ECONOMIC EVALUATION OF FIRST-LINE TREATMENTS FOR DEPRESSION IN TURKEY: A COST-EFFECTIVENESS MODEL

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Introduction

- Major depressive disorder (MDD) is a significant public health problem, presenting a considerable burden of illness to patients, health care providers and payers.[1-3]
- Prevalence rates of depressive symptoms in Turkey range between 6.0% to14.3%.[4]
- Cost-effectiveness of antidepressant drugs has been evaluated for many Selective Serotonin Reuptake Inhibitors (SSRIs) and Selective Norepinephrine Reuptake Inhibitors (SNRIs), but most of these evaluations have been performed only in major European pharmaceutical markets.
- Escitalopram, a new SSRI, has demonstrated clinical advantages compared with citalopram and similar efficacy compared with venlafaxine.[5,6]

Objective

- To investigate the cost-effectiveness of escitalopram compared with citalopram and venlafaxine over a 6-month time horizon in the treatment perspectives.

Methods

Perspective(s)

- Governmental perspective: the direct costs consisted of study medication costs (including costs of treatments when patients received augmentation treatment), outpatient psychiatrist visits, inpatient psychiatric care (e.g., psychiatrist visits, psychiatric hospitalisation), and attempted suicide.
- Societal healthcare perspective: the same direct costs as for the governmental perspective were calculated, but also included the indirect costs attributed to absenteeism from work (lost productivity).

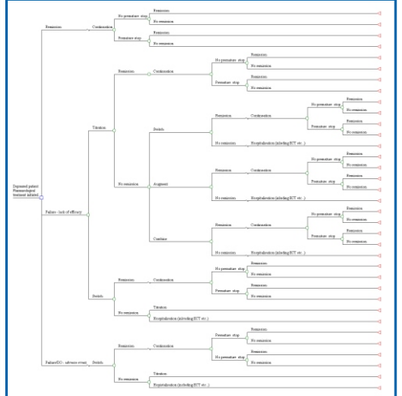
Treatment Comparisons

- Decision model that approximates "real world" or current standards of care (i.e., usual clinical practice) for the treatment of MDD [baseline scores 18 and 40 on the Montgomery-Åsberg Depression Rating Scale (MADRS)] to predict outcomes and estimate costs associated with first line treatments in Turkey.[7]
- Two parallel cost-effectiveness analyses between escitalopram and citalopram or escitalopram and venlafaxine were carried out (no head-to-head comparison exists between all 3 compounds).

Pharmacoeconomic Model

- Decision model developed to illustrate the management of Turkish patients with MDD over a period of 6-months by combining clinical outcomes with resource utilization (Figure I).
- All patients in the decision model started with antidepressant treatment (i.e., escitalopram, generic citalopram, or venlafaxine) prescribed by a psychiatrist. Based on the initial response after 8 weeks (i.e., remission of failure due to lack of efficacy or adverse events) patients could follow different pathways in the model.
- If a patient did not respond to the initially prescribed drug, the patient could either have a titration of dose or a switch.
- In case of no response to the titration of the initially prescribed drug, it was possible to have a switch, augmentation or combination of different antidepressants.
- In our decision model, suicide attempts were applied at a constant rate across the model and did not discriminate between drugs (Table 1). The probabilities of a suicide attempt were estimated based on a Turkish epidemiological study by Devrimci-Ozguven.[8] The rates for failed suicide attempt or death due to suicide came from the literature.[9]

Figure I. Decision analytic model for major depressive disorder in Turkey



Adapted from Hemels et al.[10]

Model Parameters

Clinical Inputs: Drug-specific

- Remission rates were obtained from a meta-analysis of three 8-week randomised controlled trials (RCTs).[5]
- Percentages of patients in remission after titration, and failures due to adverse events were derived from comparative clinical trials.[10,11]
- Since no head-to-head comparative data were available for relapse rates, we assumed the relapse rate for citalopram to be equal for all comparators.[12,13]
- All probabilities used in the model are listed in Table I.

