University of Szeged
Department of Clinical Pharmacy

Ph.D. Thesis

Utilization of oral antidiabetic drugs in Csongrád County between 1998 and 2004: adherence and persistence with therapy

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PUBLICATIONS RELATED TO THE SUBJECT OF THESIS

PAPERS

I. **P. Doró**, R. Benkő, M. Matuz, Gy. Soós: Seasonality in the incidence of type 2 diabetes: A population-based study.
Diabetes Care 2006 Jan;29(1):173. IF_{2005}: 7.844

II. **P. Doró**, R. Benkő, E. Kosik, M. Matuz, K. Tóth, Gy. Soós: Utilization of oral antihyperglycaemic agents over a 7-year period (1998-2004) in a Hungarian population and adherence to drug therapy
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III. **Doró P.**, Németh E., Soós Gy.: Van Önnek gyógyszerésze? [Do you have a pharmacist?]
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ABSTRACTS

IV. **Doró P.**, Kószó L., Soós Gy.: Gyógyszerész-beteg kapcsolat minőségi indikátorai [Quality indicatiors of patient-pharmacist interactions]. *Congressus Pharmaceuticus Hungaricus XII,.* Budapest, Hungary, 2003, Abstr.: P-24

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1. INTRODUCTION

As a result of an aging population, changes in lifestyle, and higher level of obesity, diabetes affects an increasing number of patients, and their number is expected to more than double worldwide by the year 2030 [1]. There are nearly half million registered diabetic patients in Hungary, but the number of people affected is thought to be much higher; the estimated prevalence of diabetes among adults was 9.7% in Hungary in 2003, one of the highest values in Europe (Figure 1) [2, 3]. The vast majority of patients, 85-95%, have type 2 diabetes [3]. An increased blood glucose level is associated with a greater risk of microvascular and macrovascular complications. It has been reported that macroangiopathy can effect up to one-third of patients diagnosed with type 2 diabetes [4]. These complications not only diminish patients' health and result in decreased quality of life, but also put a high financial burden on the health care system [5]. The United Kingdom Prospective Diabetes Study clearly proved the benefits of intensive glycemic control in patients with type 2 diabetes [6]. Previous studies have also shown that increased adherence to oral antidiabetic drugs results in better metabolic control and, consequently, in decreased hospitalization rates and lower total annual health care costs [7–9].

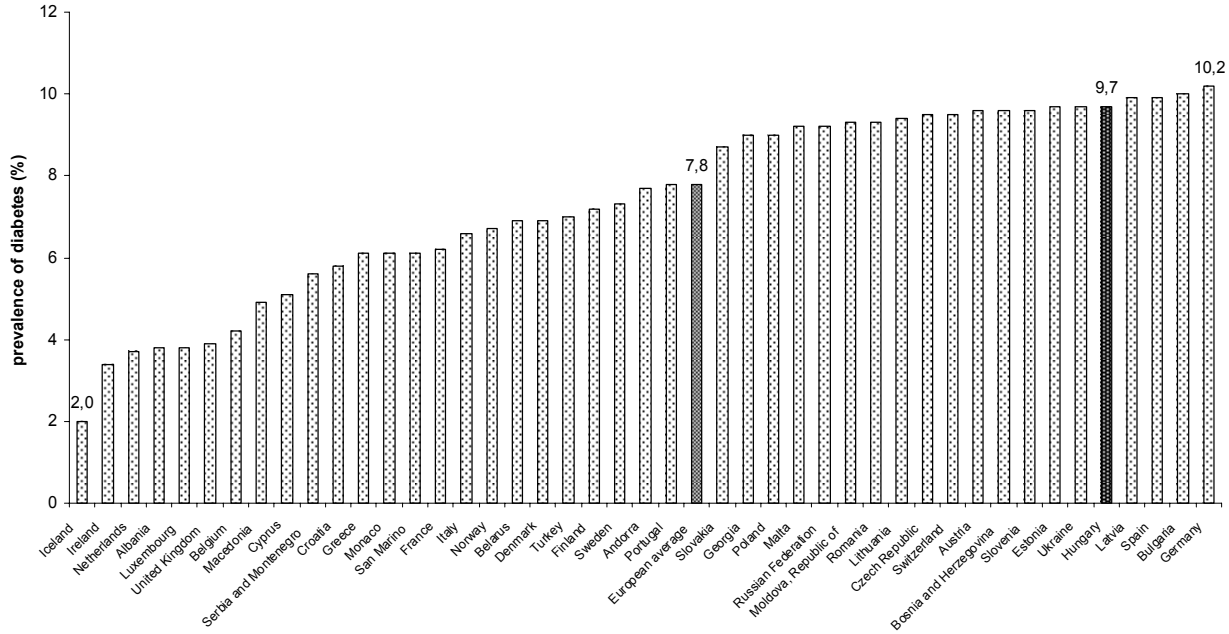

Figure 1. Estimated prevalence of diabetes among the adult population in the European countries in 2003 [3].

The successful treatment of diabetic patients require a multidisciplinary approach, involving diabetologists, general practitioners, pharmacists, nurses, dieticians and psychologists. During the past decades several countries implemented pharmaceutical care programs targeting diabetic patients, and such a program is presently in its developmental phase in Hungary.

