Pharmacoeconomic perspective on depressive disorder treatment with antidepressants

Farmakoekonomski vidiki zdravljenja depresivnih motenj z antidepresivi

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Povzetek:
Namen: Namen članka je pregled farmakoekonomskih raziskav zdravljenja depresivnih motenj z antidepresivi.
Metode: Farmakoekonomske raziskave za antidepresive registrirane v Sloveniji smo poiskali s sistematičnim pregledom bibliografske zbirke PubMed ter dodali članke, ki smo jih dobili s pregledom njihovih literaturnih virov. Zadetke smo omejili na pregledne članke ter članke z opisi meta-analiz.
Rezultati: Iskalnim kriterijem je ustrezalo 28 člankov, ki smo jih vključili v analizo, in so bili objavljeni med leti 1994 in 2006. Omejeno število izsledkov ugotavlja, da sta venlafaksin in escitalopram stroškovno učinkoviti strategiji zdravljenja depresivne motnje. Za potrditev teh rezultatov so potrebne dodatne, metodološko ustrezne raziskave.

Ključne besede: *depresivna motnja, depresija, antidepresivi, farmakoekonomika, stroškovna učinkovitost*

Abstract:
Aim: The aim of the present study is to review the results of pharmacoeconomic studies for the treatment of depressive disorder with antidepressants.
Methods: Pharmacoeconomic studies related to the antidepressants registered in Slovenia were obtained through a systematic search of PubMed, as well as manually. All the records were then limited to review articles and articles describing meta-analysis studies.
Results: A set of 28 articles published between 1994 and 2006 was eligible for inclusion in the analysis. A limited amount of evidence supports venlafaxine and escitalopram to be the most cost-effective treatment options for depressive disorder. Further studies based on robust methodologies are expected in the near future to confirm these findings.

Keywords: *depressive disorder, depression, antidepressants, pharmacoeconomics, cost-effectiveness*

1 Introduction

Depressive disorder is a common condition often unrecognized, misdiagnosed, undertreated and usually accompanied by a high level of medical morbidity (1). Since depressive disorder is associated with substantial direct and indirect costs, its managed-care systems have long become a target of special interest for decision-makers, susceptible to be frequently affected by cost-containment policies.

Pharmacoeconomic studies are becoming an essential part of drug registration process, drug pricing and reimbursement policy. Pharmacoeconomic studies analyze the various treatment alternatives and thus highlight their pros and cons, presenting decision-makers and providers with robust data concerning the "best" (i.e., the most cost-effective, the most cost-beneficial) treatment alternatives for a given condition (2).

More than 150 million persons suffer from depressive disorder at any point in time (3). The prevalence of depressive disorder and the high costs associated with its treatment are increasing the interest in pharmacoeconomic evaluations of antidepressants, as well as meta-analysis and review studies comprising scattered published data.

2 Aim

The aim of the present study is to review the results of pharmacoeconomic studies for the treatment of depressive disorder with antidepressants.

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3 Methods

Pharmacoeconomic studies related to the antidepressants registered in Slovenia were obtained through a systematic search of PubMed (4), a bibliographic database maintained by the US National Library of Medicine.

The following search profile was used:

((amitriptyline) OR (citalopram) OR (doxepin) OR (duloxetine) OR (escitalopram) OR (fluoxetine) OR (clomipramine) OR (maprotiline) OR (mianserin) OR (mirtazapine) OR (moclobemide) OR (paroxetine) OR (reboxetine) OR (sertraline) OR (tianeptine) OR (trazodone) OR (venlafaxine))

AND

(((cost) OR (economic) OR (economics) OR (econom) OR (econom*)) OR ((pharmacoeconomic) OR (pharmacoeconomic*) OR (pharmacoeconomics)) OR ((cost-minimisation) OR (cost-minimization) OR (cost-effective) OR (cost-effectiveness) OR (cost-efficacy) OR (cost-efficiency) OR (cost-utility) OR (cost-benefit))).

The search was performed on 25th August 2006. Articles were also included by reviewing the reference list of the records obtained through the systematic search.

