COSTS AND OUTCOMES OF USE OF AMITRIPTYLINE, CITALOPRAM AND FLUOXETINE IN MAJOR DEPRESSION: EXPLORATORY STUDY

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Summary: Background: The increasing cost of pharmaceuticals in the Czech Republic has led to the restriction on prescriptions of expensive new antidepressants. The aim of the study was to compare the costs and outcomes of using amitriptyline, citalopram and fluoxetine in the treatment of major depression. Methods: Ninety patients (69 women) with a mean age of 44.5 years (S.D.=14.3) suffering from major depression were treated with amitriptyline (N=31), citalopram (N=29) and fluoxetine (N=30). Direct medical costs and effectiveness (indicated by the number of hospitalization-free days) were assessed in a prospective, open, intent-to-treat study. Results: Neither cost nor effectiveness were significantly different among the treatment groups. Conclusion: Amitriptyline treatment is not less expensive nor more effective than citalopram or fluoxetine therapies. There is no advantage in restricting patients from treatment with SSRIs, which have fewer adverse effects and a decreased risk of a lethal overdosage in comparison with tricyclic antidepressants.

Key words: Depression; Amitriptyline; Citalopram; Fluoxetine; Costs; Outcomes

Introduction

Health care expenditures in the Czech Republic (CR) totaled $ 4 billion in 1998 as compared to $ 3.1 billion in 1995 (21). If health care expenditures had only increased by the general rate of inflation, they would only have equaled $ 3.6 billion in 1998 (2). One reason for this increased rate of expenditures is the significant increase in the cost of medications. Medication costs in the CR in 1996 were five times higher than in 1990 (5). Health insurance companies have set financial limits and increased administrative regulations upon drug prescriptions in order to prevent further increases in medication costs. If medication costs are too high, the prescribing physician's reimbursement is reduced. This strategy has not been entirely successful and has come at the cost of preventing patients from obtaining modern drugs that are known to cause fewer side effects.

Restrictions in the Czech Republic are designed to increase the use of older tricyclic antidepressants (TCAs) instead of selective serotonin re-uptake inhibitors (SSRIs) in the treatment of major depression. The international literature suggests that use of tricyclic antidepressants does not lead to savings in direct treatment costs in major depression in comparison with the SSRIs (4,9,13,17,18,25). No prospective pharmacoeconomic study related to this issue has been performed in a former communist country. This is an interesting setting to study this issue, given the rapid transformation of the health care system in these countries.

Amitriptyline, citalopram and fluoxetine are the most frequently used antidepressants in the CR (15).

The aim of the study was to compare the direct costs and effectiveness in reducing hospitalization of antidepressive treatment with amitriptyline in comparison with treatment with the SSRIs, citalopram and fluoxetine in the Czech Republic. The costs were assessed from a perspective of the General Health Insurance Company of the Czech Republic. This institution is a dominant health care policy maker in the CR which does not track indirect costs of diseases. Owing to this fact, the indirect costs of depression were not assessed by the authors.

This study represents a pharmacoeconomic extension of an original clinical antidepressant trial in hospitalized patients.

Material and Methods

Subjects

All patients diagnosed with depressive episodes treated with amitriptyline, citalopram or fluoxetine, who had just been discharged from the inpatient unit of the Department of Psychiatry, University Hospital in Hradec Králové from September 1st, 1994 to August 31st, 1997 were included in the study. Patients provided informed consent. Ninety patients were followed. There were more women (N=69) than men (N=21). Diagnoses according to the International Classification of Diseases-10th Version (20) were as follows:

F 31 Bipolar Affective Disorder, Most Recent Episode Depressed (N=8), F 32 Major Depressive Episode, Single (N=44) and F 33 Major Depressive Episode, Recurrent (N=38). The average score on the Hamilton Psychiatric Rating Scale for Depression was 11.8 (2-22, S.D.=6.4).

Thirty-one patients were treated with amitriptyline, 29 with citalopram and 30 with fluoxetine at the beginning of the study. The treatment groups were comparable in gender (p=0.31, Chi-square test), age (p=0.98, Kruskal-Wallis test), diagnosis (p=0.23, Fischer exact test), duration of affective disorder (p=0.45, Kruskal-Wallis test), number of previous depressive episodes (p=0.49, Kruskal-Wallis test) and duration of recent depressive episode (p=0.65, Kruskal-Wallis test).

The subjects were randomized to the study antidepressant using computer randomization program (Excel) at the beginning of the initial hospitalization at the Dpt. of Psychiatry in Hradec Králové. Inpatient treatment lasting several weeks was assessed for efficacy and tolerability (7) and not pharmacoeconomic issues. This study, which assesses aspects of the cost and effectiveness of treatment, began immediately after the discharge of the patients from the inpatient unit.

