding of collected data and ease of calculations.

Cost utility analysis was carried out in four steps as follows:

- To determine 'prevalence' of depression in 178 union councils of the city of Karachi.
- To calculate 'cost utility' (by utilizing results from calculations for 'prevalence' and the 'cost of illness' with exchange rate of Rs. 104/- per USD):
 - o The 'disability adjusted life years (DALYs)'.
 - o The 'disability adjusted life years (DALYs) per 1000 people'.

- o The 'cost of illness per disability adjusted life year' (COI per DALY).
- o The 'incremental cost effectiveness ratios' by computing the results from calculations of 'cost of illness' and the 'disability adjusted life years (DALYs)'.

The budget impact analysis was carried out in five steps:

- First step was to utilize the results of 'cost of illness' and the 'average annual household income per person (AAHIPP)' in the calculation of 'budget impact per onset (BIPO)' for each patient receiving fluoxetine or *Hypericum perforatum* treatments.
- The second step was to determine the 'budget impact per onset difference (BIPOD)' between BIPOs.
- The third step was to utilize the results of 'cost of illness' and the 'average annual household income per person (AAHIPP)' in the calculation of 'budget impact per year (BIPY)' for each patient.
- The fourth step was to calculate the 'budget impact per year difference (BIPYD)' between BIPYs.
- The fifth step was to determine and compare the 'actual savings' with the 'theoretical savings' in context of the societal perspective.

The overall perspective of data analysis was to analyze 'what if' all the patients in the city of Karachi were treated with only one of the therapies to determine pharmacoeconomically best therapy for depression in the society. For the cost utility analysis and budget impact analysis we divided the process in different stages for better understanding of collected data and ease of calculations.

Prevalence

Prevalence was calculated by summing up new cases for reported depression and the old cases existed in Karachi (Sullivan *et al.*, 2014). The data for the total population were calculated from the Pakistan Bureau of Statistics (Pakistan Statistical Pocket Book, 2006). While incidences and data of old cases were gathered from clinics and hospitals exist in all 178 union councils of Karachi. Prevalence was calculated by:

$$\text{Prevalence} = [\text{Incidence} + \text{Old Cases}]$$

where, Incidence = No. of new cases reported within time of study; Old Cases = No. of old cases reported within time of study.

Cost of Illness

Cost of illness was calculated for its utilization

for USD per DALY and in calculations for incremental cost effectiveness ratio (ICER). The cost of illness was calculated by summing up direct and indirect costs (Sullivan *et al.*, 2014):

$$\text{Cost of Illness} = [\text{Direct Costs} + \text{Indirect Costs}]$$

where, Direct Costs = Fee of Practitioner + Costs of Medicine + Transport Costs; Indirect Costs = Loss of Income + Loss due to Pain

Disability Adjusted Life Years (DALYs)

For each patient in either of the Fluoxetine and *Hypericum perforatum* treatments, the disability-adjusted life years (DALYs) were calculated, by summing up the years of lifetime lost (YLL) due to the premature death and the years that are misplaced (YLD) due to the disability. The discount rate of 3% was considered in the study utilizing the following formulas (Donev *et al.*, 2010):

$$\text{DALY} = \text{YLL} + \text{YLD}$$

where,

$$\text{YLL} = \frac{N}{r} (1 - e^{-r * L_{DT}})$$

$$\text{YLD} = \frac{P * DW (1 - e^{-r * L_{DB}})}{r}$$

therefore,

$$\text{DALY} = \left[\left\{ \frac{N}{r} (1 - e^{-r * L_{DT}}) \right\} + \left\{ \frac{P * DW (1 - e^{-r * L_{DB}})}{r} \right\} \right]$$

where, N = number of deaths; r = discount rate (constant rate of 0.03 in clinical calculations); e = natural logarithm (constant value of approx. 2.71828); L_{DT} = standard life expectancy at age of death in years; P = prevalence of depression; DW = disability weight i.e. 0.294 for depression (Haagsma *et al.*, 2015); L_{DB} = average duration of the case until remission or death (years).