All the records were then limited to review articles and articles describing meta-analysis studies. Studies with no abstract or articles available in English were not eligible for inclusion for a subsequent analysis. Moreover, studies that were outside the scope of depression disorder treatment, articles that did not include comparison between at least two of the above mentioned antidepressants or that did not specifically state economic outcomes, were excluded from the analysis.

4 Results

A final set of 28 articles published between 1994 and 2006 was included in the analysis. Five articles were classified by PubMed as meta-analyses studies and 24 as review articles. One record was simultaneously classified as a review and meta-analysis article by PubMed. Articles that were included in the analysis are summarized in Table 1.

4.1 Comparison within ATC groups of antidepressants

Among selected studies, the only possible comparison between antidepressants of the same Anatomical Therapeutical Chemical Classification (ATC) group is for the group of "Selective serotonin reuptake inhibitors (SSRIs, ATC code: N06AB). Despite long term and frequent use of tricyclic antidepressants (TCAs), none of the selected articles included a comparison between different "Non-selective monoamine reuptake inhibitors" (ATC code: N06AA). The same is valid for the rest of the ATC groups, with the exception of SSRIs.

4.1.1 Selective serotonin reuptake inhibitors

The evidence of possible differences in treatment outcomes between SSRIs is controversial. Firstly, the results of effectiveness studies of different agents within the SSRI class published to date have conflicting findings (24). Secondly, four of eight studies included in the present analysis report no evidence of economic advantage of any particular antidepressant agent. Furthermore, the ones that do suggest the existence of pharmacoeconomic differences are contradictory: Goldstein *et al.* (13) and Davis *et al.* (7) reported sertraline to be more cost-effective than fluoxetine. On the contrary, Mitchell *et al.* (11) and Wilde *et al.* (15) reported a greater cost-effectiveness for fluoxetine than sertraline. Paroxetine was reported to be less cost-effective than both sertraline and fluoxetine by Davis *et al.* and Wilde *et al.* (7, 15). It is important to note that neither citalopram nor escitalopram were considered in the above-referred analysis.

4.1.2 Escitalopram *vs* other Selective serotonin reuptake inhibitors

Escitalopram was included in four studies, all of which concluded that it holds a cost-effectiveness and cost-utility advantage over the other SSRIs including: citalopram, fluoxetine, paroxetine and sertraline (25, 26, 27, 30). Cost-effectiveness ratios (i.e., direct cost per successfully treated patient) were consistently lower for escitalopram (€ 497–1403) than the rest of the SSRIs for the treatment of major depressive disorder (ranging € 525–1526) (30). The following European countries were included in the studies: Austria, Belgium, Norway and Sweden. From a cost-utility perspective, escitalopram was consistently associated with lower expected direct (€ 952–2597) and indirect costs (€ 7552) per QALY gained than its comparators (€ 1372–3300 and € 8088–9787, respectively) in Finland and in the US (30).

4.2 Comparison between groups of antidepressants

4.2.1 Selective serotonin reuptake inhibitors *vs* Non-selective monoamine reuptake inhibitors

The great majority of studies described evidence of a greater cost-effectiveness of SSRIs over "Non-selective monoamine reuptake inhibitors" for the treatment of depressive disorder (coincidently, all of the comparators were *tricyclic antidepressants*), concluding that SSRI agents at least offset or more than offset their acquisition costs (5-7, 10-15, 17, 19, 20, 21, 24).

In most cases, SSRI agents (fluoxetine, paroxetine, sertraline) were found to hold an economic advantage over their TCA comparators (amitriptyline, doxepin), frequently presenting *dominance* (i.e., being simultaneously associated with greater effectiveness and lower costs). Many of these reviews have, however, pointed out serious methodological bias in the reviewed original papers, which can account for an unknown extension of this economic advantage (8, 11, 17). Moreover, two of the reviewed studies found no evidence suggesting a real cost-effectiveness of SSRIs over TCAs (8, 22).

4.2.2 Selective serotonin reuptake inhibitors *vs* Other antidepressants (venlafaxine)

A number of six pharmacoeconomic studies addressing the use of serotonin norepinephrine reuptake inhibitor (SNRI) venlafaxine for

Table 1: Summary of the review and meta-analysis pharmacoeconomic studies for the treatment of depressive disorder with antidepressants. Preglednica 1: Povzetek preglednih člankov in člankov, ki opisujejo meta-analize farmakoekonomskih raziskav zdravljenja depresivnih motenj z antidepresivi.