Treatment

After the initial discharge from the university hospital the patients were treated at various outpatient psychiatric clinics in Eastern Bohemia and followed for the cost and outcome of therapy. Some of the patients were rehospitalized. This open, prospective study lasted six months and was based on an intent-to-treat model. This model suggests that the investigators exercise no control over physician practice after randomization, since the intent is to observe the impact of the treatments in ordinary practice settings. The physician is free to determine dose and duration of treatment and may change therapy, including the assigned antidepressant, at any time. Nearly all patients, in whom the randomized antidepressant had been discontinued (dropout), then were treated with a tricyclic antidepressant. The drop-out patients were included into the evaluation. Eight amitriptyline patients, 4 citalopram patients and 5 fluoxetine patients were rehospitalized one time during the six month study period. Three citalopram patients and 1 fluoxetine patient were rehospitalized twice. The rest of the patients were not rehospitalized during the followed period.

Costs

Utilization data on psychotropic medications, outpatient psychiatric examinations and rehospitalizations were obtained from the outpatient psychiatrists using a questionnaire. The treatment costs were calculated by multiplying units of service by their estimated cost. The cost of antidepressants, concomitant psychotropic medications, outpatient psychiatric examinations and hospitalizations for depression were considered. The medication costs were calculated according to the Drug Price List of the General

Health Insurance Company of the CR (24). For example, the cost of amitriptyline (75 mg) was $ 0.06 (U.S. Dollars) in comparison to $ 0.80 for citalopram (20 mg) and $ 0.59 for fluoxetine (20 mg). The cost of one outpatient psychiatric examination was $ 3.5 as fixed by the General Health Insurance Company (1). The cost of one day of hospitalization at the Department of Psychiatry in Hradec Králové in 1997 was $ 21.7 as reported by the hospital Department of Finances. The cost of one hospitalization day was $ 17.2 at the Department of Psychiatry in Nová Paka, $ 16.9 in Nové Město nad Metují and $ 16.5 in the State Mental Hospital in Havlíčkův Brod. No other direct medical costs (e.g. cost of structured psychotherapy, laboratory tests, psychiatric emergency visits or medical social work) were assessed because these services are provided very rarely in the psychiatric outpatient setting in the CR. All costs were considered in 1997 Czech Crowns (Kč) and recalculated to $ (Kč 33.5 = $ 1; 1997 values) (19).

The costs were assessed from the perspective of the General Health Insurance Company of the CR. That is why charges were used instead of open market values because these are not relevant for this dominant health care policy maker in the country. The indirect costs of depression, which are usually three or more times higher than the direct treatment costs (11), were not calculated because they are not relevant for the General Health Insurance Company again.

Outcome

The outcome measure was the number of hospitalization-free days, which was defined as the number of days spent outside any psychiatric hospital during the six month follow-up period. This outcome measure was chosen because it provides a reasonable measure of the effectiveness of the therapy after the initial hospitalization. More detailed evaluations of the subjects' clinical states were not possible in this small, pilot study.

Statistical analysis

The Chi-square, Fischer exact and Kruskal-Wallis tests were used to assess the comparability of the treatment groups with each other as for gender, age, diagnosis, duration of affective disorder, number of previous depressive episodes and duration of recent depressive episode. Normality of distribution of the cost and outcome values was tested using the Smirnoff-Kolmogorof, the Skewness-Normality and the Omnibus Normality tests. Because the distribution was not normal, the Kruskal-Wallis test was used in all cases to compare the cost and outcome variables among the treatment groups as well as the sensitivity analysis. The Chi-square test was adequate for analysis of drop-out rates.

Ethical issues

The study was conducted in full conformity with the principles of the Helsinki Declaration as amended in

Tokyo, Venice and South Africa. The study protocol was accepted by the Ethics Committee of the University Hospital and the Charles University School of Medicine in Hradec Králové. The patients voluntarily signed the Informed Consent before the enrollment into the trial.

Results

Description of the study population is given in Table 1.
The results are summarized in Tables 2 and 3. Amitriptyline was found to be significantly cheaper than the other two medications (p=0.00003). Total direct medical costs as well as outcome based on the number of hospitalization-free days were not significantly different among the treatment groups.

Amitriptyline was discontinued in 26 (83.9%) patients, citalopram was discontinued in 17 (58.6%) patients, and fluoxetine was discontinued in 19 (63.3%) patients (drop-outs). Overall there was no significant difference in drop-out rates, but the numbers did suggest a trend to a significant difference in favour of the SSRIs (AMI vs CIT p=0.07, AMI vs FLU p=0.07, CIT vs FLU p=NS, chi-square value = 5.11, df=2, Chi-square test). The drop-outs were included in the assessment. Ten amitriptyline patients were switched to dosulepine, 6 to dibenzepine, 5 to imipramine, 1 to citalopram, 1 to clomipramine, 1 to moclobemide, 1 to nortriptyline, and 1 to sertraline. The medication switch in the amitriptyline patients came after 1.8 months of the treatment on average. Five citalopram patients were switched to amitriptyline, 5 to dibenzepine, 4 to dosulepine, 1 to flu-

Tab. 1: Description of the study population (N=90).

