University of Szeged
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Ph.D. thesis

ANTIDEPRESSANT CONSUMPTION IN HUNGARY AND HEALTH-RELATED QUALITY OF LIFE ASSESSMENT IN PATIENTS WITH DEPRESSION

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TABLE OF CONTENTS

1. INTRODUCTION

Depression is one of the most common psychiatric disorders in the general population, with a life-time prevalence of 24.2% in Hungary [1]. The affective disorders pose a very severe public health problem with their medical and psychosocial complications (e.g. suicide, disability, and secondary alcohol and drug abuse). The WHO reports on the global burden of disease have placed major depression fourth among the leading causes of disease burden in the developed regions of the world, and predicted that, after heart disease, it will become the second by the year 2020.

The principal treatments of mood disorders are psychopharmacological and psychosocial therapies. During recent years, international trends have indicated a dramatic increase in the use of antidepressants, particularly after the introduction of selective serotonin reuptake inhibitors (SSRIs) in the early 1990s. Several other new classes of antidepressants have emerged over the last decade, which offer the possibility of treating patients with less toxic and more tolerable agents, thereby improving the compliance and possibly improving the outcome as compared with the "classical" tricyclic antidepressants (TCAs). Without adequate treatment, depression has the tendency to assume a chronic course, be recurrent, and over time to be associated with increasing disability.

Suicidal behaviour is one of the most serious potential complications of depressive disorders. Psychological autopsy studies have shown that an affective disorder is present in 60% of suicides and a psychiatric disorder of some sort is present in approximately 90% of all suicides [2]. In recent years, considerable attention has been given to epidemiological studies that evaluated the association between increasing antidepressant consumption and decreasing suicide rates.

Besides increased morbidity and disability rate, depression produces a significant decrement in the individuals' health-related quality of life (HRQoL).

A number of trends in health care have resulted in the development and growing use of patient-based outcome measures to assess matters such as the functional status and HRQoL. It is increasingly recognized that traditional biomedically defined outcomes such as clinical and laboratory measures need to be complemented by measures that focus on the patient's concerns in order to evaluate interventions and identify more appropriate forms of health care.

Interest in patient-based measures has been fuelled by the increased importance of chronic conditions, where the objectives of interventions are to arrest or reverse a decline in function. Initially, psychiatrists showed hesitation regarding quality of life (QoL) assessment because the mainstream concept of QoL in medicine, with its emphasis on the subjective well-being and satisfaction of the patient, is less separated from psychiatric concepts of mental disorders than from medical concepts of somatic diseases. However, in the early 1980s, they came to the forefront of QoL research by conducting several studies on patients with chronic mental illnesses, such as depression. This has led to the introduction of a large number of instruments for assessment of the QoL [3].

The purpose of the present study was to apply pharmacoepidemiologic methods to investigate trends of antidepressant consumption in Hungary and its impact on suicide rates. Furthermore, I intended to develop the valid Hungarian version of a suitable depression-specific quality of life measure and to assess the health-related quality of life in depression with.

2. BACKGROUND

2.1. Drug utilization

In order to work towards a more rational use of medication, it is essential to have accurate information on patterns of drug prescription and use.

Drug utilization was defined by the WHO as an eclectic collection of descriptive and analytical methods for the quantification, understanding and evaluation of the process of the prescribing, dispensing and consumption of medicines and for the testing of interventions to enhance the quality of these processes [4].

The field of drug utilization research has attracted increasing interest since the 1960s. At a symposium in Oslo in 1969 entitled The Consumption of Drugs, the *Drug Utilisation Research Group (DURG)* was established and appointed with the aim of the development of internationally applicable drug utilization methods. In the mid-1970s, the *Anatomical Therapeutic Chemical (ATC)* classification system was developed by Norwegian researchers for the classification of medication, and the *Defined Daily Dose (DDD)* was introduced as the measurement unit to be used in drug utilization studies. The *WHO Collaborating Centre for Drug Statistics Methodology* was established in 1982, with the purpose of coordinating and improving the use of this *ATC/DDD system*.

In the ATC classification system, drugs are divided into different groups according to the organ or system on which they act and their chemical, pharmacological and therapeutic properties. Drugs are classified in groups at five different levels. There are fourteen main groups (1st level), with one pharmacological/therapeutic subgroup (2nd level). The 3rd and 4th levels are chemical/pharmacological/therapeutic subgroups and the 5th level is the chemical substance.

The structure of the code is illustrated by the complete classification of escitalopram:

N	Nervous system
	(1st level, anatomical main group)
N06	Psychoanaleptics
	(2nd level, therapeutic subgroup)
N06A	Antidepressants
	(3rd level, pharmacological subgroup)
N06AB	Selective serotonin reuptake inhibitors (SSRIs)

(4^{th} level, pharmacological/chemical subgroup)

N06AB10 Escitalopram

(5^{th} level, chemical substance)

The DDD is an internationally accepted technical unit in dug utilization studies. It means the assumed average maintenance dose per day for a drug used for its main indication in adults. Utilization is normally expressed as the number of DDDs/1000 inhabitants/day, which allows comparisons of drug use between countries, regions and other health-care settings. It also allows the evaluation of trends over time [5].

The number of drugs accounting for 90% of drug use (DU90%) may serve as an indicator of the quality of drug consumption. The method ranks drugs by volume of DDD and determines how many drugs account for the DU90% segment [5, 6].

2.2. Polypharmacy

Polypharmacy is an important risk factor as concerns the initiation of complications arising from drug therapies (e.g. drug-drug interactions, adverse drug reactions, non-compliance, or a decrease in QoL). It also imposes a substantial financial burden on both the patient and the health-care system.

The definition of polypharmacy in the literature is not uniform. There are basically two approaches to the definition. The first refers only to the number of drugs taken simultaneously. According to this, polypharmacy means the concurrent use of 2 or more drugs. However, some authors distinguish between minor polypharmacy (the concurrent use of 2 to 4 drugs) and major polypharmacy (the concurrent use of 5 or more drugs) [7-12].

The other approach to the definition focuses on the clinical indication and the effect of the administered medication. According to this definition, irrational, clinically not indicated drug use is regarded as polypharmacy [7, 13-15].

In the present study, the standard definition was used, and therefore the chronic and concurrent use of 5 or more medications was considered to be polypharmacy.

2.3. Quality of life

2.3.1. Definition

The concept of QoL is not yet defined in a uniform way. However, the WHO conceptualization of health is employed by most researchers as the theoretical origin for their study of QoL as it is influenced by health and medical care. In its 1947 constitution, the WHO

declared that "health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity". By extending the definition of health to include total well-being, traditional measures of morbidity and mortality became inadequate as the sole indicators of health [3].

Definition	***Author***
'Quality of life is an individual's perception of their position in life in the context of the culture and value system in which they live and in relation to their goals, expectations, standards and concerns.'	*WHOQOL Group, 1993*
'Quality of life refers to patients' appraisal of and satisfaction with their current level of functioning as compared to what they perceive to be ideal.'	*Cella and Tulsky, 1990*
'Quality of life in clinical medicine represents the functional effect of an illness and its consequent therapy upon a patient, as perceived by the patient.'	*Schipper et al., 1996*
'Quality of life measures the difference or gap at a particular period of time, between the hopes and expectations of the individual and the individual's experiences.	*Calman, 1984*
'Health-related quality of life refers to the level of well-being and satisfaction associated with an individual's life and how this is affected by disease, accidents and treatments from the patient's point of view.'	*Lovatt, 1992*
'Health-related quality of life is the value assigned to the duration of life as modified by the impairment, functional states, perception and social opportunities that are influenced by disease, injury, treatment or policy.'	*Patrick and Erickson, 1993*

Table 1. Illustration of the range of definitions of QoL [16]

Although the definitions vary, the concept of QoL encompasses three overarching dimensions:

- What a person is capable of doing (functional status)
- Access to resources and opportunities to use these abilities to pursue interests
- The sense of well-being

The former two dimensions are often referred to as objective QoL and the third as subjective QoL. Within these overarching dimensions, certain life domains have been identified, such as health, family, social reactions, work, financial status and living conditions. QoL is thus a complex notion. Two perspectives can be identified to frame core issues regarding QoL assessment: The *general QoL and the HRQoL* framework.

The *general QoL* underlines the considerable research that has been done as regards the general population. The goal of this line of research involves the social perspective of the status and well-being of various groups of people and the values that they and their societies place upon various aspects of life experience. Such a perspective may provide insight into what people strive for, why they choose as they do, and how different societies and subgroups within a society fare, relative to other, in their life aspirations. Measures based on this approach typically cover functional status, access to resources and opportunities, and the sense of well-being across multiple aspects of life domains.

Although a low income, a lack of freedom and poor social support may be relevant to health, there is a tendency to exclude such general aspects when dealing with QoL in terms of medical research and to focus directly on disease-related aspects of functional capacity and well-being. For this purpose, the term of *HRQoL* has been coined [3, 16].

2.3.2. Instruments for measuring HRQoL

The aim of QoL measurement is to quantify the impact of both the clinical condition and treatment on the wider aspects of a patient's life, by going beyond physician-dominated indicators of the patient's progress. The instruments used to measure the HRQoL can be classified into generic measures, and disease-specific measures.

Generic instruments are intended to capture a very broad range of aspects of health status and the consequences of illness and therefore to be relevant to a wide range of patient groups. The content of such questionnaires has been deliberately designed to be widely appropriate. Because of this, they permit comparisons across treatments for groups of patients with different groups, to assess comparative effectiveness. However, the most significant drawback of using generic instruments is their lack of sensitivity [16].

Most widely used generic instruments:

- Sickness Impact Profile (SIP) [17-21]
- SF-36 Health Survey (SF-36) [22-24]
- EuroQol Instrument (EQ-5D) [25-27]
- WHO Quality of Life Assessment Instrument (WHOQOL) [28, 29]
- Nottingham Health Profile (NHP) [30, 31]

Disease-specific instruments have been developed in order to provide the patient's perception of a specific disease or health problem (*Table 2*). These measurements are more likely to detect important changes that occur over time in the particular disease studied. They are

intended to have a very relevant content for a specific disease, and therefore all of the items in the instrument should have been developed specifically to assess the particular health problem.

Name of instrument	*Disease*	*Reference*
Arthritis Impact Measurement Scales (AIMS)	arthritis	[32]
Psoriatric Arthritis Quality of Life (PSAQoL)	arthritis psoriatrica	[33]
Ankylosing Spondylitis Quality of Life (ASQoL)	spondylitis ankylopoetica	[34]
Asthma Quality of Life Questionnaire	asthma	[35]
Diabetes-specific QoL Scale (DSQOLS)	diabetes mellitus	[36]
Functional Digestive Disorders Quality of Life (FDDQL)	functional digestive disorder	[37]
Quality of Life in Epilepsy Inventory (QOLIE)	epilepsy	[38]

Table 2. Examples for different disease-specific instruments

2.3.3. Requirements of a QoL instrument

The content of any QoL instrument must be perceived as relevant by the patients. This is achieved by deriving the content of the instrument directly from relevant patients. In this way, *face and content validity* are maximized, resulting in higher rates of completion [39].

Any QoL instrument must have good *reliability*. This is determined by the test-retest reliability (reproducibility) and internal consistency. *Test-retest reliability* is concerned with the extent to which scores on a measure can be replicated. It is expressed as a correlation coefficient, with values in excess of 0.85 generally considered to indicate adequate reliability. *The internal consistency* of an instrument is an estimate of the degree to which its constituent items in a scale are interrelated. It means that individual items should correlate highly with each other and with the summed score of the total of items in the same scale. Internal consistency is generally assessed by using Cronbach's α. An α value of 0.85 or above is indicative of adequate internal consistency [16].

All instruments must be shown to have *construct validity.* This is the degree to which the instrument measures the intended construct and can be assessed in a number of ways. The most sophisticated method of testing an instrument's construct validity is to compare scores on it with those on a proven measure of the same construct (*convergent and divergent validity*). Convergent and divergent validity are the extents to which related and unrelated variables are associated [16, 39].

Discriminative validity is the ability of the measure to distinguish between groups of respondents that differ according to some factor.

While the above-mentioned psychometric properties are essential for any instrument, perhaps one of the most crucial requirements for a measure required to show change in QoL over a particular time period is the *responsiveness* [16, 39].

2.3.4. General considerations for translation and adaptation of QoL instruments

The demand for valid QoL instruments available in several languages is growing rapidly. However, a majority of QoL instruments are developed in English-speaking countries. Since the development and validation of a new questionnaire require much time and labour and substantial monetary investment, the cultural adaptation of an internationally widely used instrument into Hungarian is the most frequently employed technique.

The translation and validation methodologies employed to adapt such measures must ensure that the adapted version is comparable with the original and other national versions. The focus is on cross-cultural and conceptual, rather than on semantic equivalence. The instrument should be equally acceptable and should perform practically in the same way. In order to achieve this, a standardized methodology should be applied to all language versions developed [40].

2.3.5. QoL assessment in depression

Recognition of the importance of HRQoL assessment in the field of chronic mental illnesses such as depression has increased during the past decade. The development of depression-specific instruments was largely motivated by the introduction of new classes of antidepressants. Two depression-specific QoL inventories were published, the Quality of Life in Depression Scale (QLDS) by McKenna and Hunt (1992), and the Smith Kline Beecham Quality of Life Scale (SBQOL) by Stocker et al. (1992) (*Table 3*). Both were primarily developed for measuring change in clinical trials of antidepressants and are self-rating instruments.

The SBQOL is a 23-item instrument that measures the dimensions of mood, psychological well-being, physical well-being, locus of control, social relationships and work/employment [41, 42].

The QLDS is a 34-item measure. It was developed in parallel in the UK and The Netherlands employing the ‘needs-based model’ of QoL. Qualitative in-depth interviews are conducted with patients with depression to explore the impact of the symptoms on their ability to fulfil

their needs and to examine the effects of medication on the patients and their illness. The items encompass 6 dimensions: domestic activities, interpersonal relationships, social life, cognition, personal hygiene, leisure activities and relaxation. The responses are recorded in a dichotomous format (true/not true), and then summed to give a total score ranging from 0 to 34 [43, 44].