The DALY per 1000 people was calculated by following formula:

$$\text{DALY per 1000 People} = \frac{\text{Prevalence}}{1000} * \text{DALY of a Single Patient}$$

The COI per DALY was calculated with the help of input cost of illness:

$$\text{COI per DALY} = \frac{\text{COI in Rs. for a Single Patient}}{\text{DALY of a Single Patient}}$$

Incremental Cost Effectiveness Ratio (ICER)

The incremental cost-effectiveness ratio (ICER) was calculated as part of cost-utility assessment, computing the costs and the disability adjusted life years (DALYs) of both Fluoxetine and the *Hypericum perforatum* therapies. A formula employed (Muennig, Bounthavong, 2016) to calculate the incremental cost-effectiveness ratio (ICER) was:

$$\text{ICER} = \left[\frac{(\text{COI}_F - \text{COI}_H)}{(\text{DALY}_F - \text{DALY}_H)} \right]$$

In the year 2016, the gross domestic product (GDP) per capita income for Pakistan was Rs. 152,692.07/- (World Bank, 2016) and with reference to it, the GDP per capita threshold (that was supposed to be 4 times less than the GDP per capita) was Rs. 38,173.02/-. In order to be identified as the preferred and economically beneficial therapy, the cost per disability-adjusted life year for either of the therapies elaborated in the treatment of depression must remain under the GDP per capita threshold (WHO, 2016).

Budget impact per onset (BIPO)

BIPOs, both for allopathic and herbal therapies of depression were calculated by the following formula:

For the allopathic therapy with Fluoxetine:

$$\text{BIPO}_F = \frac{[AAHIPP - (AAHIPP - \text{COI}_F)]}{AAHIPP}$$

For the herbal therapy with *Hypericum perforatum*:

$$\text{BIPO}_H = \frac{[AAHIPP - (AAHIPP - \text{COI}_H)]}{AAHIPP}$$

where, BIPO_F = budget impact per onset for the Fluoxetine; BIPO_H = budget impact per onset for the *Hypericum perforatum*; COI_F = cost of illness with the fluoxetine; COI_H = cost of illness with the *Hypericum perforatum*; AAHIPP = average annual household income per person.

Budget impact per onset difference (BIPOD)

For budget impact per onset difference, again the fluoxetine therapy was given a benefit of doubt and therefore, the budget impact per onset in the *Hypericum perforatum* therapy (BIPO_H) was subtracted from the

budget impact per onset in Fluoxetine therapy ($BIPY_F$). The budget impacts per onset difference (BIPOD) between BIPO of allopathic and herbal therapies of depression (i.e. $BIPY_F$ and $BIPY_H$) were calculated by following formula:

$$BIPOD = BIPY_F - BIPY_H$$

or

$$BIPOD = \left[\frac{\{AAHIPP - (AAHIPP - COI_F)\}}{AAHIPP} \right] - \left[\frac{\{AAHIPP - (AAHIPP - COI_H)\}}{AAHIPP} \right]$$

Budget impact per year (BIPY):

The budget impacts per year (BIPY) were calculated by the following formula:

For the allopathic therapy with Fluoxetine:

$$BIPY_F = \frac{[AAHIPP - \{AAHIPP - (COI_F * f)\}]}{AAHIPP}$$

For the herbal therapy with *Hypericum perforatum*:

$$BIPY_H = \frac{[AAHIPP - \{AAHIPP - (COI_H * f)\}]}{AAHIPP}$$

Budget impact per year difference (BIPYD)

Like the budget impact per onset difference, the budget impact per year in the *Hypericum perforatum* therapy ($BIPY_H$) was subtracted from the budget impact per year in the Fluoxetine therapy ($BIPY_F$). To calculate the budget impact per year difference (BIPYD) following formula was used:

$$BIPYD = BIPY_F - BIPY_H$$

OR

$$BIPYD = \left[\frac{\{AAHIPP - (AAHIPP - (COI_F * f))\}}{AAHIPP} \right] - \left[\frac{\{AAHIPP - (AAHIPP - (COI_H * f))\}}{AAHIPP} \right]$$

where, $BIPY_F$ = budget impact per year for the Fluoxetine therapy; $BIPY_H$ = budget impact per year for the *Hypericum perforatum* therapy; f = approx. yearly frequency of the depression.