Clinical Practice Pattern Inputs: Non-drug-specific

- Clinical practice patterns were derived from the literature and from consultation with clinical experts. These included rates for premature discontinuation, remission after switch, augmentation or combination treatment, relapse after switch or after premature discontinuation, suicide attempts, and death due to suicide attempts.
- Rates that described the clinical management by a psychiatrist of depressed patients in Turkey were obtained through an ad hoc survey and were comprised of rates of titration or switch after no response, switch, combination or augmentation after no response to titration, and titration and hospitalisation after no response to switch.
- The ad-hoc survey was performed from a randomly selected group of 90 psychiatrists throughout Turkey.
- All non-drug-specific probabilities used in the model are listed in Table I.

Probability	Type	Description	Base Case Value in % (range)	Source(s)
Drug specific	Remission rate*	escitalopram vs.	52.8 (47.5-58.3)	Einarson [5]
		citalopram	43.5 (38.2-48.8)	Einarson [5]
		escitalopram vs.	69.9 (62.4-77.3)	Einarson [5]
		venlafaxine	69.7 (62.1-77.3)	Einarson [5]
	Remission rate* after titration	escitalopram	36.2 (24.9-49.2)	Lepola[10]
		citalopram	23.8 (14.9-35.8)	Lepola[10]
		venlafaxine	36.2 (24.9-49.2)	Lepola[10]
	Relapse rate	Escitalopram, citalopram, venlafaxine	12.5 (8.3-16.7)	Montgomery, [12]Robert[13]
		no treatment (placebo)	27.5 (18.3-36.8)	Montgomery, [12]Robert[13]
	Adverse Events	escitalopram vs.	2.6 (1.0-6.7)	Lepola[10]
		citalopram	3.8 (1.7-8.1)	Lepola[10]
		escitalopram vs.	8.0 (4.2-13.1)	Montgomery[22]
		venlafaxine	11.0 (7.0-17.5)	Montgomery[22]
Non drug specific		Premature discontinuation	50.0	Demyttenaere[21]
		Remission rate after switch†	43.8	Pahis,[23] Bougerol,[3] IMS[24]
		Relapse rate after switch	12.5	Montgomery, [12]Robert[13]
		Relapse rate after discontinuation	27.5	Montgomery, [12]Robert[13]
		Suicide attempt§	0.02	Devrimci-Ozguven [8]
		Death due to suicide attempt	10.0	Khan[9]
		Titration after no response	73.0	Turkish expert survey
		Switch after no response	27.0	Turkish expert survey
		Switch after no response to titration	52.0	Turkish expert survey
		Augment after no response to titration	21.0	Turkish expert survey
		Combine after no response to titration	27.0	Turkish expert survey
		Remission after Augmentation	33.3	Fava[25]
		Remission after Combination	33.1	Amsterdam[26]
		Titration after no response to switch†	61.0	Turkish expert survey
		Hospitalisation after no response to switch	39.0	Turkish expert survey

*Remission rate defined as MADRS score 12 after 8 weeks of treatment; †Weighted (by volume) average remission rate of antidepressants; §Suicide attempts were applied at a constant rate across the primary care model and did not discriminate between drugs

Table I. Probabilities used in the analysis

Resource Utilization

- For each branch of the decision tree, the number of drug resource units, psychiatrist visits, attempted suicides, deaths due to suicide, and hospitalisation was estimated.
- Unit costs were in 2004 $US (1 US$ ~ 0.8 Euro).
- Estimates of resource use in terms of the number of visits required and days absent from work were determined through the survey.
- Indirect costs attributed to lost productivity were calculated using the human capital approach based on the minimal industrial wage in Turkey.[14,15]
- The resource utilisation and absenteeism of work due to depression are listed in Table II and unit costs are presented in Table III.