Authors	Year	Publication Type	Comparators	Resume of Results and Conclusions
Le Pen, *et al.* (5)	1994	Meta-Analysis	Fluoxetine *vs* TCAs	Fluoxetine could be beneficial to society provided society values a year of human lifeabove a determined threshold. Fluoxetine may induce short-term financial savings for society.
Wilde, *et al.* (6)	1995	Review	Paroxetine *vs* SSRIs/TCAs	Despite higher acquisition costs paroxetine and other SSRIs are no more costly than TCAs when total costs per successfully treated patient or expected costs per patient are considered. Paroxetine should be considered as an effective alternative to TCAs as a first-line treatment of depression.
Davis, *et al.* (7)	1996	Review	Sertraline *vs* SSRIs/TCAs	Reviewed studies generally showed that overall treatment costs with sertraline and other SSRIs are no greater than those for TCAs; this is despite the lower acquisition costs of the latter agents. Two studies stated that sertraline was more cost-effective than TCAs. Sertraline can be considered as a first-line alternative to TCAs and other SSRIs for the treatment of depression on both clinical and pharmacoeconomic grounds.
Hotopf, *et al.* (8)	1996	Meta-Analysis	SSRIs *vs* TCAs	Insufficient evidence to support use of SSRIs as a cost-effective first-line treatment of depression. There is no evidence to suggest that SSRIs are more cost-effective than TCAs.
Priest, *et al.* (9)	1996	Review	Venlafaxine *vs* SSRIs/ TCAs/HCAs	Venlafaxine suggests a reduction in the overall costs associated with treating depression in hospitalized patients. Venlafaxine was found more cost-effective than SSRIs and TCAs (but not more than HCAs).
Hughes, *et al.* (10)	1997	Review	SSRIs *vs* TCAs	Available evidence across all groups of patients suggests that SSRIs may be more cost-effective than TCAs.
Mitchell, *et al.* (11)	1997	Review	SSRIs *vs* TCAs/SSRIs	SSRIs have its costs offset by lower medical utilization costs, when compared to TCAs. Fluoxetine seems to be more favourable economically than sertraline.
Stokes, *et al.* (12)	1997	Review	Fluoxetine *vs* TCAs/SSRIs	Total healthcosts lower or similar for fluoxetine (vs TCAs). No economic diferences observed between fluoxetine and other SSRIs.
Goldstein, *et al.* (13)	1998	Review	SSRIs *vs* TCAs/SSRIs	SSRIs, despite higher prescription costs, have been demonstrated to be a more cost-effective option than the TCAs. There is evidence that the emerging clinical differences between SSRIs may translate into significantly different economic outcomes within the group.
Montgomery, *et al.* (14)	1998	Review	SSRIs *vs* TCAs	Pharmacoeconomic studies show that an apparently cheaper antidepressants TCAs may turn out to be more expensive than the better tolerated antidepressants (SSRIs).
Wilde, *et al.* (15)	1998	Review	Fluoxetine *vs* TCAs/ SSRIs/Nefazodone	Nefazodone was associated with slightly lower lifetime direct medical costs and slightly more QALYs per patient.Total healthcare costs for patients who start with fluoxetine are similar to, or lower than, those for patients who start therapy with TCAs or other SSRIs. The evidence that fluoxetine has cost advantages over other SSRIs requires confirmation.
Casciano, *et al.* (16)	1999	Meta-Analysis	Venlafaxine *vs* SSRIs/ TCAs	Venlafaxine XR is generally a cost-effective treatment of MDD. The results suggest that increased utilization of venlafaxine XR will favorably impact the Servizio Sanitario Nazionale (SSN).