Variable	Mean value	Minimum	Maximum	S.D.
Age (years)	44.5	17	71	14.3
Duration of the mood disorder (months)	63.4	1	396	93.7
Duration of the most recent depressive episode (months)	5.9	1	36	6.7
Number of previous depressive episodes	1.7	0	28	3.5
Number of previous manic episodes	0.1	0	3	0.5
Number of previous psychiatric hospitalizations	2.1	0	29	4
Weight (kg)	67.2	41	101	12.2

Tab. 2: Costs of the six month continuation treatment with amitriptyline, citalopram and fluoxetine in major depression.

Variable	Amitriptyline (N=31)	Citalopram (N=29)	Fluoxetine (N=30)	Analysis Kruskal-Wallis test
Cost of antidepressant ($)	Median 122 Minimum 11 Maximum 841	Median 341 Minimum 0 Maximum 841	Median 307 Minimum 42 Maximum 841	P=0.00003 1 differs from 2,3 (Duncan's multiple comparison test)
Cost of other psychotropic drugs ($)	Median 19 Minimum 0 Maximum 231	Median 24 Minimum 0 Maximum 60	Median 14,5 Minimum 0 Maximum 101	P=0.50
Cost of outpatient examinations ($)	Median 39 Minimum 0 Maximum 109	Median 31 Minimum 0 Maximum 148	Median 35 Minimum 0 Maximum 101	P=0,59
Cost of rehospitalizations for depression ($)	Median 742 Minimum 0 Maximum 3261	Median 562 Minimum 0 Maximum 3261	Median 641 Minimum 0 Maximum 2137	P=0,59
Total direct treatment cost ($)	Median 1067 Minimum 32 Maximum 3548	Median 1128 Minimum 23 Maximum 3667	Median 1083 Minimum 175 Maximum 2757	P=0,97

Tab. 3: Outcome of the six month continuation treatment with amitriptyline, citalopram and fluoxetine in major depression.

Variable	Amitriptyline (N=31)	Citalopram (N=29)	Fluoxetine (N=30)	Analysis Kruskal-Wallis test
Number of hospitalization-free days	Median 140 Minimum 35 Maximum 180	Median 155 Minimum 35 Maximum 180	Median 152 Minimum 85 Maximum 180	P=0,18

voxamine, 1 to moclobemide, and 1 to sertraline. The treatment with citalopram usually lasted 2.2 months on average in the citalopram drop-outs. Six fluoxetine patients were switched to dibenzepine, 5 to dosulepine, 3 to amitriptyline, 2 to citalopram, 1 to clomipramine, 1 to imipramine, and 1 to maprotiline. The average duration of the treatment with fluoxetine in the drop-outs was 2.1 months. The antidepressants were switched because of a lack of efficacy or adverse effects.

One-way sensitivity analysis in which all variables were sequentially multiplied and divided by a coefficient of 2, 5 and 10 revealed that the cost of antidepressant was the most sensitive factor influencing the overall direct costs (coefficient 10, amitriptyline differs from citalopram and fluoxetine, p=0.03, Kruskal-Wallis test). No significant sensitivity was proven in all other variables (coefficients 2, 5 and 10, p<0.98, Kruskal-Wallis test).

Discussion

The results suggest that treatment of major depression with the SSRIs is neither more expensive nor less effective than therapy with amitriptyline. Limitation of prescription of the SSRIs by health insurance companies does not appear to lead to cost savings, while it may lead to patients suffering unnecessarily from adverse effects of TCAs (10,14,22). The adverse effects may be the cause of the high drop-out rate in the amitriptyline patients. Good clinical practice requires at least six months continuation of antidepressant treatment following successful acute treatment in major depression and may even require chronic antidepressant treatment in cases of recurrent depression (12,23). Continued treatment with TCAs entails greater risks to patients given the higher risk of lethal overdose in suicidal patients with TCAs (8). These facts should persuade the Czech health insurance companies not to punish physicians for prescribing the SSRI antidepressants.

It is necessary to state the limitations of the study. The number of the subjects in the individual treatment groups was relatively small. That is why the study can only be considered exploratory. Drop-outs were included into the final evaluation when nearly all drop-out patients were switched to a tricyclic antidepressant. This change of medication caused decreased costs in the citalopram and fluoxetine groups but was counterbalanced by an increase in adverse effects. The intent-to-treat approach in pharmacoeconomic research is fully accepted in the literature (16) and widely used because it reflects real clinical practice. The fact that the analysis was focused on psychiatric treatment while the majority of the depressive patients are treated by general practitioners may be considered problematic, but in fact, it represents the actual clinical situation in the CR. Indirect costs were not considered even if they are more important than the direct ones in depression (6,11). Evaluation of indirect costs would be necessary to conduct a true cost-effectiveness study.

There are also some strengths in this study. Patients, health care providers and policy makers in communist countries were educated that money was irrelevant in a fully communist regime (3). Even after the fall of communism economic considerations in the health care system are often considered as unethical. However, the reality is that economic forces are present in any health care system and need to be addressed. This paper describes the first prospective pharmacoeconomic study in psychiatry in the postcommunist world to the authors' knowledge.

Further research through a larger, controlled, prospective, intent-to-treat, long-term medical effectiveness study of the treatment of depression by general practitioners which considers indirect costs and quality of life of the patients should be performed to confirm or reject the results presented in this exploratory study.

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