Type of instrument	*Instrument*	*Reference*
Generic	SF-36 Health Survey (SF-36)	[45-56]
	Sickness Impact Profile (SIP)	[57]
	WHO Quality of Life Assessment Instrument:	
	WHOQOL-100	[58-61]
	WHOQOL-BREF	[62-66]
	EuroQol (EQ-5D)	[67-72]
Depression-specific	Smith Kline Beecham Quality of Life Scale (SBQOL)	[73-75]
	Quality of Life in Depression Scale (QLDS)	[67, 72, 75-83]

Table 3. Instruments appropriate for measuring QoL in depression

Studies designed to asses QoL in depression concluded consistently that depression has an impairing effect on the HRQoL [39, 62, 75, 83-88,]. Other psychiatric disorders, such as anxiety disorders or schizophrenia, are also known to decrease the QoL, but not to the same extent as major depression [75, 86, 89]. Impairment among depressive patients was observed for all dimensions of HRQoL. This suggests that depression is not only reflected in mood and other mental symptoms, but also impairs an individual's functioning ability in a number of ways. Depression has a significant effect on perceived physical functioning and bodily pain, and even on general health perceptions. Consequently, such impairment appears as reduced vitality, feeling ill, and having a limited social functioning ability.

Evidence has been reported that the severity of depression is strongly associated with all dimensions of QoL [3, 83]. Furthermore, the effect of depression on the QoL was found to be comparable with those of other chronic conditions, e.g. arthritis, diabetes and hypertension [58, 84, 90, 91].

3. AIMS

3.1. Drug utilization

The aim of the drug utilization study was to analyse the changes in the amount and structure of Hungarian antidepressant consumption at national and regional levels between 1993 and 2006. The possible relationship between antidepressant sales and trends in suicide rates was also investigated. To explore the reasons for regional differences in antidepressant consumption and suicide rates, their possible determinants, such as the indicators of psychiatric service and socio-economic factors, were also tested.

Comparative analysis of hospital antidepressant consumption was performed through data derived from the four university-affiliated Psychiatric Departments. Since these are the leading professional medical institutions in the certain counties, there was an intention to compare the pattern of their antidepressant use with the county data too.

3.2. Polypharmacy among psychiatric patients

In recent years, no published data have been available regarding the quantitative analysis of multiple drug consumption in Hungary. Accordingly, a further objective of my studies was to evaluate the frequency of polypharmacy among psychiatric patients. The effects of comorbidity and demographic characteristics on multiple drug use were also analysed.

3.3. Quality of life in depression

As no suitable disease-specific measure of QoL in depression was available for Hungary, the decision was made to adapt an extensively used depression-specific QoL instrument, to evaluate its psychometric properties, and to assess the QoL in Hungarian patients with depression, employing the adapted QoL instrument in the clinical setting. The relationship of psychiatrist-rated and self-rated depression severity with the subjective QoL was also investigated.

4. METHODS

4.1. Drug utilization study

4.1.1. National and regional trends of antidepressant consumption

Retrospective analysis of sales data from the wholesalers to pharmacies and hospitals was performed on a 14-year period (1993-2006), applying the ATC/DDD methodology and classification system developed by the WHO (version 2006) [92]. Antidepressant drugs feature in the N06A therapeutic subgroup. For each Hungarian region (county), yearly crude wholesale data were kindly provided by the IMS PharmMIS Consulting Company. Nationwide and regional consumption was expressed as the number of DDDs per 1000 inhabitant-days. Additionally, the number of active ingredients accounting for 90% of the total national antidepressant use was calculated. The DU90% segment was also determined at the regional level.

A linear regression model was set up to investigate the trends in antidepressant utilization. The max./min. ratio was calculated to assess the interregional variation in antidepressant consumption.

4.1.2. Hospital antidepressant consumption

A 5-year (1999-2003) retrospective study of hospital antidepressant consumption was carried out at four university-affiliated Psychiatric Departments (in Budapest, Pécs, Debrecen and Szeged). The crude data on drug utilization were obtained from the hospital electronic patient health and medication record systems for the four Psychiatric Departments. The consumption was expressed as DDD/100 bed-days. The qualitative differences between the studied departments were determined on the basis of the DU90% segments.

The study had the limitation that data on hospital antidepressant consumption were not available for the year 1999 at the Psychiatric Department in Debrecen.

4.1.3. Relationship between antidepressant consumption and suicide rate

Data on suicide rates were retrieved from the national mortality statistics (Hungarian Central Statistical Office) and were expressed in number of suicides/100000 inhabitants/year [93]. After the testing of normality (one-sample Kolmogorov-Smirnov test), the association

between the regional antidepressant consumption and the suicide rate was measured with the Pearson correlation.

Regional data on psychiatric service indicators (the number of outpatient departments, the number of attendances, the number of new patients taken into care per 10000 inhabitants, and the number of hospital admissions per year) and the number of alcohol-abuse disorders were used to explore reasons for regional differences in antidepressant consumption and suicide rates; these data were provided by the NIPN (National Institute of Psychiatry and Neurology). Socio-economic data (GDP per inhabitant and unemployment rate) were extracted from the yearbooks of the Hungarian National Statistical Office [93]. After the testing of normality (one-sample Kolmogorov-Smirnov test), the Pearson correlation was employed to evaluate the impact of the above-mentioned determinants on the antidepressant consumption and suicide rates. An α level of 0.05 was adopted for all statistical analyses.

4.1.4. Polypharmacy among psychiatric patients

A cohort study was performed for a 1-year period. All inpatients (n = 983) admitted to the Psychiatric Department at the University of Szeged in 2001 were enrolled in the study. The patient characteristics (age, gender and diagnoses according to ICD-10) and all prescribed drugs (with their dose regimen) at discharge were collected from the electronic patient health and medication record system used at the Department.

The generally accepted definition of polypharmacy is the chronic and concurrent use of 5 or more drugs [8, 94-96]. Accordingly, the patients were divided into two groups: the PP group: patients on 5 or more drugs; and the non-PP group: patients on less than 5 drugs.

Student's t-test was used to compare continuous or discrete data (the mean age, the mean numbers of used psychiatric drugs, other drugs and total drugs used). Linear regression was performed to examine the correlation between the increasing number of drugs used and the mean number of psychiatric drugs. Logistic regression was used to investigate the importance of factors predisposing to polypharmacy. p-values less than 0.05 ($p < 0.05$) were accepted as statistically significant.

4.2. Measuring quality of life in depression

4.2.1. Selection criteria of the QoL instrument employed

- It should be easy for the patients to complete (average time for completion the questionnaire should be less than 10 min) [16, 97].

- ❖ The items should be generated directly from patients with depression as its content should be relevant to this population, and expressed in the actual words of the depressed patients [39].
- ❖ It should be easy for the physician or researcher to administer.
- ❖ There should be strong evidence of its validity, good reliability and internal consistency.
- ❖ There should be responsiveness to changes in health status and QoL [16].

The QLDS is a widely used depression-specific instrument that satisfies the above-mentioned requirements of a good QoL measure. The questionnaire has been adapted and re-validated for use in almost 20 countries worldwide in the last few years. [98].

4.2.2. Hungarian adaptation of the QLDS

4.2.2.1. Patients and study design (procedures)

The Hungarian adaptation of the QLDS consisted in three stages:

1. Translation of the questionnaire into Hungarian from the original English
2. Field-testing of the translated QLDS for face and content validity
3. Assessment of the psychometric properties of the Hungarian QLDS

Translation

In the translation process, the dual panel approach was employed. This methodology involves two separate translation panels (bilingual and lay) and focuses on the conceptual equivalence of the target questionnaire to the original, rather than attempting to achieve linguistic or semantic equivalence.

The aim of the bilingual panel was to produce an initial translation for each of the measure's 34 items. The panel consisted of 5 Hungarians fluent in the English language. Emphasis was placed on achieving conceptual equivalence and cultural relevance of the translated items.

The lay panel (composed of 7 monolingual Hungarians without academic education) considered the translation provided by the bilingual panel to ensure that the wording of the items would be appropriate for an average patient.

Field-testing of the translated QLDS for face and content validity

The aim of the field-test interviews was to assess the face and content validity of the translated QLDS. Field-test interviews were conducted by myself with 25 inpatients with

depression at the Department of Psychiatry (affiliated to the University of Szeged Faculty of Medicine). The patients were diagnosed as depressed according to the diagnostic criteria of ICD-10 by a psychiatrist. In the course of the field-test interview, the patients were asked to provide demographic information and then to complete the QLDS. The patients were observed while they completed the questionnaire and were then asked a number of questions concerning the suitability and acceptability of the QLDS.

Assessment of the psychometric properties of the Hungarian QLDS

The psychometric properties of the Hungarian measure were tested by means of a postal survey with 50 out-patients with depression. Patient recruitment was arranged during regular psychiatric appointments at the Department of Psychiatry (affiliated to the University of Szeged, and Semmelweis University, Budapest). The ICD-10 diagnosis was established by the psychiatrist at the same visit. The patients who agreed to take part in the study were given a package consisting of the Hungarian QLDS, a demographic questionnaire, the Shortened Beck Depression Inventory (BDI) and the Nottingham Health Profile (NHP). The participants completed the questionnaires at home (Time 1) and sent them back to the researcher. Two weeks after receipt of the completed questionnaires, the participants were sent a similar package by post (Time 2).

In order to achieve a homogeneous sample, patients were excluded from the study if they had a diagnoses other than F30-F39 and F4120 (mixed anxiety and depressive disorder) according to the ICD-10 diagnostic criteria system.

The study was approved by the appropriate institutional ethical committee and all patients provided their written consent prior to study entry.

4.2.2.2. Instrument used

The ***QLDS*** consists of 34 items with dichotomous responses (’yes/no’) scored 0 or 1. The total score on the scale can therefore range from 0 to 34, with a higher score indicating a lower QoL [43, 44].

The ***demographic questionnaire*** collected sociodemographic information about the patients and asked the respondents to rate their general health and the severity of their depression.

The ***Nottingham Health Profile*** (NHP) is a generic measure containing 38 items in 6 sections (physical mobility, pain, emotional reactions, energy level, social isolations and sleep). The scores in each of the sections can vary from 0 to 100, with a higher score indicating greater distress in that section. An index of distress (the NHPD) can be calculated from the responses

to the NHP. This scale, which consists of 24 items, can vary from 0 to 24, with a higher score indicating greater distress [30, 31, 40].

The severity of depression was determined with the 9-item Shortened ***Beck Depression Inventory*** (BDI). Individual item scores range from 0 to 3 and the total scores from 0 (no depression) to 60 (severe depression) [99-101].

4.2.2.3. Statistical analysis

Reliability (determined by establishing the test-retest reliability of the measure) was expressed as a two-tailed Spearman's coefficient. The test-retest reliability of a measure is an estimate of its reproducibility over time when no change in condition has taken place. It is assessed by correlating scores on the QLDS collected through two separate administrations. A high correlation indicates that the instrument produces low random measurement error, with a minimum value of 0.85 required [16, 39].

The ***internal consistency*** of the instrument was calculated by using the Cronbach's α. A value above 0.70 indicates that the items in the scale are adequately related [16, 39].

Evidence of construct validity for the Hungarian QLDS was provided by estimating the ***convergent and divergent validity***, assessed by relating the scores on the QLDS to those on the NHP. It was predicted that the QLDS scores would be more closely related to the NHP scores in the emotional reactions and social isolation sections than to those in the pain and physical mobility sections. The two-tailed Spearman's coefficient was used to assess the level of this association.

The ***discriminative validity*** of the QLDS was assessed by determining the scale's ability to distinguish between groups of respondents differing according to the perceived health status, the perceived severity of depression (demographic questionnaire) and the severity of depression measured by the BDI. Kruskal-Wallis tests were employed to compare different subgroups. The ability of the QLDS to discriminate between participants on the basis of their ICD severity diagnosis (clinically depressed or in remission) was tested by using the Mann-Whitney U test.

p values < 0.05 were considered statistically significant. Statistical analyses were performed with the 13.0 version of SPSS program package.

4.2.3. Clinical performance of the Hungarian QLDS in measuring QoL for patients with depression

4.2.3.1. Patients and study design

The subjects were 48 outpatients recruited by psychiatrists during regular psychiatric appointments at three psychiatric departments (in Szeged, Pécs and Budapest). All these patients were diagnosed with a depressive disorder by the psychiatrist according to the ICD-10 diagnostic criteria system. The patients were requested to complete a questionnaire package consisting of the Hungarian QLDS, a demographic questionnaire, the shortened BDI and the NHP. The severity of depression was established on two psychiatrist-administered scales: the Hamilton Depression Rating Scale (HAM-D) and the Montgomery-Asberg Depression Rating Scale (MADRS). Questionnaires were completed and the scores for each scale were collected after a 4-5-week follow-up period, during the next psychiatric appointment.

Written informed consent was obtained from all subjects, and the study was approved by the institutional ethical committee at all sites.

4.2.3.2. Statistical analysis

Comparative analysis of the obtained QLDS scores regarding gender and subtypes of depression was performed with the Mann-Whitney U test.

The differences in QoL between groups of respondents who differed in severity of depression as measured by the HAM-D were assessed with the Kruskal-Wallis test.

The two-tailed Spearman's coefficient was used to assess the correlation between the psychiatrist's rating of the severity of depression (HAM-D and MADRS) and the patient's perception of the HRQoL (QLDS and NHP) and of the severity of depression (BDI). Because of the multiplicity, a more conservative α-value of 0.01 was used to test significance.

The hypothesis that a clinical improvement in depression rating would result in an improvement in QoL was tested with the two-tailed Spearman correlation between the changes in the HAM-D and MADRS score and the QLDS score.

5. RESULTS

5.1. Drug utilization study

5.1.1. National trend of antidepressant consumption

The nationwide use of antidepressants progressively increased in Hungary during the studied period, from 4.03 in 1993 to 25.71 DDD/1000 inhabitants/day in 2006. It means a more than 6-fold increase as compared to the base year (*Figure 1*).