Authors	Year	Publication Type	Comparators	Resume of Results and Conclusions
Conner, *et al.* (17)	1999	Review	SSRIs *vs* TCAs/SSRIs	SSRIs maybe more cost-effective than TCAs in the treatment of acute depression. There is no clear evidence of greater cost-effectiveness of any agent within the SSRIs class.
Holm, *et al.* (18)	2000	Review	Mirtazapine *vs* amitriptyline/fluoxetine	Available data suggest that mirtazapine is a cost-effective alternative to amitriptyline and fluoxetine for the treatment of depression.
Skaer, *et al.* (19)	2000	Review	SSRIs *vs* TCAs	First-line use of SSRIs in the treatment of depression is clinically warranted and represents value for money.
Woods, *et al.* (20)	2000	Review	Venlafaxine/SSRIs *vs* TCAs	Venlafaxine is more cost effective for inpatient treatment and as second-line therapy than TCAs. SSRIs at least offset or more than offset their higher aquisitions costs, compared to TCAs.
Frank, *et al.* (21)	2001	Review	SSRIs *vs* TCAs/SSRIs	Compared to TCAs, SSRIs offset or more than offset their higher aquisitions costs. Studies from mid-1990s on show general equivalence in terms of cost within the SSRIs class.
Laux, *et al.* (22)	2001	Review	SSRIs/SNRIs *vs* TCAs	The available data do not allow the conclusion that SSRIs should be preferred over TCAs with the argument that the treatment as a whole is more cost effective in spite of the higher costs.
Morrow, *et al.* (23)	2001	Review	Venlafaxine *vs* SSRIs/TCAs	In both inpatient and outpatient settings both immediate release and venlafaxine XR have a lower expected cost than comparable treatment.
Panzarino, *et al.* (24)	2001	Review	SSRIs *vs* TCAs/SSRIs	SSRIs more cost-effective than TCAs when overall healthcare utilization and expenses are considered. Further research is needed to examine the cost-effectiveness within the SSRIs class.
Croom, *et al.* (25)	2003	Review	Escitalopram *vs* SSRIs/SNRI (venlafaxine XR)	Escitalopram holds a cost-effectiveness and cost-utility advantage over the other SSRIs (citalopram, fluoxetine, sertraline) and venlafaxine XR (SNRI). Pharmacoeconomic data supports the use of escitalopram as first-line therapy in patients with MDD.
Waugh, *et al.* (26)	2003	Review	Escitalopram *vs* SSRIs/SNRI (venlafaxine XR)	Escitalopram holds a cost-effectiveness and cost-utility advantage over the other SSRIs (citalopram, fluoxetine) and venlafaxine XR (SNRI).
Croom, *et al.* (27)	2004	Review	Escitalopram *vs* SSRIs/SNRI (venlafaxine XR)	Escitalopram holds a cost-effectiveness and cost-utility advantage over the other SSRIs (citalopram, fluoxetine, sertraline) and venlafaxine XR (SNRI). Pharmacoeconomic data supports the use of escitalopram as first-line therapy in patients with MDD.
Barrett, *et al.* (28)	2005	Review + Meta-analysis	SSRIs *vs* TCAs Venlafaxine/ /Mirtazepine/ Nefazodone	It is not possible to identify the most cost-effective strategy for alleviating the symptoms of depression, although the SSRIs and newer antidepressants consistently appear more cost-effective than TCAs in many patient groups. Better quality economic evidence is needed.
Han, *et al.* (29)	2005	Review	Venlafaxine *vs* SSRIs	Venlafaxine has a lower average cost per patient achieving remission or per symptom-free day compared with SSRIs. Venlafaxine is a cost-effective strategy for the treatment of depression.
Murdoch, *et al.* (30)	2005	Review	Escitalopram *vs* SSRIs/SNRI (venlafaxine XR)	Escitalopram holds a cost-effectiveness and cost-utility advantage over the other SSRIs (citalopram, fluoxetine, sertraline) and venlafaxine XR (SNRI). Pharmacoeconomic data supports the use of escitalopram as first-line therapy in patients with MDD.
van Baardewijk, *et al.* (31)	2005	Meta-Analysis	Venlafaxine XR *vs* duloxetine	Modest differences in pharmacoeconomic outcomes favour venlafaxine-XR over duloxetine.
Baca Baldomero, *et al.* (32)	2006	Review	Venlafaxine *vs* SSRIs/TCAs	Venlafaxine generates lower total costs (due to the reduction of treatment failure costs) than SSRI and TCA for the treatment of MDD.