Projected actual savings

Projected actual savings were calculated on basis of choice and the use of preferred treatment. To differentiate actual savings scenario from the theoretical/ideal saving scenario (where the inflation does not take part), the actual savings for current year with inflation were calculated by:

$$\text{Projected actual savings for a year} = [\text{Savings of Last Year} \times \{1 - (2 \times 0.0786)\}]$$

Extrapolation of the internal and external validity of the study findings

Internal Validity: The univariate analysis of variance (One-way ANOVA) was performed, individually taking sex, age group, age, cost of illness, DALYs and BIPO as independent variables versus DALYs, DALYs/1000, BIPO, and ICER as dependent variable to find out the potential relationship among independent and dependent variables via identification of level of significance to validate internally the authenticity of the study findings.

External Validity: The same methodology was replicated for the dissimilar conditions such as common cold and trauma among a population in the city of Karachi, for retrospective cost-utility and budget impact assessments to carry out the external validity of the study findings.

RESULTS

The results for the cost utility and the budget impact analysis were:

Prevalence of depression

The prevalence of depression in selected population of Karachi was found to be at 2,268,127 (approx. 2.27 million) people (Table IV).

Costs of Illness

The annual cost of illness in Fluoxetine based allopathic therapy (Table IV) was estimated at Rs. 218.07/- billion (USD 2 billion and 96.83/- million) while for *Hypericum perforatum* based therapy at Rs. 171.25/- billion (USD 1 billion and 646.63/- million). There was a clear difference of Rs. 46.82/- billion (USD 450.19/- million) between the two therapies if projected over the patients of depression in the city of Karachi.

Cost utility analysis

Disability adjusted life years (DALYs)

The mean disability adjusted life years (DALYs) in cases of therapies with Fluoxetine and *Hypericum perforatum* were found to be 499,020.37 years and 353,150.95 years respectively, with a difference of 145,869.42 years (i.e. 29.23%).

TABLE IV - Cost, burden of illness and budget impact assessment of fluoxetine and *Hypericum perforatum* based therapies for the depression in the city of Karachi

Prevalence	Fluoxetine Based Therapy						Hypericum perforatum Based Therapy								
	COI _F (Rs.in Billion)	DALY _F	COI _F / DALY _F (Rs.in Billion)	DALY _F /1000	BIPO _F	BIPY _F	COI _H (Rs.in Billion)	DALY _H	COI _H / DALY _H (Rs.in Billion)	DALY _H /1000	BIPO _H	BIPY _H	BIPOD	BIPYD	ICER
2,268,127	218.07	499020.37	0.0004	6,362,436.45	96.97%	96.97%	171.25	353150.95	0.0005	5,372,875.33	76.15%	76.15%	20.82%	20.82%	0.0003

UC: Union Council; Pt.: Patient; Rs.: Pakistani Rupees; COI: Cost of illness; DALY: Disability adjusted life years; COI/DALY: Cost per disability adjusted life year; BIPO: Budget impact per onset; BIPY: Budget impact per year; BIPOD: Budget impact per onset difference; BIPYD: Budget impact per year difference; ICER: Incremental cost effectiveness ratio

Disability adjusted life years (DALYs) per 1000 people

The disability adjusted life years (DALYs) per 1000 people were 6,362,436.45 years and 5,372,875.33 years in case of treatment with fluoxetine and *Hypericum perforatum* respectively, with a difference of 989,561.13 years. Considering the selected union councils population, disability adjusted life years (DALYs) per 1000 people were 36,474.07 years and 89,753.35 years for fluoxetine and *Hypericum perforatum*, with a difference of 53279.28 years (Figure 2B).

COI per DALY

The COI per DALY was found to be at Rs. 35.23/- and Rs. 32.80/- in Fluoxetine and *Hypericum perforatum* based therapies, with difference of Rs. 2.43/-.

Incremental cost-effectiveness ratio (ICER)

Mean ICER in Fluoxetine and *Hypericum perforatum* therapies (Table III) was observed to be at 36.95 per patient per onset of depression with SD of ± 270.74 in the overall population. The ICER percentile 25th and percentile 75th were estimated at -0.03 and 82.28 respectively among 178 union councils of city of Karachi. The ICER with reference to the prevalence of depression was found to be at 0.0003 for city of Karachi (Table IV).

Budget impact analysis

Budget impact per onset and budget impact per year

Since, the depression is a multiple years long condition, the budget impact per onset (BIPO) and the budget impact per year (BIPY) based on average annual household income were both the same. It was estimated at 96.97% and 76.15% for fluoxetine and *Hypericum perforatum* therapies (Figure 3A). During the study, a direct relationship of COI was identified with BIPO and BIPY.