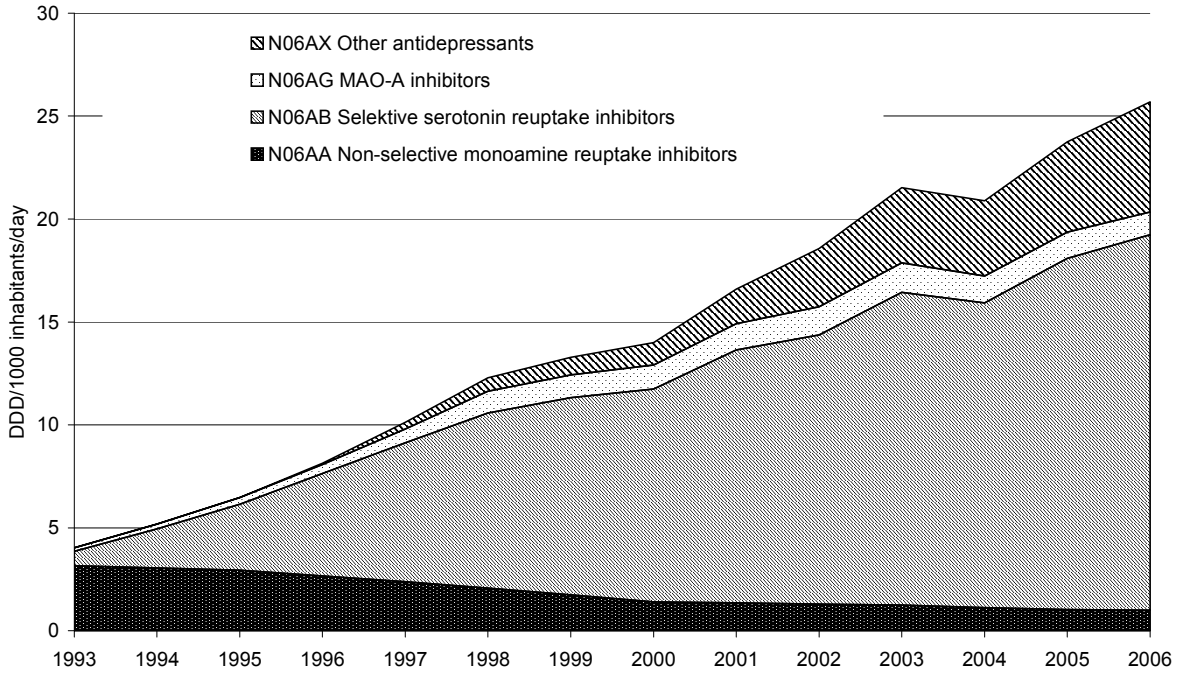

Figure 1. Structure of antidepressant consumption in Hungary

An extensive increase in the number of registered products was observed during the studied 14-year period. Whereas 23 antidepressant preparations were on the Hungarian market at the beginning of the study, at the end this number had risen to 133. This was not merely a result of the broader selection of active ingredients (11 new substances were introduced), but rather reflected the availability of generic drugs.

After the marketing authorization of SSRIs, not only the volume of antidepressant consumption, but also the structure altered considerably. The changes in the utilization of active ingredients are demonstrated by the trend analysis in *Table 4*.

The sales of the TCAs decreased slightly during the studied period (from 3.17 DDD/1000 inhabitants/day to 1.00 DDD/1000 inhabitants/day). The results of the trend analysis indicated that the usage of clomipramine underwent a moderate increase, and was responsible for the highest consumption in this group. However, the use of amitriptyline declined, from 0.85 in 1993 to 0.07 DDD/1000 inhabitants/day in 2000, it had a 3-fold elevation to 0.21 DDD/1000 inhabitants/day in the last 6 years. Imipramine, dibenzepine and maprotiline exhibited continuously decreasing consumption. Nevertheless, maprotiline remained the second most prominent active ingredient in this group (*Figure 2*; see page 20)

	First year*	***2006***	***Diff.***	***Diff.%***	***R***	***p***
N06A Antidepressants	4.03	25.71	21.68	418	0.991	<0.05
N06AA Non-selective monoamine reuptake inhibitors	3.17	1.01	2.16	-68	-0.967	<0.05
N06AA02 imipramine	0.35	0.06	0.29	-82	-0.911	<0.05
N06AA04 clomipramine	0.06	0.44	0.38	633	0.604	<0.05
N06AA06 trimipramine	0.15	0.02	0.13	-86	-0.902	<0.05
N06AA08 dibenzepin	0.46	0.05	0.41	-89	-0.948	<0.05
N06AA09 amitriptyline	0.85	0.21	0.64	-75	-0.878	<0.05
N06AA21 maprotiline	1.37	0.21	1.16	-85	-0.958	<0.05
N06AB Selective serotonin reuptake inhibitors	0.69	18.24	17.55	2543	0.992	<0.05
N06AB03 fluoxetine	0.18	1.23	1.05	583	0.533	<0.05
N06AB04 citalopram	0.60	5.75	5.15	858	0.958	<0.05
N06AB05 paroxetine	0.06	5.12	5.06	8433	0.977	<0.05
N06AB06 sertraline	0.04	4.70	4.66	11650	0.984	<0.05
N06AB08 fluvoxamine	0.67	0.60	0.07	10	0.231	0.427
N06AB10 escitalopram	0.015	0.83	0.815	5433	0.871	0.129
N06AG MAO-A inhibitors	0.17	1.10	0.93	547	0.869	0.143
N06AG02 moclobemide	0.17	1.10	0.93	547	0.869	0.143
N06AX Other antidepressants	0.05	5.35	5.3	10600	0.943	<0.05
N06AX03 mianserin	0.05	0.59	0.54	1080	0.870	<0.05
N06AX05 trazodone	0.01	0.01	0	0	0.283	0.327
N06AX11 mirtazapine	0.10	1.62	1.52	1520	0.855	<0.05
N06AX14 tianeptine	0.18	0.89	0.71	394	0.903	<0.05
N06AX16 venlafaxine	0.001	1.51	1.50	150000	0.864	<0.05
N06AX18 reboxetine	0.004	0.09	0.086	2150	0.731	<0.05

* first year when consumption was indicated according to the data of the wholesalers

Table 4. Trend analysis of antidepressant consumption in Hungary in the period 1993-2006

A marked elevation was observed in the consumption of SSRIs (from 0.69 to 18.24 DDD/1000 inhabitants/day). The share of this group in the total consumption of antidepressants gradually increased from 17% to 71% by 2006 (*Figure 3;* see page 21). The usage of sertraline and paroxetine displayed the most marked increases among the SSRIs. Citalopram was the most frequently used active ingredient in this group at the end of the studied period. Fluvoxamine was the most rarely used SSRI; its consumption remained

relatively unchanged throughout the studied 14-year period. The utilization of fluoxetine rose 9-fold from 0.18 to 1.62 DDD/1000 inhabitants/day in the 5 five years, but then remained relatively constant. Since the marketing authorization of escitalopram occurred at the end of 2002, a measurable consumption was indicated only during the last 2 years of the studied period.

From the MAO-A inhibitors group, merely moclobemide is registered in Hungary, and its consumption demonstrated a slow, moderate increase (from 0.17 to 1.10 DDD/1000 inhabitants/day). It accounted for only the 4% of the total antidepressant consumption.

A considerable utilization of the "other antidepressants" (N06AX group) was detected for 1996, due to mianserin (0.35 DDD/1000 inhabitants/day in 1997) at that time. The consumption of this group rose to 5.35 DDD/1000 inhabitants/day in 2006 (i.e. 20% of the total consumption). Mirtazapine, venlafaxine and tianeptine were the most widely used agents in this group (Figure 4; see page 22).

The DU90% segment underwent an enlargement during the last 14 years. While only 6 active ingredients accounted for 90% of the use in 1993, this number had risen to 10 in 2006 (*Figure 5*).

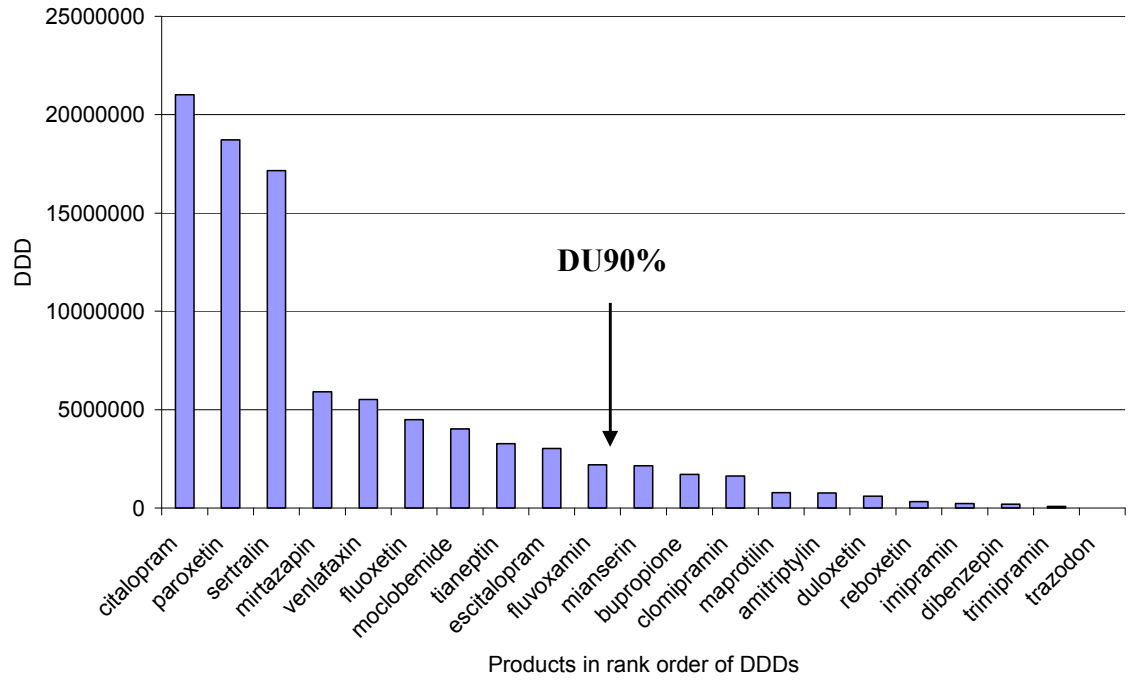

Figure 5. Antidepressant consumption in 2006, DU90% segment

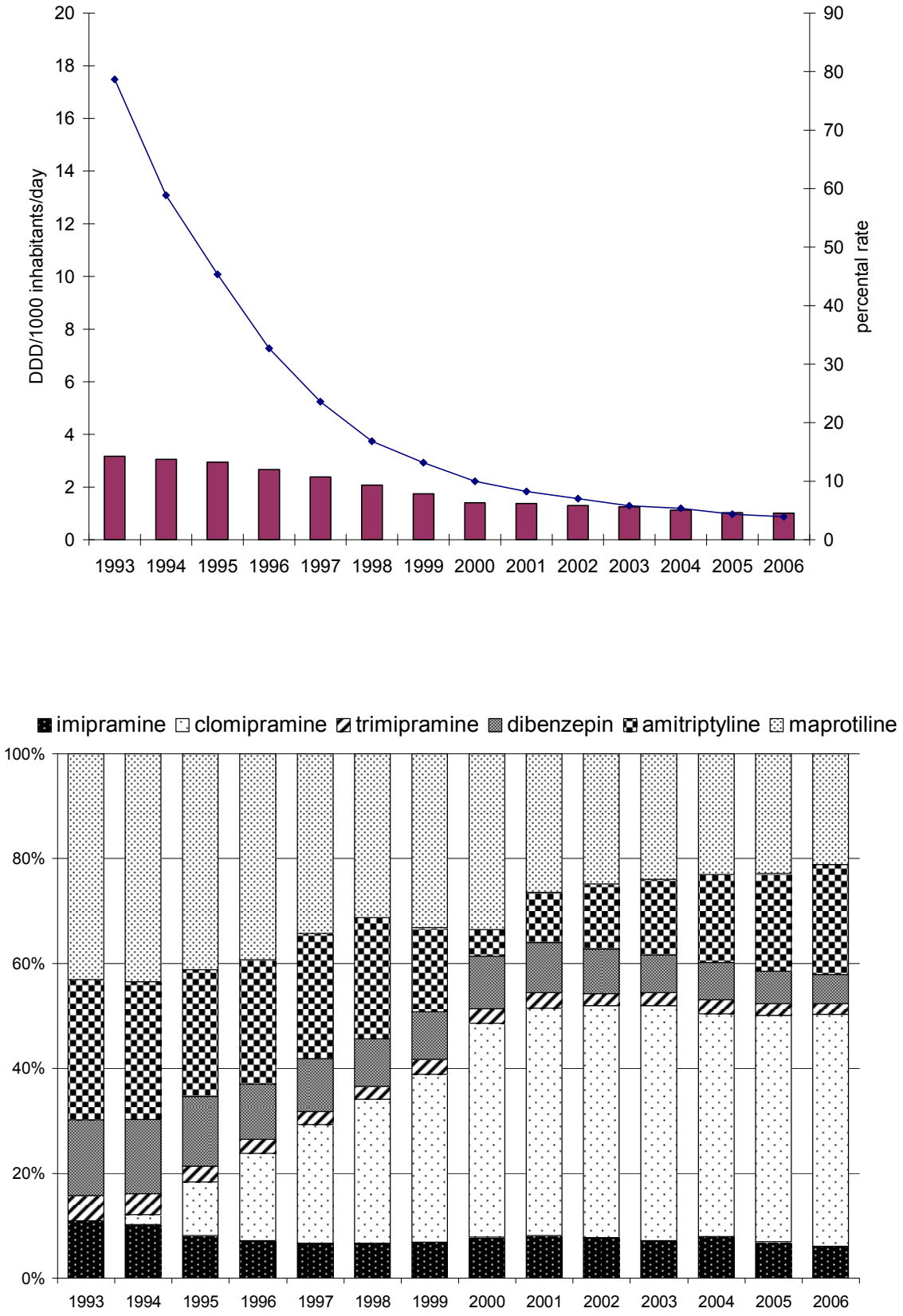

Figure 2. Consumption of non-selective monoamine reuptake inhibitors (N06AA): percental rate of total consumption, and structure