treatment of depressive disorder suggested an economical advantage of this pharmacological agent over the SSRI class (the study included: fluoxetine, paroxetine and sertraline; escitalopram was excluded), with both the immediate release and extended release formulation (9, 16, 23, 29, 31, 32). A study published early in 1996 estimated a combination of a 20% effectiveness increase and potential 10% savings in total costs associated with the substitution of venlafaxine for fluoxetine in hospitalized depressed patients in the UK (9). In a cost-effectiveness analysis performed under the perspective of the Italian Health Service (Servizio Sanitario Nazionale), Casciano and his collaborators estimated a lower expected inpatient and outpatient costs for the treatment of major depressive disorder with extended release venlafaxine (venlafaxine XR), while exhibiting simultaneously better effectiveness than its comparators (16). In a 6-month Canadian decision model, venlafaxine was found to produce lower costs per successfully treated outpatient ($Can 6044) and inpatient ($Can 17235) than SSRIs ($Can 6633 and $Can 20479, respectively) (20). A US model estimated incremental cost-effectiveness ratios of $US 14.20 per depression-free day gained and $US 586.08 per patient in remission for venlafaxine *versus* the SSRI class, concluding a greater economic advantage of the first agent (29). In a direct comparison with duloxetine, venlafaxine XR also beneficiated from modest differences in pharmacoeconomic outcomes (31).

4.2.3 Escitalopram vs venlafaxine

Reference to cost-effectiveness and cost-utility advantage of escitalopram over venlafaxine XR was found in four articles (25, 26, 27, 30). Results from a prospective study described that direct costs for an average patient were 40% lower for escitalopram than venlafaxine XR (30), while a Markov-model estimated for escitalopram a better cost-effectiveness ratio than for venlafaxine XR in Germany (ICER of €6800–7400, for primary and specialist care, respectively) (30). From a cost-utility perspective, escitalopram was associated with lower expected direct costs than venlafaxine (including venlafaxine XR) in Finland (€2597 *vs* €2738, respectively) (30).

4.2.4 Selective serotonin reuptake inhibitors *vs* Non-selective monoamine reuptake inhibitors vs mirtazapine

Regarding mirtazapine, available data reviewed in 2000 suggested the existence of cost-effectiveness of this agent over amitriptyline and fluoxetine for the treatment of depressive disorder (18). Mirtazapine treatment dominated amitriptyline therapy and presented lower total (direct and indirect) healthcare costs per successfully treated patients in four European countries. The direct cost per successfully treated patient with mirtazapine was consistently lower than that with fluoxetine. The incremental cost effectiveness (i.e. additional cost of mirtazapine for each additional successfully treated patient) valued in S 11732, SEK 17229, £ 750 and FF 3342 in the Austrian, Swedish, UK and French analysis, respectively (18).

4.2.5 Venlafaxine *vs* Non-selective monoamine reuptake inhibitors

A number of five pharmacoeconomic studies addressing the use of venlafaxine for treatment of depression suggested an economical advantage of this pharmacological agent over the TCA class, with both the immediate release and extended release formulation (19, 16, 20, 23, 32). Casciano's study estimated a lower expected inpatient and outpatient costs for venlafaxine XR, while exhibiting simultaneously better effectiveness than the TCA comparators (16). In the 6-month Canadian decision model, venlafaxine was found to produce lower costs per successfully treated out ($Can 6044) and inpatient ($Can 17235) than TCAs ($Can 9035 and $Can 20479, respectively) (20).

5 Discussion

In the present review we have addressed the available pharmacoeconomic literature concerning the treatment of depressive disorder, specifically meta-analysis and review studies. Since we did not intend to accomplish a broad and comprehensive review of all the literature available, it is possible further relevant literature was left outside the present review, which was not included in the review and meta-analysis studies published at the date of the analysis.

6 Conclusions

A limited amount of evidence supports venlafaxine and escitalopram to be the most cost-effective treatment options for depressive disorder. Further studies based on robust methodologies are needed and expected in the near future.

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