Budget impact per onset difference and budget impact per year difference

The budget impact per onset difference (BIPOD) and the budget impact per year difference (BIPYD) were both estimated at 20.82%.

Actual savings

An annual savings of Rs.46.82/- billion (USD 450.19/- million) was calculated as a difference when using *Hypericum perforatum* as a mode of treatment (Figure 3B). However, the five-year savings of Rs.171.19/- billion (USD 1 billion and 646.06/- million) was found due to the dual impact of inflation rate in Pakistan (Table II)

Analysis of age and gender homogeneity

Although five (5) age groups, i.e. '25 – 29 yrs.', '40 – 44 yrs.', '50 – 54 yrs.', '55 – 59 yrs.' and '70 – 74 yrs.' (Table I; Figure 1) were found with more males than females; the four (4) age groups, i.e. '30 – 34 yrs.', '35 – 39 yrs.', '60 – 64 yrs.', and '65 – 69 yrs.' were found with more females than males. While only two (2) age groups, i.e. '45 – 49 yrs.' and '75 yrs. and up' were found with equal genders. Therefore, in overall 356 patients for both Fluoxetine and *Hypericum perforatum* based therapies, the number of males were found higher, i.e. 184 males than 172 females.

Internal and external validation

The univariate analysis of variance (One-way ANOVA) for the variables pointed out a very strong relationship between the cost of illness and the budget impact per onset by having significance level < 0.05 . No other potential relationship was identified among the variables, i.e. pointing towards the authenticity of the results of the study. The extrapolation of results of the study was expanded to two other retrospective studies on the same population of the city of Karachi for conditions of common cold and trauma revealing the preferences

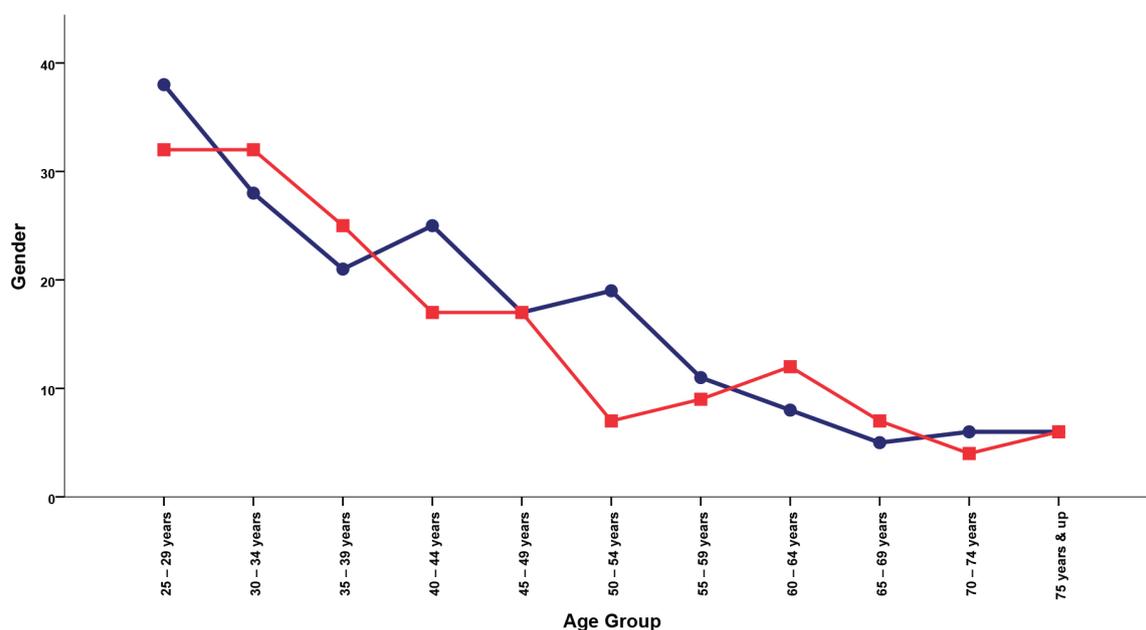


FIGURE 1 - Analysis of age and gender homogeneity in cost-utility and budget impact assessments of *Hypericum perforatum* in contrast with fluoxetine treatment (blue line with ● marker: Male; red line with ■ marker: Female).

of herbal therapies over allopathic therapies in terms of providing more utility with less impact on the household budgets of patients.