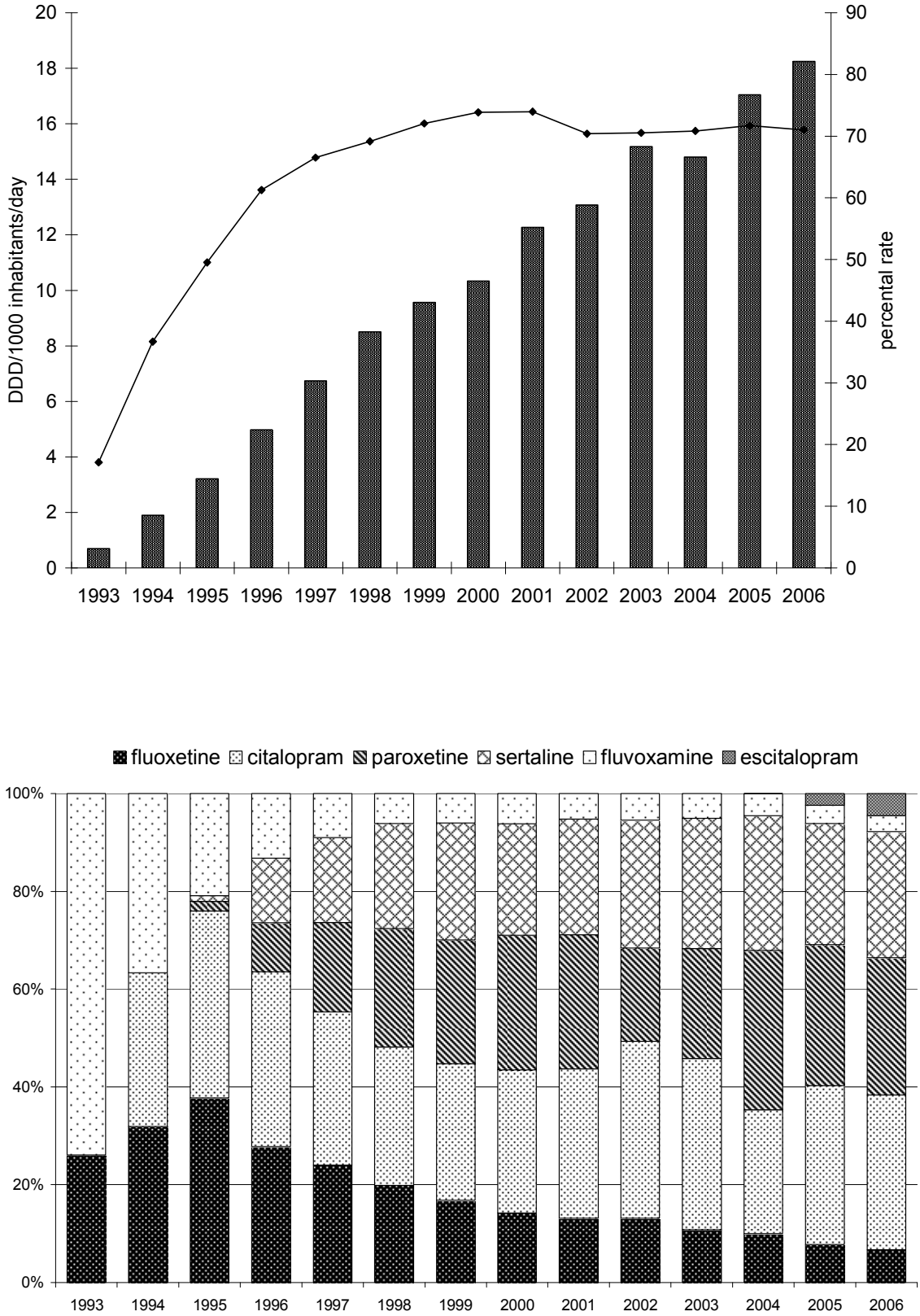

Figure 3. Consumption of selective serotonin reuptake inhibitors (N06AB): percental rate of total consumption, and structure

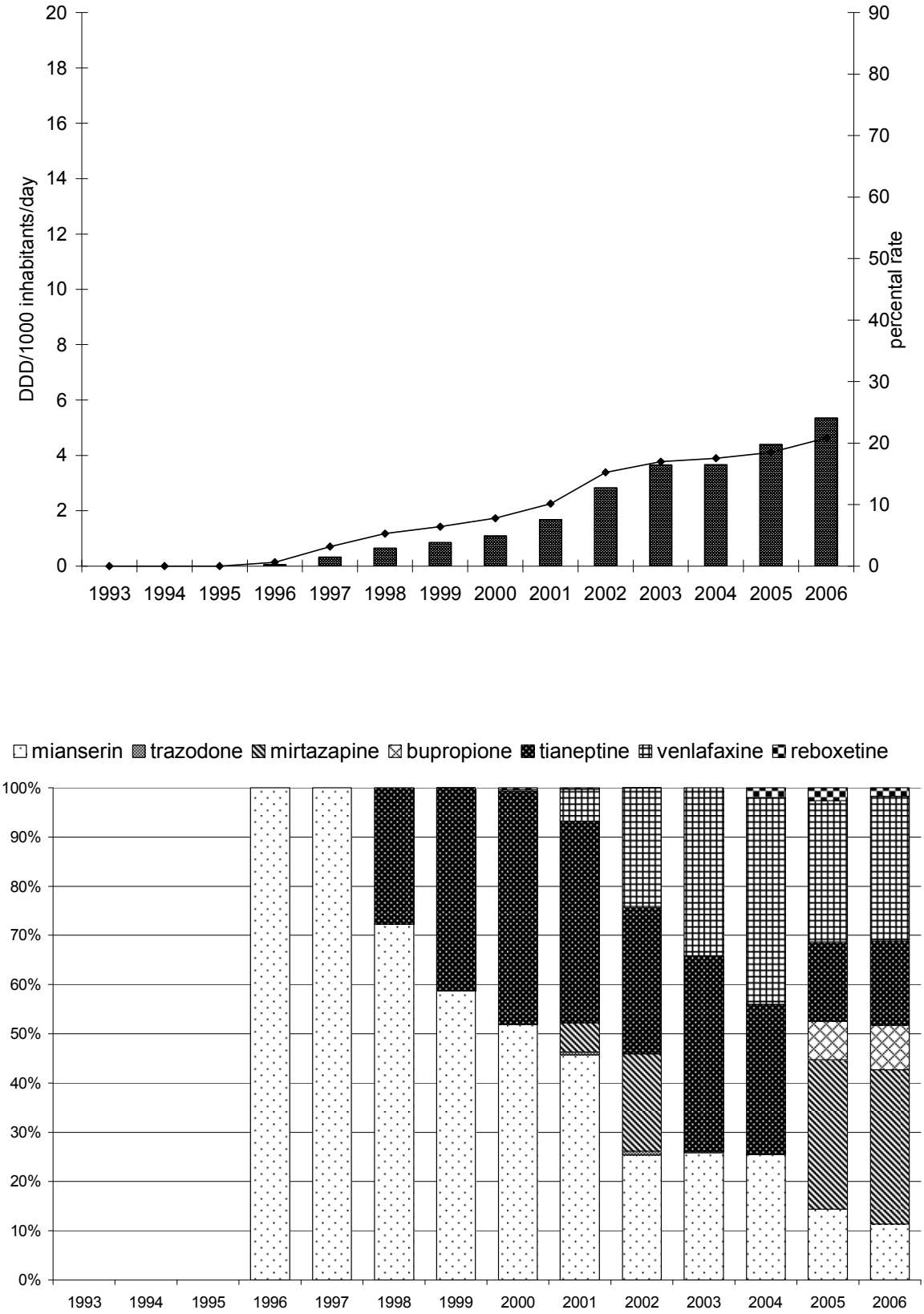

Figure 4. Consumption of" other antidepressants" (N06AX): percental rate of total consumption, and structure

5.1.2. Regional differences in antidepressant consumption

The antidepressant consumption in the 19 counties and the capital (Budapest) exhibited a marked elevation during the studied period, similarly to the national trend. However, significant quantitative differences were observed between certain counties. For each year in the period 1993-2006, there was a 1.6-2.6 (min.-max.)-fold difference between the regions with the lowest and the highest antidepressant consumption (*Table 5*).

The ranking of the individual regions according to their total antidepressant consumption was basically the same throughout the 14-year study period (Spearman, $0.533 < r < 0.988$; $p < 0.05$ for all years tested); hence certain regions were permanently high consumers, whereas others remained permanently low consumers. Budapest, Békés, Bács-Kiskun and Csongrád counties generally proved to be the most prominent antidepressant consumers. However, Győr-Moson-Sopron took over the leading position with the highest antidepressant usage in 2005 and 2006. Zala, Szabolcs-Szatmár-Bereg, Jász-Nagykun-Szolnok and Borsod-Abaúj-Zemplén counties were the lowest consumers during the studied period.

	Antidepressant utilization (DDD/1000 inhabitants/day)				***Suicide rate (suicide/100000 inhabitants)***			
County	***1993***	***2006***	***Diff.***	***Diff.%***	***1993***	***2006***	***Diff.***	***Diff.%***
Bács-Kiskun	4.7	29.1	24.4	519	50.4	34.3	-16.1	-31.9
Baranya	3.2	28.9	25.7	803	32.4	23.9	-8.5	-26.2
Békés	4.0	29.9	25.9	647	47.9	34.6	-13.3	-27.7
Borsod-Abaúj-Zemplén	3.1	19.0	15.9	513	36.4	25.5	-10.9	-29.9
Budapest	5.3	26.8	21.5	405	28.1	18.4	-9.7	-34.5
Csongrád	4.9	29.9	25.0	510	50.1	35.6	-14.5	-28.9
Fejér	2.0	22.1	20.1	1005	32.4	23.3	-9.1	-28.0
Győr-Moson-Sopron	3.5	30.8	27.3	780	19.0	19.5	0.5	2.6
Hajdú-Bihar	4.3	24.0	19.7	458	46.8	36.2	-10.6	-22.6
Heves	4.8	28.8	24.0	500	31.9	20.3	-11.6	-36.4
Jász-Nagykun-Szolnok	4.0	19.4	15.4	385	45.2	31.8	-13.4	-29.6
Komárom-Esztergom	2.3	22.5	20.2	878	36.8	19.4	-17.4	-47.3
Nógrád	4.1	21.5	17.4	424	28.8	23.4	-5.4	-18.7
Pest	3.7	25.6	21.9	592	36.1	20.1	-16.0	-44.3
Somogy	2.9	22.1	19.2	662	33.3	25.2	-8.1	-24.3
Szabolcs-Szatmár-Bereg	2.3	21.9	19.6	852	47.0	24.1	-22.9	-48.7
Tolna	3.4	20.8	17.4	512	45.5	21.9	-23.6	-51.8
Vas	4.4	24.4	20.0	454	19.4	16.3	-3.1	-15.9
Veszprém	2.8	21.6	18.8	671	23.8	20.9	-2.9	-12.2
Zala	2.4	18.0	15.6	650	30.5	19.4	-11.1	-36.4
Total (national level)	4.0	25.7	21.7	542	35.7	24.4	-11.3	-31.6

Table 5. Regional differences in antidepressant consumption and suicide rate

The most pronounced elevation in antidepressant consumption occurred in Fejér country (1005%, from 2.0 in 1993 to 22.1 DDD/1000 inhabitants/day in 2006), whereas Jász-Nagykun-Szolnok county showed the lowest elevation, 385% (from 4.0 in 1993 to 19.4 DDD/1000 inhabitants/day in 2006).

Basically, the structure of antidepressant consumption in the counties was similar to the national pattern. The increasing use of SSRIs and "other antidepressants" the usage of TCAs pushed into the background.

Both at the start and at the end-point of the study, all the antidepressant classes displayed a large interregional variation in their use (max./min. ratio > 2) (*Table 6*).

The relative use of the different antidepressant groups did not differ between the regions. The number of active ingredients in the DU90% ranged from 8 to 10 at the end of the studied period. The pattern of the regional DU90% segment was similar to that observed for the total national consumption (*Figure 5*).

		1993				***2006***			
		DDD/1000 inhabitants/day				***DDD/1000 inhabitants/day***			
		Mean ± SD	***Min.***	***Max.***	***Ratio max./min.***	***Mean ± SD***	***Min.***	***Max.***	***Ratio max./min.***
N06A	***Antidepressants***	3.65 ± 1.01	2.01	5.3	2.64	24.32 ± 4.02	18.02	30.82	1.71
N06AA	***Non-selective monoamine reuptake inhibitors***	2.92 ± 0.89	1.50	4.16	2.79	0.92 ± 0.24	0.58	1.58	2.73
N06AB	***Selective serotonin reuptake inhibitors***	0.57 ± 0.21	0.28	1.09	3.91	17.09 ± 2.70	12.48	21.43	1.72
N06AG	***MAO-A inhibitors***	0.15 ± 0.06	0.03	0.25	8.33	1.13 ± 0.46	0.60	2.12	3.54
N06AX	***Other antidepressants***	n.c.*				5.17 ± 1.20	3.56	7.44	2.09

* not calculable (not detectable consumption)

Table 6. Mean, minimum and maximum regional antidepressant consumption in 1993 and 2006

The only determinant among the psychiatric service indicators which showed a significant association with the antidepressant consumption at the regional level was the number of attendances in outpatient departments (*Table 7*). No correlation was found with the number of outpatient departments, the number of new patients taken into care per 10000 inhabitants, or the number of hospital admissions. Moreover, the number of alcohol-abuse disorders did not indicate a significant correlation with the antidepressant consumption. There was a trend towards a positive association with the GDP per inhabitant, but this did not reach statistical

significance in any year. The regional unemployment rates likewise did not indicate a significant association with the antidepressant use.