Parameter	Unit(s) over 6 month period	Range for sensitivity analysis	
		Low range*	High range**
Psychiatrist visit – Acute phase	3.1	1.9	4.2
Psychiatrist visit – Continuation phase Additional visits (in case of relapse, switch or titration)	4.7	3.3	6.8
Psychiatrist visit – Relapse	3.5	2.2	5.0
Psychiatrist visit – Switch	3.7	2.3	4.6
Psychiatrist visit – Titration	3.6	2.0	4.4
Psychiatrist visit – Augment or Combine	3.7	2.2	4.8
Workdays lost – Response	18.1	10.2	33.3
Additional workdays lost			
Workdays lost – Switch or AEs	15.0	9.2	22.8
Workdays lost – Lack of efficacy	19.3	13.6	32.1
Number days hospitalisation	22.1	11.5	47.8

The resource utilization data were derived from the Turkish expert survey. AEs = Adverse Events
*Best-case scenario; ** Worst-case scenario

Table II. Resources used in model with range for sensitivity analysis

Cost item	Cost/unit ($)	Source(s)
Direct medical costs		
Drugs		
Escitalopam (10mg/day)*	0.73	Standard price lists
Escitalopam (20mg/day)*	1.45	Standard price lists
Citalopram (generic 20mg/day)*	0.51	Standard price lists
Citalopram (generic 40mg/day)*	1.01	Standard price lists
Venlafaxine XR (75mg/day)*	1.17	Standard price lists
Venlafaxine XR (150mg/day)*	2.33	Standard price lists
Lithium (750mg/day)	0.09	Standard price lists
Average cost†	0.57	Standard price lists, IMS[24]
Psychiatrist consultation	10.0 (5.0-15.0)	Governmental hospitals
Hospitalisation / day	25.6 (16.035.2	Governmental hospitals
Suicide and suicide attempt	565.1 (353.8-777.2)	Governmental hospitals
Indirect costs		
Cost absenteism from work /day	17.3	Eurostat 2004[14,15]

*In the cost effectiveness analysis the cost per average dose was used representing the average dose used in the clinical trials;† Weighted cost of the average daily of all antidepressant drugs (N06A) used in Turkey

Table III. Indirect costs (2004 US$) used in model according to the Turkish setting

Outcomes

- Patients were considered successfully treated if they presented remission of symptoms at 8-weeks after the start of treatment (defined as a MADRS score 12), and had no relapse at 6-months.
- The results of this pharmacoeconomic analysis were presented as incremental cost-effectiveness ratios (ICERs) and were calculated by dividing the incremental cost of treatment by the incremental outcome measure.
- In case of dominance (i.e. one drug being more effective and less costly than the other), cost-savings were reported.

Sensitivity analyses

- Sensitivity analyses were performed to test if variations in assumptions or uncertainties in estimates changed the results.
- Impact of changes in resource utilization and absenteeism of work were evaluated in a best-case (using the low ranges) worst-case (using the high ranges) scenario sensitivity analyses.
- For all input parameters in the decision analytic model a Monte Carlo simulation (See explanation in Figure II) was carried out with 10 000 iterations varying estimates between the upper and lower limits of the 95% confidence interval for escitalopram versus citalopram and venlafaxine.

Results

Escitalopram vs. citalopram

- From both the government and societal perspectives, escitalopram was the dominant strategy compared with citalopram. The overall success rate was higher for escitalopram [63.2% (CI_{95}: 61.1%-65.3%)] than for generic citalopram [57.6% (CI_{95}: 55.3%-59.9%)].
- escitalopram was associated with improved patient management outcomes compared to citalopram in terms of first-line success (success without switch), titration, augmentation or combination rate, switching to another anti-depressant, and hospitalisation rate.
- At 6-months, from the governmental perspective, patients treated with escitalopram accounted for lower total expected direct costs than generic citalopram: US$ 297 (US$ 282 - US$ 313) vs. US$ 305 (US$ 288 - US$ 322), despite slightly higher drugs cost for escitalopram. The expected total costs per successfully treated escitalopram patient were US$ 470 and US$ 530 for each generic citalopram-treated patient.
- From the societal perspective, indirect expected costs represented approximately 57% of total costs for both treatments. The expected direct costs were US$ 678 (US$ 653 - US$ 705) for escitalopram and US$ 709 (US$ 682 - US$ 736) for generic citalopram. Per successfully treated patient, escitalopram presented a $158 (14.7%) cost saving compared with generic citalopram at 6-months. Results of the cost-effectiveness analyses are shown in table IV.