DISCUSSION

It is well understood that in the cost utility analysis, the cost per disability-adjusted life years for either of the therapies calculated in terms of ICER (Muennig, Bounthavong, 2016) must remain under the GDP per capita threshold (WHO, 2016). As the study concluded that the ICER was 36.95 per patient per onset of depression with reference to the GDP per capita income for Pakistan (i.e. Rs. 152,692.07/- (World Bank, 2016), the ICER was found well below the GDP per capita threshold of Rs. 38,173.02/- (WHO, 2016).

Hypericum perforatum was found to have more utility than Fluoxetine because of lesser disability adjusted life years (i.e. having 145,869.42 years lesser; Figure 2A). Also, with reference to the comparative mean cost per DALY, it has the lower cost with a percentage difference of 6.90, i.e. Rs. 2.43/-.

The budget impact analysis in the current study established the utility value of *Hypericum perforatum* as compare with the Fluoxetine based therapy. The budget impact per onset difference of 20.82% (or Rs. 46.82 billion, i.e. USD 450.19/- million) was found less impactful and could be hypothetically saved on a societal level, only if the patients with depression would

get oral infusion of *Hypericum perforatum* as a medicine. This difference could be theoretically projected into five-years savings of Rs. 234.1/- billion (USD 2 billion and 250.96/- million). However, in practice, an annual savings (Figure 3B) of Rs.46.82/- billion (USD 450.19/- million) would translate into five-year savings of Rs.171.19/- billion (USD 1 billion and 646.06/- million) due to the dual impact of inflation rate in Pakistan (Table II). This dual impact of inflation affects the supply of *Hypericum perforatum* against annual demand as well as on savings generated by *Hypericum perforatum* therapy. It must be noted that this value of accumulated savings is close to the cost incurred by the *Hypericum perforatum* therapy for the whole year in the city of Karachi. Therefore, the use of the *Hypericum perforatum* therapy is still beneficial in developing country like Pakistan where the poverty rate is very high due to the poor economic development and inequality in the society (Piazza, 2006; Fuentes-Nieva *et al.*, 2014).

CONCLUSION

Considering the results of cost utility and the budget impact analysis along with the projected actual accumulative savings, the utilization of *Hypericum perforatum* based herbal therapy proved more pharmaco-economically beneficial than the Fluoxetine based therapy for the treatment of depression in population of the city of Karachi.