	Antidepressant consumption (r_{min}; r_{max})	***Suicide rate*** (r_{min}; r_{max})
Economic factors:		
Unemployment rate	-0.140; -0.441	0.014; 0.484
GDP/inhabitant	0.232; 0.547	-0.301; -0.443
Psychiatric service indicators:		
Number of outpatient departments	0.268; 0.440	-0.093; -0.293
Number of attendances	0.445; 0.584	-0.009; -0.231
New patients taken into care per 10000 inhabitants	0.078; 0.132	0.055; 0.268
Number of patients sent to hospital	0.056; 0.335	-0.111; -0.309
Alcohol abuse and addiction	0.017; 0.293	0.054; 0.271

Table 7. Associations between antidepressant consumption or suicide rate and various determinants

5.1.3. Relationship between antidepressant consumption and suicide rate

The national suicide rate has undergone a steady, moderate decline, from 35.7 suicides/100000 inhabitants/year in 1993 to 24.4 suicides/100000 inhabitants/year in 2006 (*Figure 6*).

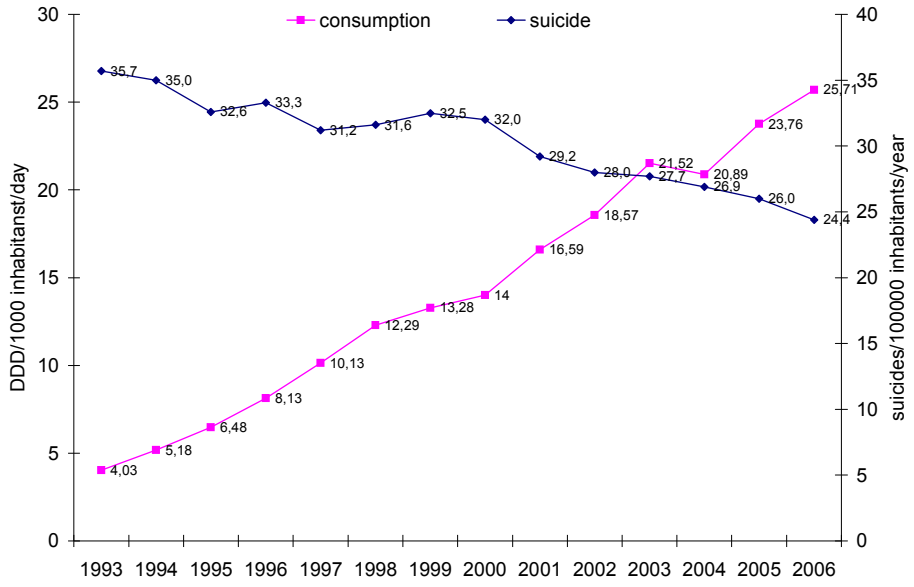

Figure 6. Antidepressant consumption and suicide rate in Hungary, 1993-2006

Significant differences were found between regions as regards the suicide rate (*Table 5*). For each year in the period 1993-2006, there was a 2.2-3.8 (min.-max.)-fold difference between the regions with the lowest and the highest suicide rate. An increasing suicide rate was experienced only in the case of Győr-Moson-Sopron county. The analysis of the regional differences in suicide rates demonstrated heterogeneity between the western and southern regions (*Figure 7*). The suicide rate was found to be about 3 times higher in the central and southern part of Hungary than in the west. The correlation between antidepressant consumption and suicide rate did not prove to be statistically significant in terms of the regional data (r_{min} = -0.053; r_{max} = -0.314). There was a trend towards a negative relationship between the psychiatric service indicators and the suicide rate, but this did not reach the level of statistical significance (*Table 7*). Moreover, the GDP per inhabitant was negatively associated with the regional suicide rate. No significant correlation was found for the other tested determinants at a regional level, e.g. the unemployment rate, or alcohol-abuse disorders.

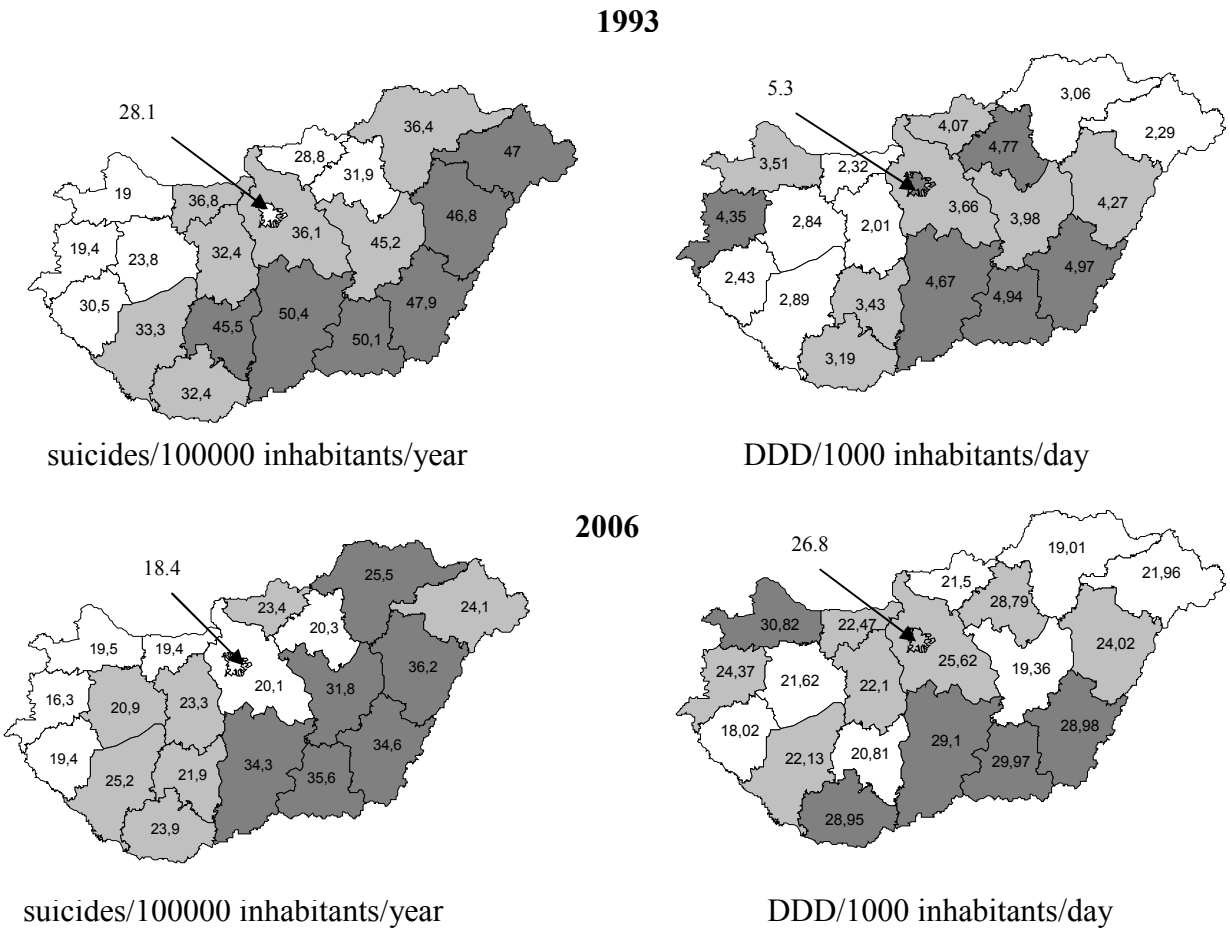

Figure 7. Regional suicide rates and antidepressant consumption in 1993 and 2006

5.1.4. Hospital antidepressant consumption

The hospital antidepressant consumption displayed a significant elevation at each of the four university-affiliated psychiatric departments during the studied 5-year period (1999-2003). However, considerable quantitative differences were noted between certain departments (*Figure 8*).

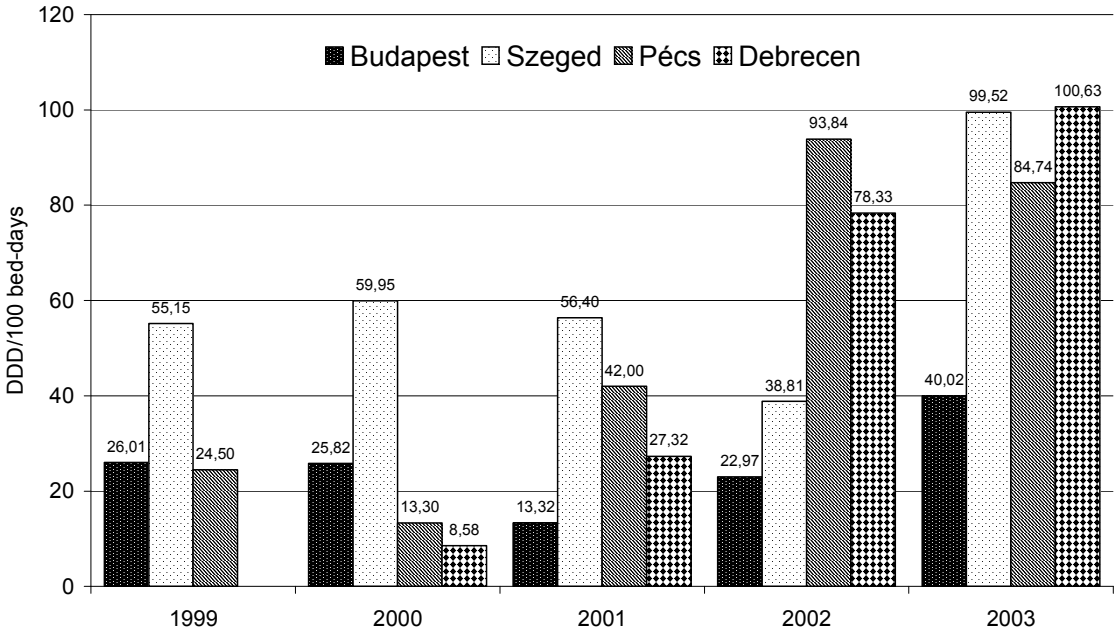

Figure 8. Antidepressant consumption at the four university-affiliated Psychiatric Departments

The following significant differences were found in relation to the structure of antidepressant consumption between the four psychiatric departments:

- The numbers of active ingredients in the DU90% segment were significantly different in Szeged and Budapest (*Table 8*).
- The Psychiatric Department in Budapest reported the most considerable use of TCAs (mean: 9.1 ± 2.1 DDD/100 bed-days).
- While clomipramine was the most prominent TCA at the Psychiatric Department in Budapest, Debrecen and Szeged, dibenzepine and maprotiline were preferred in Pécs.
- As concerns the use of SSRIs, the trends moved in parallel at the four Departments with the exception of escitalopram. Exclusively, the Psychiatric Department in Pécs indicated a detectable escitalopram consumption.

- Budapest proved to be the lowest consumer of "other antidepressants", which reached only 5.1 DDD/100 bed-days in 2003, whereas the use of this group rose to 29.7 in Pécs, to 38.8 in Szeged, and to 28.9 DDD/100 bed-days in Debrecen.

Szeged	*Debrecen*	*Pécs*	*Budapest*
Venlafaxine	Citalopram	Paroxetine	Citalopram
Citalopram	Paroxetine	Venlafaxine	Paroxetine
Mirtazapin	Tianeptine	Mirazapine	Clomipramine
Sertraline	Mianserin	Sertraline	Mianserin
Paroxetine	Sertraline	Escitalopram	
Fluoxetine	Venlafaxine	Citalopram	
Moclobemide			

Table 8. DU90% segments at the four Psychiatric Departments, 2003

5.2. Polypharmacy among psychiatric patients

In the studied group (n = 984) 33.6% of the patients (331) were found to be on 5 or more drugs.

The mean age of the PP group was 61 (±15.94) years, which was significantly ($p < 0.001$) higher than the 41 (±15.21) years mean age of the non-PP group (*Table 9*).

	PP group n = 331	***Non–PP group n = 653***
***n* (%)**	33.6	66.4
Female (%)	75	64
Male (%)	25	36
Mean age (±SD)	60.8 (±15.94)*	41.5 (±15.21)
Mean number of drugs used (±SD):		
total	7.3 (±2.35)	2.8 (±0.93)
psychiatric	3.2 (±1.11)*	2.4 (±0.85)
other	4.1 (±2.54)	0.4 (±0.67)

* Statistically significant PP group vs Non-PP group; $p < 0.001$, t-test

Table 9. Patient characteristics and mean number of drugs used

Both groups were characterized by a female dominance. The mean age of the females was 52 (±16.68) years, which was significantly ($p < 0.001$) higher than the 47 (±18.05) years mean age of males among all the patients involved in the study.

In the overall group involved in the study, 70% of the patients were prescribed 2 or 3 psychopharmacons simultaneously.

In the PP group, the mean number of drugs used concurrently and chronically was 7.3 (±2.35; max = 16), of which the mean number of drugs with psychiatric indications was 3.2 (±1.11)

(*Table 9*). In the non-PP group, the mean number of drugs used concurrently and chronically was 2.8 (±0.93), of which the mean number of drugs with psychiatric indications was 2.4 (±0.85).

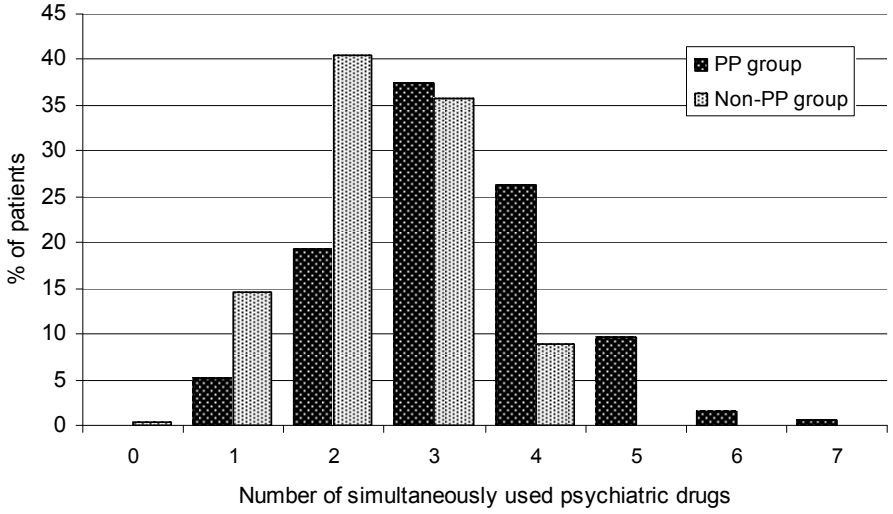

Figure 9. Distribution of patients as concerns the number of psychiatric drugs used in the PP group and the non-PP group

Figure 9 depicts the distribution of the patients concerning the number of psychiatric drugs used simultaneously.