	escitalopram vs. citalopram		escitalopram vs. venlafaxine	
	escitalopram	citalopram	escitalopram	venlafaxine
Overall Success*	63.2% [61.1-65.3]	57.6% [55.3-59.9]	68.6% [66.4-70.7]	68.2% [65.9-70.3]
First-line Success (without switch)	54.2%	45.9%	61.8%	60.8%
Titration rate	39.7%	47.3%	22.0%	20.3%
Switch rate	25.7%	33.4%	19.5%	21.2%
Hospitalisation rate	15.8%	21.8%	9.4%	9.9%
Augmentation rate	4.2%	5.9%	2.1%	1.8%
Combination rate	5.4%	7.7%	2.7%	2.3%
Cost				
Direct cost per treated patient*				
Antidepressant drug cost	124	93	117	177
Suicide and attempted suicide	1	1	1	1
Psychiatrist visit	84	88	78	76
Hospitalisation	89	122	52	50
Indirect cost per treated patient*				
Cost absenteeism†				
Expected total indirect cost per treated patient	381 [371-391]	404 [393-415]	349 [339-360]	345 [334-356]
Governmental Perspective				
Expected total direct cost per treated patient	297 [282-313]	305 [288-322]	246 [229-263]	304 [286-322]
Expected total direct cost per successfully treated patient	470	530	359	446
Societal Perspective				
Expected total cost per treated patient	678 [653-705]	709 [682-736]	594 [567-622]	649 [621-678]
Expected total cost per successfully treated patient	1073	1231	866	952

* After 6 months of treatment; †The indirect cost associated with death due to suicide was not taken into account in the analysis.

Table IV. Results of the cost-effectiveness analysis by outcome in 2004 US$

Escitalopram vs. venlafaxine

- Overall success of treatment at 6-months was similar for escitalopram [68.6% (CI_{95}: 66.4% - 70.7%)] and venlafaxine [68.2% (CI_{95}: 65.9% - 70.3%)].
- From the governmental perspective, total expected direct costs per patient were lower for escitalopram compared with venlafaxine [US$ 246 (US$ 229 - US$ 263) vs. US$ 304 (US$ 286 - US$ 322)]. From the societal perspective, total expected costs per successfully treated patient were reduced by $86 after 6-months in favour of escitalopram. These differences were mainly due to lower drug costs.

Sensitivity analyses

- Results of univariate and multivariate sensitivity analyses are summarised in Table V.