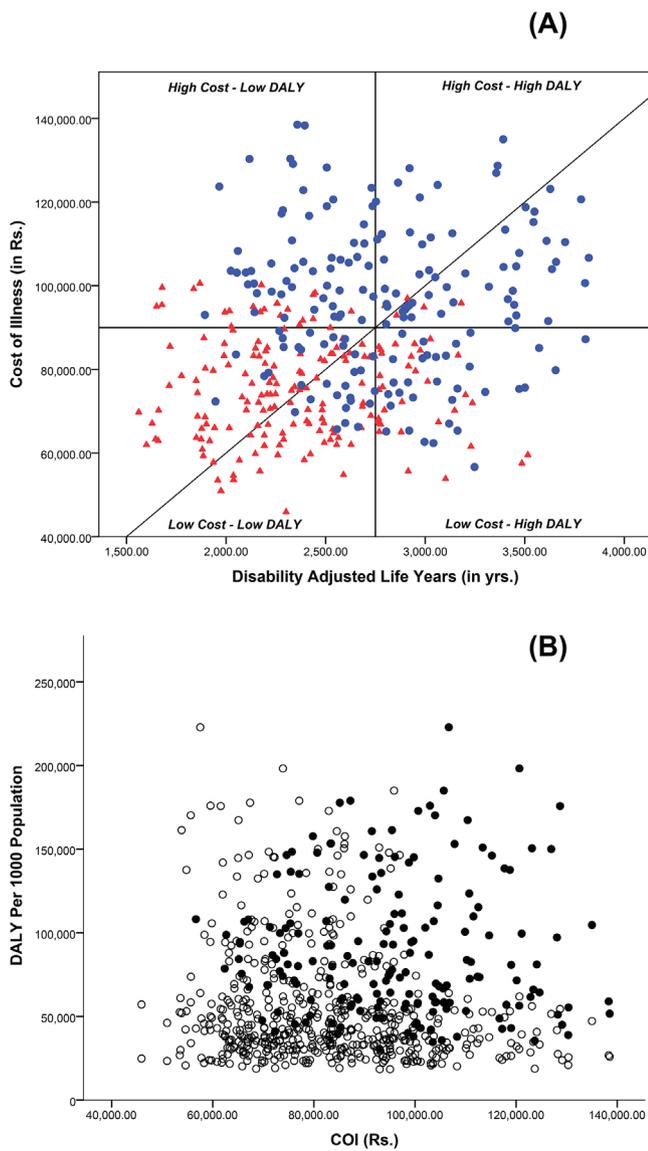


FIGURE 2 - Cost-utility assessment of *Hypericum perforatum* in contrast with fluoxetine treatment (A) COI Vs DALY – fluoxetine and *Hypericum perforatum* in UCs (● blue marker - fluoxetine; ▲ red marker - *Hypericum perforatum*); (B) DALY 1000 Vs COI – fluoxetine and *Hypericum perforatum* in UCs (● fluoxetine; ○ *Hypericum perforatum*).

ETHICAL CONSIDERATIONS

Ethical issues (including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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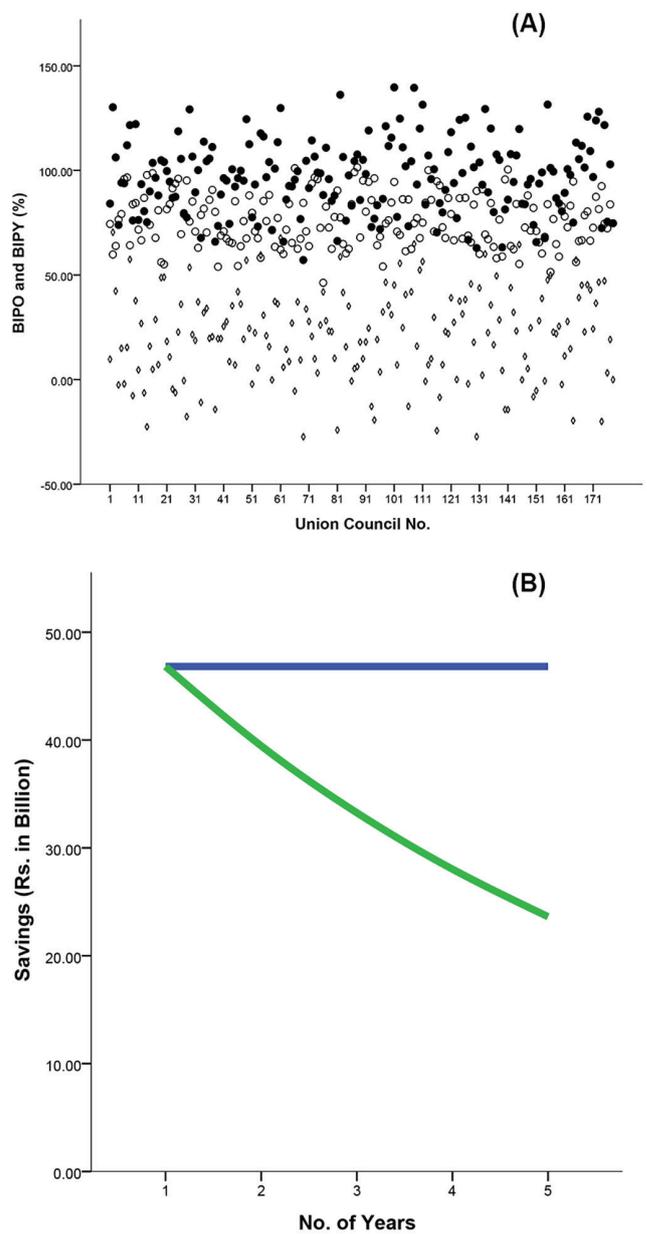


FIGURE 3 - Budget impact assessments of *Hypericum perforatum* in contrast with Fluoxetine treatment (A) Budget Impact Per Onset and Budget Impact Per Year in UCs (● BIPO and BIPY Fluoxetine; ○ BIPO and BIPY *Hypericum perforatum*; ◇ BIPOD and BIPYD); (B) Theoretical Vs Actual Savings (Blue line: Theoretical Savings; Green line: Actual Savings).

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CONFLICT OF INTEREST

The authors declare no conflict of interest regarding the publication of this paper.

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