The mean number of drugs with psychiatric indications among the patients in the PP group was significantly ($p < 0.001$) higher than that among the patients in the non-PP group. The number of psychiatric drugs in the PP group did not increase as the number of concurrently used drugs increased, the average number remaining at about 3. The linear regression analysis revealed that the mean number of psychiatric drugs was not significantly associated with the increasing number of drugs used ($r = 0.45$; $p = 0.15$; $b = 0.07$; $a = 2.71$) (*Figure 10*).

The prevalence of monotherapy in psychiatric treatment was 5.1% in the PP group and 14.5% in the non-PP group.

The mean value of "other medication" (those with a non-psychiatric indication) was 4.1 (±2.54; max. = 13) in the PP group, and 0.4 (±0.67; max. = 3) in the non-PP group.

The number of drugs used (both psychiatric and "other" medications) in the two genders did not indicate a significant difference in either group.

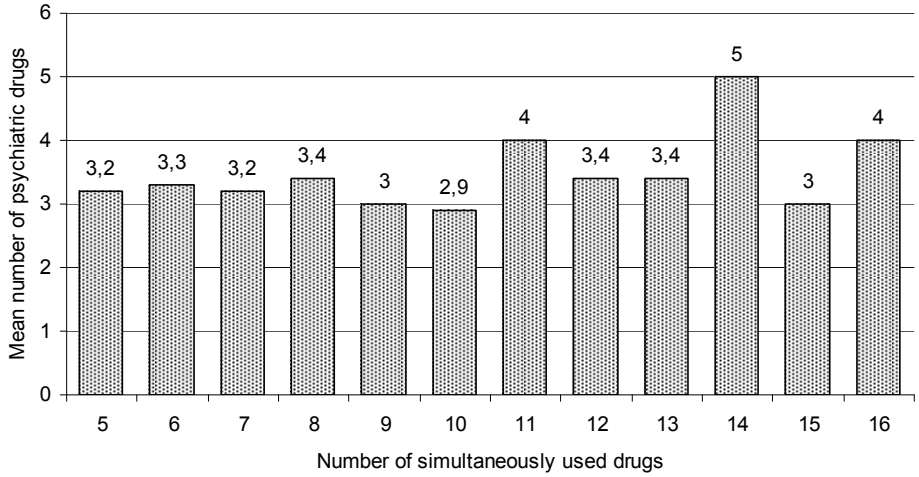

Figure 10. The average number of psychiatric drugs used by polypharmacy patients

Logistic regression demonstrated a significant correlation between the polypharmacy and the assessed factors (comorbitity, age and gender). The value of the constant of the logistic regression equation was a = -4.8803. According to this analysis, comorbidity is the most important predisposing factor for PP among the investigated factors (OR = 3.5670). The value of odds ratio (OR) for gender proved to be 1.4480. *Exp* b_{age} (1.0571) is the increase in the OR of becoming polypharmacy for every increase of 1 year age (*Table 10*).

Variable	b_i	***S.E.***	$Expb_i$***=OR***	***95% CI***		***p***
Gender	0.3702	0.1768	1.4480	1.0240	2.0476	0.0362
Age	0.0555	0.0053	1.0571	1.0462	1.0680	0.0000
Comorbidity	1.2717	0.1581	3.5670	2.6164	4.8630	0.0000

Table 10. Edited output from logistic regression analysis

The most common psychiatric diagnoses are the different types of mood disorders (F30-F39 according to the ICD-10 diagnostic criteria system) in both groups: PP group: 49%; non-PP group: 48% (*Table 11*). 92% of the patients with a diagnosis of depression were on monotherapy in terms of antidepressant use, and only 7.7% were prescribed 2 antidepressants simultaneously.

Diagnosis	*ICD-10*	*PP group (%)*	*Non-PP group (%)*
Mood disorders	F30-F39	49	48
Organic, including symptomatic, mental disorders	F00-F09	40	10
Neurotic, stress-related and somatoform disorders	F40-F48	27	33
Schizophrenia, schizotypal and delusional disorders	F20-F29	12	29
Disorders of adult personality and behaviour	F60-F69	4.3	14

Table 11. The most common psychiatric diagnoses

Piracetam leads the toplist of psychiatric drugs in the PP group. Antidepressants (citalopram and carbamazepine) and anxiolytics (alprazolam and clonazepam) are the most frequently used psychiatric drugs in both groups (*Table 12*). Carbamazepine is utilized as a mood stabilizer in psychiatry. Drugs with a cardiovascular indication lead the toplist of "other" medication (in both groups), which is justified by the fact that cardiovascular diseases are the most common diagnoses among the comorbidity. 68% of the patients suffered from cardiovascular disease.

Polypharm group					
Psychiatric drugs			***Other drugs***		
ATC		***% of users***	***ATC***		***% of users***
N06BX03	Piacetam	36	C07AB02	Metoprolol	34
N05BA12	Alprazolam	33	C07AA02	Enalapril	26
N03AB01	Clonazepam	32	B01AA02	Acetylsalicylic acid	24
N06AB04	Citalopram	22	A02BA03	Famotidine	21
N03AF01	Carbamazepine	16	C04AD03	Pentoxyphylline	10
Non-polypharm group					
Psychiatric drugs			***Other drugs***		
ATC		***% of users***	***ATC***		***% of users***
N03AB01	Clonazepam	34	C07AB02	Metoprolol	4
N05BA12	Alprazolam	27	C07AA02	Enalapril	3
N03AF01	Carbamazepine	14	A02BA03	Famotidin	2,2
N06AB04	Citalopram	12	H03AA01	L-thyroxine	1,9
N05AH03	Olanzapine	11	A06AB06	Sennosides	1,8

Table 12. List of most frequently used drugs

5.3. Hungarian adaptation of the QLDS

5.3.1. Translation

No major difficulties were experienced in producing conceptually equivalent items. The bilingual panel was unable to make a decision on 6 items and 2 alternative translations of each were sent for consideration by the lay panel. The lay panel had no problem with the translations provided and was able to select the most appropriate of the alternative versions presented to them.

5.3.2. Field-test interviews

The QLDS was completed satisfactory by the field-test sample (n = 25) with no missing responses. The mean time required to complete the QLDS was 9.2 (±3.9) min. The sociodemographic characteristics of the field-test sample and the distribution of the patients according to the depression subtypes are shown in *Table 13*.

	Field-test sample (n=25)	***Postal survey sample (n=50)***
Gender	***n (%)***	***n (%)***
Male	7 (28)	13 (26)
Female	18 (72)	37 (74)
Age (years)		
Range	22-68	23-80
Mean (SD)	46.9 (12.0)	48.7 (13.2)
Marital status	***n (%)***	***n (%)***
Married	16 (64)	30 (60)
Divorced	8 (32)	7 (14)
Single	-	9 (18)
Widowed	1 (4)	4 (8)
Employment status	***n (%)***	***n (%)***
Employed (full/part-time)	6 (24)	12 (24)
Disability pensioner	14 (56)	19 (38)
Retired	2 (8)	3 (6)
Long-term sick	2 (8)	7 (14)
Homemaker	1 (4)	3 (6)
Unemployed	-	5 (10)
Student	-	1 (2)
Duration of illness (years)		
Range	1-30	0.5-38
Mean (SD)	10.7 (7.8)	10.2 (8.9)
Median	10.0	8.0
Subtypes of depression	***n (%)***	***n (%)***
Organic mood disorder	1 (4)	1 (2)
Bipolar affective disorder	2 (8)	5 (10)
Unipolar affective disorder	15 (60)	33 (66)
Persistent mood disorder	2 (8)	1 (2)
Mixed anxiety and depressive disorder	5 (20)	10 (20)

Table 13. Details of the field-test and postal survey samples

5.3.3. Assessment of psychometric properties (postal survey)

Details of the postal survey participants (n = 50) are shown in Table 13. The scores obtained on the QLDS, NHP and BDI are presented in *Table 14*.

No significant differences in QLDS scores were detected between participants who were above and below the median sample age (51 years) or between males and females (Mann-Whitney U test: $p > 0.05$ at each time point).

	Time 1			*Time 2*		
	Mean (SD)	***Range***	***Median (IQR)***	***Mean (SD)***	***Range***	***Median (IQR)***
QLDS	14.4 (5.6)	20.0	13.0 (10.0-19.2)	14.4 (5.8)	19.0	13.0 (10.0-20.0)
BDI	11.5 (5.8)	49.0	28.0 (13.0-38.0)	11.6 (6.1)	51.0	27.0 (15.25-36.5)
NHPD	10.5 (5.6)	22.0	10.0 (5.75-15.2)	10.6 (5.6)	22.0	11.0 (5.0-15.0)
energy level	65.3 (35.6)	100.0	66.6 (33.3-100.0)	68.0 (36.8)	100.0	66.6 (33.3-100.0)
pain	21.2 (26.6)	75.0	12.5 (0.0-37.5)	20.2 (26.5)	87.5	6.25 (0.0-37.5)
emotional reactions	50.9 (29.8)	100.0	44.4 (22.2-77.7)	51.5 (29.4)	100.0	55.5 (30.5-77.7)
sleep	43.6 (32.2)	100.0	40.0 (15.0-60.0)	43.6 (30.4)	100.0	40.0 (20.0-60.0)
social isolation	46.4 (31.1)	100.0	40.0 (20.0-65.0)	46.0 (33.9)	100.0	40.0 (20.0-80.0)
physical mobility	28.2 (24.3)	75.0	25.0 (12.5-50.0)	29.5 (23.2)	87.5	31.25 (12.5-50.0)

QLDS, Quality of Life in Depression Scale; BDI, Beck Depression Inventory; NHPD, Nottingham Health Profile distress index

Table 14. Descriptive statistics for main outcome measures (postal survey, n = 50)

Test-retest reliability and internal consistency

The test-retest reliability coefficient was 0.89, indicating that the measure had good reproducibility and produced a low level of random measurement error. The internal consistency (as measured by the Cronbach's α coefficient) was 0.945 at Time 1 and 0.951 at Time 2, showing an adequate interrelatedness of the items.

Construct validity

The QLDS indicated appropriate levels of convergent and divergent validity at both applications (*Table 15*).

The QLDS demonstrated the expected strong correlations with the scores on the emotional reactions (Time 1: r = 0.75; Time2: r = 0.76) and social isolation (Time 1: r = 0.68; Time 2: r = 0.79) sections of the NHP. As anticipated, lower correlations were found between the

QLDS and the pain (Time 1: $r = 0.39$; Time 2: $r = 0.22$) and physical mobility (Time 1: $r = 0.39$; Time 2: $r = 0.49$) sections of the NHP.

A high correlation was found with the BDI score at each time point (Time 1: $r = 0.83$; Time 2: $r = 0.83$).

	QLDS Time 1 (Spearman coefficient)	***QLDS Time 2 (Spearman coefficient)***
NHP section		
Energy level	0.54	0.43
Pain	0.39	0.22
Emotional reactions	0.75	0.76
Sleep	0.47	0.24
Social isolation	0.68	0.79
Physical mobility	0.39	0.50
BDI score	0.83	0.83

NHP, Nottingham Health Profile; BDI, Beck Depression Inventory

Table 15. Correlation between QLDS and NHP section scores and BDI score in the postal survey (Spearman coefficient)

Discriminative validity

The participants who perceived their depression to be worse had significantly higher QLDS scores, as did the patients who rated their general health to be poorer (*Table 16*).

The participants who were currently classified as clinically depressed according to their ICD-10 diagnosis had significantly higher QLDS scores than the patients who were in remission on the basis of the Mann-Whitney U test ($p_{time1} = 0.018$; $p_{time2} = 0.012$).

Additional evidence for the discriminative validity of the Hungarian QLDS was gained from the differences in QLDS scores related to the severity of depression as assessed by the BDI. On the basis of the BDI score, the participants who were considered 'mildly depressed gave significantly lower QLDS scores (Time 1: 10.11±3.10; Time 2: 10.4±2.45) than those considered 'severely depressed' (Time 1: 17.88±5.36; Time 2: 17.51±5,546). Results of Kruskal-Wallis test: $p_{time1}, p_{time2} < 0.05$.

	Time 1			***Time 2***		
	n	***Median (IQR)***	***p****	***n***	***Median (IQR)***	***p****
Perceived severity of depression						
mild	10	10.5 (8.5-12.3)		7	10.0 (8.0-14.0)	
moderate	33	13.0 (10.0-19.0)	0.002	33	12.0 (10.0-16.5)	0.001
severe	7	21.0 (17.0-24.0)		10	21.0 (19.5-23.5)	
Perceived general health						
excellent/good	5	12.0 (7.5-13.5)		9	10.0 (7.5-12.0)	
fair	30	11.0 (9.0-16.8)	0.009	31	12.0 (10.0-19.0)	0.001
poor	15	17.0 (13.0-21.0)		10	21.0 (16.75-23.5)	

** Kruskal-Wallis test*

Table 16. QLDS scores relating to perceived general health and severity of depression

5.4. Clinical performance of the Hungarian QLDS in measuring QoL for patients with depression

The sociodemographic characteristics of the sample and the patient distribution according to the depression subtypes are shown in *Table 17*. Most of the patients were female (71%). The mean age was 50.5 years.