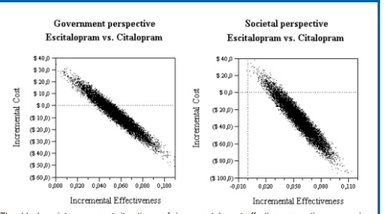
Parameter for univariate sensitivity analysis	Base case (Range for sensitivity analysis)	Effect (E) on expected total cost per patient (in 2004 US$)					
		escitalopram vs, citalopram			escitalopram vs, venlafaxine		
Probabilities		Direct / Total cost*	Overall success	E	Direct / Total cost*	Overall success	E
Remission rate	52.8 (47.4-58.3)	282 – 312/655-701	61,3-45,1	o	na	na	na
Remission rate	69.9 (62.4-77.3)	na	na	na	225-286/583-626	71,3-46,0	o
Remission rate after titration	36.2 (23.5-49.4)	284-312/692-703	61,5-45,1	o	239-253/583-607	67,5-49,6	o
Discontinuation rate due to AEs	2.6 (0-5.4)	295-301/674-686	63,3-63,5	o	na	na	na
Discontinuation rate due to AEs	8.0 (5.0-11.0)	na	na	na	243-249/589-602	68,3-68,9	o
Relapse rate	12,5 (8,3-16,7)	297-299/678-679	61,8-64,5	o	245-246/594-595	67,0-70,2	o
Premature discontinuation	50,0 (40,0-60,0)	290-304/671-685	62,9-64,4	o	236-253/587-602	67,3-69,9	o
Remission after switch	43,8 (36,0-49,6)	292-303/666-687	63,0-64,4	o	242-246/585-601	67,7-69,5	o
Relapse after switch	12,5 (8,3-16,7)	297-297/678-678	62,9-63,5	o	245-245/594-595	68,4-68,8	o
Relapse rate after premature discontinuation	27,5 (19,5-35,5)	296-298/677-679	63,0-63,5	o	244-247/593-596	65,2-72,0	o
Titration rate after no response	73,0 (65,0-81,0)	292-302/671-685	62,7-63,7	o	243-245/591-598	68,3-68,8	o
Switch after no response to titration	52,0 (45,0-59,0)	295-299/676-680	63,5-63,3	o	245-246/593-596	68,5-68,6	o
Augment after no response to titration	21,0 (17,0-25,0)	297-297/678-678	63,2-63,2	o	245-246/594-595	68,6-68,6	o
Remission after augmentation	33,3 (29,0-37,5)	296-298/677-680	63,0-63,3	o	245-246/594-595	68,5-68,7	o
Remission after combination	33,1 (29,0-37,2)	296-298/676-680	63,0-63,3	o	245-246/594-595	68,5-68,7	o
Titration after no response to switch	61,0 (55,0-67,0)	295-299/674-682	63,2-63,2	o	244-247/591-598	68,6-68,6	o
Hospitalisation after no response to switch	39,0 (33,0-45,0)	295-299/674-682	63,2-63,2	o	244-247/591-598	68,6-68,6	o
Suicide	10,0 (7,5-12,5)	297-297/678-678	63,2-63,2	o	245-245/594-594	68,6-68,6	o
Suicide attempt	0,02 (0,015-0,1)	297-297/678-678	56,9-62,6	o	245-245/594-594	61,8-68,0	o
Unit costs(in 2004 US$)		**escitalopram**	**citalopram**	**E**	**escitalopram**	**venlafaxine**	**E**
Government perspective							
Cost Psychiatrist	10 (5–15)	255-339	260-349	*	207-283	286-342	*
Hospitalisation (cost/day)	25,57 (16,01-35,17)	259-330	264-350	*	226-305	285-323	*
Suicide and attempted suicide	565,1 (353,8-777,2)	297-297	304-305	*	245-246	304-304	*
Societal perspective							
Cost per workday lost	17,31 (12,0-21,0)	561-759	585-795	*+	487-669	544-723	*+
Worst-case best-case scenario: Effect (E) on expected total* cost per patient (in 2004 US$)							
		escitalopram	**citalopram**	**E**	**escitalopram**	**venlafaxine**	**E**
Ambulatory care (best case – worst case)		575-681	577-677	o/+	525-724	581-776	o/+
Workdays lost (best case – worst case)		559-919	594-945	o/+	465-838	524-890	o/+

*Total costs based on societal perspective; E = Relative effect of changes on expected cost per patient (if E=o, not sensitive; if E=o/+, moderately sensitive; if E=+, sensitive; if =++,very sensitive); AEs = adverse events; n/a =not applicable

Table V. Results of univariate and worst-case best-case sensitivity analyses on the total cost per successfully treated patient