Gender	***n* (%)**
Male	14 (29)
Female	34 (71)
Age (years)	
Range	17-80
Mean (SD)	50.5 (13.5)
Marital status	***n* (%)**
Married	19 (40)
Divorced	9 (19)
Single	14 (29)
Widowed	6 (12)
Employment status	***n* (%)**
Employed (full/part-time)	10 (21)
Disability pensioner	17 (35)
Retired	9 (21)
Homemaker	2 (4)
Unemployed	7 (15)
Student	2 (4)
Duration of illness (years)	
Range	0-21
Mean (SD)	6.2 (4.97)
Median	6.0
Subtypes of depression	***n* (%)**
Organic mood disorder	1 (2)
Schizoaffective	2 (4)
Bipolar affective disorder	2 (4)
Unipolar affective disorder	39 (82)
Mixed anxiety and depressive disorder	4 (8)

Table 17. Details of the sample

5.4.1. Associations between outcome scores and demographic factors

No significant difference in QLDS scores was found between the different subtypes of depression. The females gave a higher QLDS score at each time, which revealed a poorer QoL related to depression. The mean QLDS scores ±SD: $males_{time\ 1}$ = 13.7±6.4; $females_{time\ 1}$ = 16.5±5.9; $males_{time\ 2}$ = 10.5±4.5 $females_{time\ 2}$ = 14.2±9.3. However, these differences did not prove significant on the basis of the Mann-Whitney U test ($p > 0.05$ at each time point).

5.4.2. Associations between psychiatrist-rated severity of depression and self-rated QoL

The correlations between HAM-D and QLDS and between MADRS and QLDS were significant (*Table 18*). A higher HAM-D or MADRS score, which indicated severe depression, was associated with a poorer QoL as assessed by QLDS. The correlation between

the psychiatrist-related severity of depression and the different dimensions of the QoL as measured by the generic QoL instrument (NHP) was also found to be significant in most cases (*Table 18*).

	Time 1		*Time 2*	
	HAM-D	***MADRS***	***HAM-D***	***MADRS***
BDI	0.680**	0.741**	0.659**	0.702**
QLDS	0.554**	0.550**	0.441**	0.5533**
NHP distress index	0.425**	0.507**	0.593**	0.668**
Energy level	0.310*	0.435**	0.458**	0.493**
Pain	0.179	0.3.85*	0.313	0.241
Emotional reaction	0.477**	0.599**	0.647**	0.775**
Sleep	0.284	0.328*	0.464**	0.502**
Social isolation	0.390**	0.369**	0.659**	0.741**
Physical mobility	0.321*	0.405*	0.332	0.323

**Spearman correlation significant at the level of 0.01
*Spearman correlation significant at the level of 0.05

Table 18. Correlation between psychiatrist-rated severity of depression and patient's perception of HRQoL (QLDS and NHP) and severity of depression (BDI)

The power of the QLDS scores to discriminate between patients with different levels of depression severity was good (*Table 19*). (Kruskal-Wallis test: $p > 0.001$ at each time point) Severe depression was associated with higher QLDS scores, which emphasizes a decreased QoL.

	Time 1			*Time 2*		
	n	***Median (IQR)***	***p****	***n***	***Median (IQR)***	***p****
Severity of depression (HAM-D)						
mild	12	10.0 (8.0-13.75)		24	9.5 (8.25-11.0)	
moderate	3	12.0 (1.0-17.0)	0.001	10	12.5 (8.75-16.25)	0.004
severe	28	19.0 (13.5-22.0)		14	16.0 (12.75-21.5)	

* Kruskal-Wallis test

Table 19. QLDS scores in relation to severity of depression

5.4.3. Clinical improvement and changes in QoL

An improvement in depression, as measured by the statistical changes in the HAM-D total score from the baseline after 4-6 weeks, was significantly correlated with an improvement in QLDS ($r = 0.588$; $p < 0.001$). The corresponding correlation in terms of MADRS also showed a tendency to significance ($r = 0.499$; $p = 0.002$).

75% of the patients achieved remission in the severity of their depression according to the MADRS scores, and 73% according to HAM-D, after the 4-5-week follow-up period.

5.4.4. Associations between QLDS outcome scores and treatment

9% of the patients were on TCA (clomipramine) treatment, and 4% on a TCA + SSRI combination (*Table 20*). Most patients (39%) were on SSRI therapy, and 10% received "other" antidepressant (N06AX) besides SSRI. Citalopram was the most preferred drug among SSRIs. The most definite change in severity of depression measured by the HAM-D score was observed for the SSRI group (median: -10.0). This is in good correlation with the changes in QLDS scores (*Table 20*).

Patients on some "other" antidepressant (e.g. SNRI, NARI or SSRE) treatment accounted for 29%.

Benzodiazepine augmentation was present in 71% of the cases, and the prevalence of antipsychotic augmentation was 10%.

9% of the patients were on benzodiazepine monotherapy; they had not been prescribed any antidepressant during the follow-up period studied.

		Time 1	***Time2***
	n %	***Median (IQR)***	***Median (IQR)***
TCA	9	12.5 (11.25-18.25)	18.5 (10.75-46.5)
TCA + SSRI	4	18.5 (16.0-21.0)	17.0 (16.0-18.0)
SSRI	39	18.0 (12.0-22.0)	11.0 (8.0-15.0)
SSRI + „other antidepressant"*	10	9.0 (6.0-26.0)	9.0 (4.0-17.0)
„Other antidepressant"	29	15.0 (9.75-19.25)	10.5 (8.75-14.5)
Benzodiazepine	9	13.5 (3.25-20.75)	13.0 (10.75-14.5)

* „other antidepressant" = N06AX group

Table 20. QLDS scores in different treatment groups

25% of the patients received supportive psychotherapy besides pharmacotherapy (*Table 21*). At the end of the studied period, significantly lower QLDS scores were observed among the patients on supportive psychotherapy, indicating a better QoL (Kruskal-Wallis test, $p < 0.05$).

	Pharmacotherapy with supportive psychotherapy	***Pharmacotherapy without supportive psychotherapy***
n (%)	12 (25)	36 (75)
QLDS median (IQR)	9.0 (7.25-11.75)	13.0 (9.0-18.0)*

*Kruskal-Wallis test, significant difference, $p < 0.05$

Table 21. QLDS scores in different therapeutic subgroups

6. DISCUSSION

Antidepressant consumption in Hungary exhibited a more than 6-fold increase during the period 1993-2006. Not only the volume, but also the structure of antidepressant consumption changed considerably: while the sales of TCAs slightly decreased, a marked elevation was observed in terms of SSRIs and "other antidepressants". Similar trends were recorded in Ireland, Australia, Italy, Iceland, the Nordic countries, France, Slovenia, Lithuania, Canada and Serbia and Montenegro [102-111]. In contrast with these countries, the preferred use of TCAs and St. John's wort over SSRIs has been reported in Germany [112, 113].

The international literature suggests, that the dramatic rise in antidepressant consumption in the last decade may be related to various factors, including changes in the prevalence of depression, consultation and prescription habits, the improved diagnosis and treatment of psychiatric patients, changes in the patterns of help-seeking behaviour, the introduction of new antidepressants with extensive promotion by drug companies, and the high level of reimbursement [2, 103, 105, 109, 114, 115].

Population-based data concerning the changes in the prevalence of depression and in the number of recognized psychiatric patients are limited in Hungary. An earlier study performed by Kopp et al. using the Beck Depression Inventory concluded that the prevalence of depression had displayed only a moderate rise in the adult Hungarian population, from 24.3% in 1988 to 27.3% in 2002 [116, 117]. The data of the Hungarian Central Statistical Office indicated that the number of patients with a diagnosis of depression (on the basis of the ICD-10 diagnostic criteria system: F30-39) who attended out-patient psychiatric departments increased by 28% during the studied period [93]. Further psychiatric service indicators suggested that a moderate improvement occurred between 1993 and 2006. The number of out-patients psychiatric departments rose by 8%, the annual number of new patients taken into care by 19%, and the total number of attendances by 53% [93]. It remains unclear whether the prevalence of depression really increased or only whether more patients were recognized and treated.

The definition of depression has changed over the years, the criteria for defining depression are now wider and the diagnostic methods have become more refined; furthermore, a marked change may be experienced in the attitude of society towards psychiatric diseases. These facts may account for the increasing number of recognized and treated patients.

The introduction of new antidepressants may contribute to the large increase in the consumption rate of this drug group. Eleven new substances (110 products) were introduced into the Hungarian market during the studied 14-year period [118]. These new antidepressants offer a possibility to treat patients with less toxic and more tolerable agents, thereby improving the compliance and possibly improving the outcome.

The increase in overall antidepressant use may also be due to a longer average duration of treatment, which is emphasized by the guidelines [119-121]. Additionally, the expanded fields of indication of a certain active agent (e.g. posttraumatic stress disorder, insomnia, panic disorder, anorexia nervosa, attention deficit disorder and autism) may contribute to the observed increased consumption.

During the studied period, all antidepressant preparations were reimbursed at the 90% or 100% level by the Hungarian National Health Insurance Fund. We assume that this permanent low economic burden on the patients may affect the high level of antidepressant prescription.

A moderate drop in antidepressant consumption occurred in 2004. This can be explained by the fact that the co-payment by patients increased by 64% in the first part of the year, through the previous situation was later restored. A similar trend was observed by Poluzzi et al. in Italy. Whereas, Italy was traditionally reported as a country with a low prescription of antidepressants, the removal of reimbursement restriction was followed by a marked overall increase in antidepressant consumption [115].

The analysis of regional quantitative differences in antidepressant consumption demonstrated a considerable degree of heterogeneity between different parts of Hungary. While the central eastern regions were the most prominent antidepressant consumers, the north-eastern regions proved to be the lowest consumers. However, the Hungarostudy 2002 reported the highest BDI scores in the north-eastern counties. The mean BDI score for these counties was 9.46, indicating a higher depression prevalence, and a basically poorer mental health status [122]. The above-mentioned discrepancy may point to the problem of the underdiagnosis and undertreatment of depression in this region.

Such regional differences have likewise been reported in Italy, where the interregional variations of antidepressant consumption revealed a north-south gradient reflecting industrial and economic development [104]. However, in the Italy, not only the volume, but also the pattern of antidepressant use differed considerably between the northern and southern regions. The increased use of SSRIs was considered one of the parameters of development in the north, i.e. an indicator of affluence.

My present study also suggested an association between antidepressant use and regional economic differences, with positive directions.

In agreement with earlier studies performed by Laukkala et al [123] and Nakagawa et al [124], I found that the unemployment rate and alcohol-abuse disorders are independently related to the use of antidepressants in Hungary. However, the unemployment rate consistently exhibited a negative, and alcohol consumption consistently a positive correlation with the antidepressant use.

The quantitative differences observed in hospital antidepressant use between the four Psychiatric Departments can be partly explained by the various degree of free drug sample donation provided by pharmaceutical companies. The pattern of the antidepressant consumption in the studied four university-affiliated Psychiatric Departments and in the counties was very similar. These results underline my hypothesis that the leading medical departments determine the therapeutic modalities in the surrounding areas.

Without doubt, suicide is one of the most serious consequences of affective disorders. Unfortunately, Hungary is still one of the leading countries in the international suicide statistics, despite the slightly decreasing tendency in recent years [2]. The causes of suicide are complex and multifactorial (sociological, psychological and biological factors have been identified as contributors). Mood disorders are regarded as among the most important predictors of suicide attempts. This assumption has been confirmed by several studies on the Hungarian population. Balázs et al. identified major depressive episodes in 69% of suicide victims or suicide attempters [125]. In terms of prevalence data, similar results were found by Szadóczky et al. Their results indicated that some kind of affective disorder was present in 65% of females and 72% of males among patients with a history of suicide attempts. [126]. Vörös et al. reached the same conclusion: 60% of suicidal patients had a current depressive episode [127]. Zonda et al. also confirmed such results by in an 11-year follow-up study [128].

In my study, the results of the regional-level data cast doubt on the hypothesis of a simple relation between antidepressant consumption and suicide rate. Although significant regional variations made the interpretation difficult, I did not find any statistically significant correlation between the increased antidepressant consumption and the decreased suicide rate at a regional level.

The relationship between antidepressant consumption and suicide rate is a controversial issue in the literature. Many epidemiologic studies have found a reduction of suicidality in regional populations in association with increasing antidepressant prescription [129]. The

epidemiological study published by Isacsson et al. described an association between the greater prescription of antidepressant drugs and the reduced suicide rate in Sweden [130]. These findings were extended to other Nordic countries [114, 131]. In agreement with Isacsson's findings, Carlsten et al. reported that the suicide rate in Sweden declined during the 20 years between 1977 and 1997, but that the rate of decline accelerated after the introduction of SSRIs in 1990. [132] A study in Northern Ireland found a statistically significant association between the increased antidepressant prescription and a fall in suicide rate in the population over 30 years of age [102]. (Unemployment was also inversely associated with suicide in this age group.) Ohberg et al. found that suicide mortality declined in Finland during the years 1990-1995, and the prescription of SSRIs increased during the same period [133]. Hall et al. also came to the conclusion that there seemed to be an association between increased antidepressant prescription and the decreased suicide rate in Australia [103]. The results of Grunebaum's study are likewise consistent with the hypothesis that the more widespread treatment of depression and the greater use of non-TCAs have contributed to the decline in the U.S. suicide rate [134]. The analysis carried out by Morgan et al. in England between 1993 and 2002 came to the same conclusion [135]. In Japan, an increase of 1 DDD of SSRI use/1000 population/day was associated with a 6% decrease in suicide rate. Exploratory analysis suggested a stronger association in males, who experienced a greater increase in antidepressant use [124].

In contrast, the analysis of long-term trends in suicide, carried out by Guaiana et al. did not suggest that increases in antidepressant prescription lie behind the reduction in suicides in Italy [136]. This was supported by another Italian study, performed by Barbui et al. [104]. Helgason et al. similarly reached the conclusion that the suicide rate was not affected by the sales of antidepressants, which have increased 9-fold during the last 20 years in Iceland [105]. In contrast to Isacsson's findings, Reseland et al. found no association between antidepressant prescription and suicide rates in the Nordic countries [106].

There may be different possible reasons for the discrepancy between the findings of the above-mentioned national studies. It may be presumed that various social, cultural and economic factors influence the suicide rate. The diverse methodology applied in the various studies may be a further reason for these contrary results. Several authors suggest concordantly that, despite increasing antidepressant prescription, the underdiagnosis, non-treatment or undertreatment of depression seem to be the great problems in affective patients who have committed suicide [137-143]. This hypothesis may be supported by the present study, since there was a trend to a negative association with psychiatric service indicators,

though this did not reach the level of statistical significance. Moreover, there was also a trend towards a negative association between the suicide rates and a poor economic status in the counties. The suicide rate was found to be about 3 times higher in the central and southern part of Hungary than in the west, which is generally in a better economic situation.