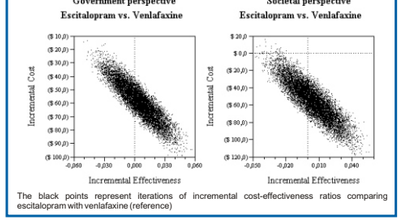
- Univariate sensitivity analyses on drug specific and non-drug specific probabilities had no large impact on overall success and total expected costs from the IS perspective.
- Expected direct and total costs ranged respectively between US$ 282 and US$ 312 and between US$ 655 and US$ 703 in the escitalopram vs. citalopram comparison.
- In the escitalopram vs. venlafaxine comparison, expected direct and total costs ranged between US$ 225 and US$ 266 and between US$ 563 and US$ 626 respectively.
- Sensitivity analyses on extreme values of (unit) costs did not influence the relative difference in total expected direct costs at 6-months for all treatment groups.
- A sensitivity analysis on the acquisition cost of citalopram demonstrated that escitalopram remained the dominant strategy even at US$0.46 for generic citalopram from the governmental perspective and at US$ 0.31 from the societal perspective.
- The worst-case and best-case scenario sensitivity analyses showed that resource use associated with direct costs had no large impact on total expected costs whereas resource use associated with indirect costs (workdays lost) had a larger impact. This was to be expected since the best-case and worst-case scenarios modelled extreme situations in number of workdays lost which represent about 55% of total expected costs.
- The Monte-Carlo probabilistic sensitivity analysis demonstrated that escitalopram was the dominant strategy compared with citalopram in 93.5% (quadrant IV) of the cases from the IS perspective and in 99.7% (quadrant IV) of the cases from the societal perspective (Figure II).
- In comparison with venlafaxine, escitalopram was the dominant strategy from the IS and societal perspectives (61.4% and 61.6% in quadrant IV, respectively) despite the relatively small difference in effectiveness (Figure III).

Figure II. Incremental cost-effectiveness scatterplots of the probabilistic sensitivity analyses of escitalopram compared with citalopram from the government and societal perspectives



The black points represent iterations of incremental cost-effectiveness ratios comparing escitalopram with citalopram (reference)

Figure III. Incremental cost-effectiveness scatterplots of the probabilistic sensitivity analyses of escitalopram compared with venlafaxine from the government and societal perspectives



The black points represent iterations of incremental cost-effectiveness ratios comparing escitalopram with venlafaxine (reference)

Discussion

- Escitalopram is the therapeutically active S-enantiomer of citalopram. While the recommended dose of escitalopram is half that of citalopram, research has indicated that escitalopram, even at half the citalopram dose, is approximately twice as potent in serotonin uptake inhibitory activity.[16] This difference in potency may come apparent in a significantly higher remission rate.[5] The higher remission rate (both at recommended dose and at double dose for non-responding patients) was the greatest driver of the decision analytic model.
- As in all decision analytic models, different sources of data were used which may have affected the internal validity of the model. We attempted to reduce these potential biases by conducting a systematic review of published literature and by building the model on local data collected through a survey of psychiatrists to determine clinical management patterns, resource utilisation, and loss of productivity and not by relying solely on expert opinion.
- In our economic analysis we used the meta-analysis by Einarson[5] for the main outcome. The meta-analysis, however, was carried out on clinical data derived from patients in the first line of depression in primary care. As GPs in Turkey are very restricted in prescribing SSRIs or SNRIs, we assumed that the data on these patients would be similar to patients who would get a prescription for a first-line antidepressant from a specialist in Turkey.
- Another limitation was the absence of direct comparative clinical trial data between escitalopram, citalopram and venlafaxine. As indirect comparisons are sometimes criticized, we preferred to carry out parallel analyses that still permit the reader to conduct an indirect comparison based on the given results.
- All assumptions, as well as the uncertainty in estimating the variables, were tested in extensive sensitivity analyses to verify the validity of the conclusions, estimates and different hypotheses. The results confirmed that no variable significantly affected the primary outcome and costs coming from the model. The results reported in this study are consistent with previous evaluations of cost-effectiveness of escitalopram.[17-19]
- We were unable to compare our results with other cost-effectiveness studies of antidepressant treatment in Turkey, as no other studies could be found in published literature.
- Compared to other countries, antidepressant drug costs in Turkey represent a relatively large fraction of total costs. If remission is not achieved within the first two months, higher costs are incurred as the result of more intensive patient management (additional visits to adjust or change the treatment), and eventual hospitalisations.

Conclusion

- **The results from this analysis indicate that treatment with escitalopram is a cost-effective alternative compared with citalopram and venlafaxine**
- **It leads to better clinical outcomes and cost savings compared with citalopram and to cost savings compared with venlafaxine.**

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