A variety of social factors such as unemployment and alcohol abuse have been associated with the suicide rate in some [102], but not all studies [114, 124]. My findings suggested that changes in unemployment and alcohol consumption rates did not explain the association, although alcohol-abuse disorders are a major public health issue in Hungary.

My present analysis has some limitations. First, I employed ecological analysis rather than a patient-based study. Furthermore, the distribution-based antidepressant sales data may overestimate the real number of patients on antidepressant treatment.

The above-mentioned exponential increase in drug consumption experienced in the last decade imposes a heavy burden on society. The financial authorities often report that the national drug expenditure is very high. Health-care professionals do not agree with this general statement, but they accept the fact that there are problems with drug prescription, and consumption is sometimes inappropriate. Polypharmacy is also an important issue in the international literature. A survey published in 2002 analysed polytherapy among psychiatric patients over the last 30 years: the patients participating in the study were from 39 psychiatric departments or clinics from the 11 countries involved (n = 23428). The mean number of concurrently taken drugs with psychiatric indications in the studied group of patients was 2.2 before 1980, 2.3 between 1981 and 1990, and 2.9 between 1991 and 2000. This latter was significantly higher than the mean number for the period prior to 1980 [144]. The mean number of psychiatric drugs taken by the patients involved in my study was similar (2.7) to that in the previously mentioned survey.

The trends of mono and polytherapy among psychiatric patients were also analysed by the survey. The frequency of monotherapy significantly decreased: it was 47.8% before 1980, 31.1% between 1981 and 1990, and 19.6% between 1991 and 2000 [144]. A higher monotherapy rate (26%) as regards psychiatric drugs was found by Gaszner et al. in the NIPN (National Institute of Psychiatry) in a study performed under the tutelage of the Drug Safety Program in Psychiatry (AMSP), 2004 [145]. The drug consumption habits of 952 psychiatric inpatients were analysed in 2004.

In comparison with the above-mentioned data, I found a lower prevalence of monotherapy in the studied group at the Psychiatric Department in Szeged (PP group: 5.1%; non-PP group: 14.5%).

Monotherapy should be applied whenever possible, but there are several indications for adequate polypharmacy according to the recommendation of the guidelines for the treatment of different psychiatric diseases. Mood disorders, which are among the most prevalent diagnoses in both groups, can often occur in association with other psychiatric diseases, primarily with anxiety disorders. (This trend is reflected by the toplist of drugs used.) The treatment of these cases requires concomitant drug use [120, 121]. Furthermore, it should be mentioned that the inpatients at the university-affiliated hospitals are the most severe cases. They are often considered treatment-resistant and may require combination therapy. Augmentation is a frequently applied strategy, especially among those patients who respond poorly to the medication. The concomitant use of an antidepressant with levothyroxine or lithium is a typical example of augmentation.

The most popular drug in the PP group was a nootropic agent, piracetam. This can be explained by the advanced age in this group and the high frequency of the different types of organic, including symptomatic, mental disorders. In these conditions, piracetam is used as an adjuvant agent.

The results of various surveys show that the prevalence of polypharmacy increases with the mean age of the patients. The frequency of PP is significantly higher over the age of 65 [8,9,11]. In one of my previous surveys, in which I analysed the drug utilization of traumatology and dermatology patients and patients treated in GP care, the mean age of the polypharmacy patients was again found to be over 60 years of age (traumatology: 70 years; dermatology: 60; GP: 65) [146]. In the present study, the mean age of the PP group was 61 years, which is in good agreement with the earlier-published data.

The female dominance found in my study may result from several factors, e.g. the characteristics of the studied patient group, as the ratio of females among psychiatric patients is higher. This is supported by the results of OLEF 2000 (National Health Survey) conducted by the Health Statistics Unit of the Health Promotion Research Institute [147]: the decrease in mental function in all age groups was higher among females (16.3%) than among males (8.8%). To study the extent of mental health problems, the GHQ-12 self rating scale (General Health Questionnaire) was used in OLEF 2000. Although the GHQ is not appropriate for a more specific identification of the nature of the mental decrement and to set up psychiatric diagnoses, the results achieved through the GHQ and other additional methods show a good correlation, and high scores can indicate the necessity for medical intervention [147].

Demographic surveys show the number of females to be 1.5 times higher than the number of males in the age group over 60 years [147]. In my study, the mean age of the PP group was 61 years, which may partly explain the female dominance.

Polypharmacy studies indicate that, besides age, the female gender is also an important factor predisposing to polypharmacy [11, 148, 149]. This finding correlates well with the present study because gender proved to be the second factor predisposing to polypharmacy on the basis of the OR values.

According to certain studies, the prevalence of PP in the total population is 1.2% [11, 149], while it is 39% in the elderly population (over the age of 65 years) [148-151]. The most commonly used drug groups are those for the treatment of: diseases of the cardiovascular system, the central nervous system, the gastrointestinal system, the endocrine system and the musculoskeletal system. Besides age, comorbidity is also a major factor contributing to polypharmacy [152]. My investigations confirmed this correlation. In the present study, this is the most important factor for polypharmacy.

Cardiovascular diseases are in the leading position for comorbidity [9, 11]. In my previous study, the vast majority of the psychiatric, traumatology and dermatology patients and patients treated in GP care also suffered from cardiovascular diseases (psychiatry: 68%, traumatology: 74%, dermatology: 53%, and GP: 51%) [146].

For the treatment of various cardiovascular diseases, e.g. hypertension, the therapeutic guidelines currently recommend the use of 2 or 3 drugs in combination rather than monotherapy. (Only 25% of patients with hypertension are on monotherapy [11].)

In conclusion, numerous facts indicate that polypharmacotherapy is necessary in certain diseases or when different forms of comorbidity are present. At the same time, it must be considered that an increasing number of concurrently used drugs elevates the possibility of drug-drug interactions and other unwanted effects. This is particularly so in the elderly population, as their pharmacodynamic and pharmacokinetic parameters can differ extremely. Consequently, special attention should be paid to the pharmacotherapy of this age group.

The compliance with treatment regimens is dependent on the impact of that treatment on the patients' well-being. HRQoL improvements due to rational medical interventions recently have received increasing attention. Physicians have begun focusing on optimal treatment options that also improve the patient's QoL. This has led to a growing demand for the development of valid disease-specific QoL instruments which are applicable to determine the outcome of interventions from the patients' perspective.

The development of the Hungarian version of the QLDS followed the standard methodology employed in all adaptations of needs-based measures. The application of standard methodology is essential to produce high-quality adaptations and to allow data from different countries to be combined. The dual panel translation methodology ensured that the translated instrument was fully comprehensible for Hungarian-speaking patients.

Evidence from the field-test interviews indicated that the content of the instrument was relevant to the patients and it was well completed by them. The mean time required to complete the Hungarian QLDS was less than 10 minutes. This is one advantage of employing a depression-specific instrument [16, 153].

The Hungarian adaptation of the QLDS has been shown to have excellent psychometric properties. The high test-retest correlations indicate an excellent degree of reproducibility, with no evidence of excessive random measurement error. The internal consistency of the measure was confirmed, with items adequately interrelated. The reliability and internal consistency are similar to those of the original English version and other language versions (*Table 22*) [98, 153-155].

Language version	***n***	***Test-retest reliability***	***Internal consistency***	
			Time 1	***Time2***
English (original, UK)	74	0.81	0.95	0.94
Canadian (French)	38	0.96	0.95	0.96
Canadian (English)	31	0.95	0.95	0.96
Danish	23	0.89	0.93	0.91
French	12	0.94	0.89	0.92
German	18	0.93	0.96	0.93
Italian	40	0.95	0.96	0.96
Moroccan	34	0.85	0.88	0.90
Spanish	27	0.94	0.94	0.93
US	29	0.82	0.93	0.94
Hungarian	**50**	**0.89**	**0.95**	**0.95**

Table 22. Test-retest reliability and internal consistency for new-language versions of the QLDS

The association between the scores on the QLDS and the NHP sections confirmed the convergent and divergent validity of the new instrument. The correlation coefficients were in the expected directions and of the predicted strength. The correlations were higher for those sections of the NHP that were most relevant to depression (emotional reactions and social isolation). Lower correlations were found between the QLDS and the more physical aspects of distress (pain and physical mobility).

The QoL would be expected to be sensitive to the general health status as well as to severity of depression. The scores on the Hungarian QLDS were clearly related to the perceived severity of depression. Similarly to other national versions, these differences in the QLDS scores between the perceived severity groups were statistically significant, confirming the sensitivity of the instrument (*Table 23*) [98].

Country	*Self-perceived severity of depression*					*p*
	mild	*mild/ moderate*	*moderate*	*moderate/ severe*	*severe*	
Denmark	4.5			15.0		<0.0001
France	12.0		15.0		23.0	<0.01
Germany		14.0			18.5	ns
Morocco		22.0			29.0	<0.001
Hungary Time 1	**10.5**		**13.0**		**21.0**	**<0.001**
Time 2	**10.0**		**12.0**		**21.0**	**<0.001**

Table 23. Median QLDS scores in relation to self-rated severity of depression

Further evidence of the validity of the QLDS was gained by examining the measure's ability to distinguish between groups of patients who differed according to the severity of depression as assessed by the BDI (self-rating scale), and the HAM-D or the MADRS (psychiatrist-rating scales).

My findings are consistent with the results of studies which confirmed a significant association between the subjective QoL and the clinician-rated psychopathology [76, 98, 156]. Similar Spearman coefficients were found in these studies designed to assess the correlation between the QLDS and the HAM-D scores ($r_{Spearman}$ = 0.61 in the US; $r_{Spearman}$ = 0.68 in Morocco; $r_{Spearman}$ = 0.43 in Germany; $r_{Spearman}$ = 0.57 in North America; and $r_{Spearman}$ = 0.39-0.75 in The Netherlands). Only one study (Doraiswamy et al.) reported a weak correlation ($r_{Spearman}$ = 0.23) between the satisfaction with life and the clinically assessed symptom severity in their study with the same instruments [83].

The QLDS scores appeared not to be related to the patient's gender according to the statistical analysis. However, females had a higher score at each time, indicating a poorer HRQoL.

My results are in agreement with those of other studies that have shown a high degree of association between depression and disability [156]. More than one-third of the investigated subjects in my study were on a disability pension.

The results of the present study provide data emphasizing the importance of psychotherapy intervention simultaneously with pharmacotherapy as a more efficacious means of improving the QoL for depressed patients.

Furthermore, I observed that the QLDS promotes a quite precise appraisal of the improvement in QoL related to the course of mood. My results suggest that the instrument is sensitive for changes in depression symptoms. A clinical improvement in depression rating resulted in an improvement in QoL scores. The correlation between the changes in the psychiatrist-administered depression severity scales (HAM-D and MADRS) and those evaluated with the QLDS demonstrated this phenomenon. This finding is consistent with previous reports of the sensitivity of the QLDS to changes in depression severity [75, 76, 78, 79, 155, 157].

The present study confirmed that the QoL data measured by the QLDS may help in the design of appropriate, reliable outcomes for clinical trials and the routine follow-up of depressed patients. Self-rating scales can provide important additional information for therapy evaluation as they reflect the patient's personal experience of illness and recovery.

7. SUMMARY

The dramatic increase in the use of antidepressants in the last decade may be related to a variety of factors, including a steadily rising prevalence of depression, the improved recognition and the treatment of psychiatric patients in Hungary, better safety and tolerability of new antidepressants and the high level of reimbursement. The pattern of consumption is consistent with the national and international recommendations.

There are relatively constant and large interregional differences in antidepressant consumption and suicide rate in Hungary, which are primarily associated with socio-economic determinants. The relationship between antidepressant consumption and suicide rate is a controversial issue. My results suggest that the marked elevation in antidepressant consumption has not had any statistically significant impact on the declining suicide rate at a regional level in Hungary.

At the same time, it should be emphasized, that improved detection, the appropriate treatment of depression, and adequate aftercare of persons with a high suicidal risk are the critical components of all suicide prevention-strategies. More attention should be given to this population, since underdiagnosis and undertreatment still seem to be the most serious problems, despite the major increase in the use of antidepressants among patients who have attempted suicide

Depression is associated with considerable decrements in the QoL. Since the compliance with medical interventions is largely dependent upon the impact of treatment on a patient's feelings of well-being, stress should be placed on the increasing importance of QoL assessment.

The adaptation of the QLDS into Hungarian proved successful. The new-language version was shown to have excellent psychometric properties. It is regarded as the official Hungarian QLDS version by the original authors (Hunt and McKenna). Given the absence of a depression-specific QoL instrument in Hungary, the Hungarian QLDS will be a reliable and valid outcome measure in clinical and health economic trials as well as in the routine monitoring of depressed adult patients.

QoL measures may provide an adjunct to clinical decisions, widening the lens through which patients are viewed and facilitating their input to the treatment process; furthermore, they may form a basis for improvements in health care.

In conclusion, depression should be managed as an important public-health priority to reduce disease burden and disability, and to improve the overall health of the population.

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10. ANNEX

I. **R Viola,** K Csukonyi, P Doró, Z Janka, Gy Soós. Reasons for polypharmacy among psychiatric patients. *Pharmacy World Science 2004; 26: 143-147.*

II. **R Viola,** Gy Soós, G Nagy. Antidepresszáns-felhasználás Magyarországon, 1993-2004. *Gyógyszereink 2006; 56 (9): 315-324.*

III. **R Viola**, K Lovas, Z Szabó, Zs Czenner, D M Meads, Gy Soós, S P McKenna. A depressziós betegek életminőségének meghatározására szolgáló kérdőív magyarországi adaptációja. *Orvosi Hetilap 2007; 148 (13): 603-608.*

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V. **R Viola**, R Benkő, G Nagy, Gy Soós. National trend of antidepressant consumption and its impact on suicide rate in Hungary. *Pharmacoepidemiology and Drug Safety (accepted, in press)*