The thorough design of the care programs necessitates the detailed studying and understanding of past and present trends in the treatment of the disease, and the investigation of patients' behavior in order to optimize future therapeutic outcomes and to lower health care expenditures. Pharmacoepidemiologic studies provide valuable information regarding the uses and effects of pharmacological treatment in a defined time, space and population [10].

The purpose of the present study was to investigate the escalation of diabetes in Csongrád County and to evaluate the pharmacological treatment of patients, through patient specific population level data applying pharmacoepidemiologic methods.

2. BACKGROUND

2.1. Pharmacoepidemiology

Pharmacoepidemiology is the study of the utilization and effects (beneficial and adverse) of drugs in large numbers of people. Its main goal is to describe, explain and forecast the use and effects of pharmacologic treatments in a defined time, space and population [10]. Pharmacoepidemiology is referred to as a bridge science as it blends clinical pharmacology and epidemiology through the application of epidemiological methods to pharmacological matters [11]. Pharmacoepidemiologic studies can supply information on various features of medication utilization and prescribing: pattern of use, quality of use, determinants of use, and outcomes of use [12]. The ultimate purpose of pharmacoepidemiologic research is to enhance the rational medication use of the population; where rational use means the application of a well-documented drug at an optimal dose, together with the correct information and at an affordable price [13]. National drug policies should be based on – and regularly reevaluated on the bases of – the results of comprehensive national drug utilization data [14]. Pharmacoepidemiologic studies can identify the areas that require attention and action, but they do not necessarily offer the solutions for the problems [12].

Pharmacoepidemiology is a relatively new branch of pharmaceutical sciences, it roots from the 1960s, when early drug utilization studies were performed in Northern Europe and Great Britain [12]. It was soon recognized that data of different studies and countries were not comparable as they used different methodologies and units to measure drug use. In 1969, at the symposium entitled 'The Consumption of Drugs' organized by the World Health Organization (WHO) Regional Office for Europe, the Drug Utilization Research Group (DURG) was established and appointed with the development of internationally applicable drug utilization methods [15]. In the mid 1970s, for the classification of medication, Norwegian researchers developed the Anatomic Therapeutic Chemical Classification (ATC), and for the measurement unit the Defined Daily Dose (DDD) was introduced to be used in drug statistics [15]. In 1981, the ATC/DDD system was proposed by the WHO Regional Office for Europe for international drug utilization studies. The following year, in 1982, and the WHO Collaborating Centre for Drug Statistics was

established, with the purpose of coordinating the use of the ATC/DDD system [14]. In 1996, WHO realized that the ATC/DDD system should be implemented and used outside of Europe, as well, and the expert panel of WHO International Working Group for Drug Statistics Methodology was founded to facilitate the globalization of the ATC/DDD system.

2.1.1. The ATC/DDD methodology

The ATC classification is a five level, seven digit coding system. Drugs are categorized into 14 main (*anatomic*) groups (1st level) based on the targeted organ (Table 1). The 2nd level of the classification is based on the drug's main *therapeutic* category, while the 3rd level refers to the pharmacological subgroup. The 4th level is the chemical/pharmacological/therapeutic subgroup, and the 5th level is the *chemical* substance. Pharmaceutical products are classified in the ATC system according to their main therapeutic indication. An active ingredient can be classified under more than one ATC codes, if it is marketed in different strength and/or formulation with clearly different therapeutic uses [15]. New agents can be easily added to the system.

A	Alimentary tract and metabolism
B	Blood and blood forming organs
C	Cardiovascular system
D	Dermatologicals
G	Genito urinary system and sex hormones
H	Systemic hormonal preparations, excl. sex hormones and insulins
J	Anti-infectives for systemic use
L	Antineoplastic and immunomodulating agents
M	Musculo-skeletal system
N	Nervous system
P	Antiparasitic products, insecticides and repellents
R	Respiratory system
S	Sensory organs
V	Various

Table 1. ATC main (anatomic) groups

DDD is the average daily maintenance dose of the medication in its main therapeutic indication. DDD is initially based on the manufacturers' recommendation, and after marketing, it is regularly reevaluated (in every 3 years) on the bases of actual prescribed daily doses [14]. The medication use of large populations is often expressed as the number of DDDs per 1000 inhabitants per day (DDD/1000 inhabitants/day), which technical unit enables researches to compare the drug use of populations of different sizes [13].

2.1.2. Pharmacoepidemiology in Hungary

According to the 12/1978 ordinance of the Ministry of Health, the National Institute of Pharmacy (OGYI) was appointed to execute the adaptation of the ATC/DDD system, and to perform national drug utilization statistics in Hungary. The ATC classification has become widely known and used (medication compendiums include the ATC codes), but the DDD is still seldom used for drug utilization studies. Most statistics rather focus on the financial aspect of drug uses, and often, as a measuring unit, the number of boxes is used, which greatly jeopardize the comparability of the studies.

Beside the official drug utilization duties of the OGYI, a few clinical pharmacists took the initiatives in the country, and have carried out valuable drug utilization studies [16]. Some university research groups have also performed quality pharmacoepidemiologic research.

Most of these studies provide an overall view on the nation's consumption of some specific groups of medication (e.g. antiepileptic drugs, antimicrobial drugs), but they lack patient specific information, which would allow for more in-depth analyses.

There has been a few studies were previously published on the antidiabetic drug utilization in Hungary [17–21], but only one had some patient specific information on a research cohort of limited size and time span [21].

The present pharmacoepidemiologic research on oral antidiabetic drugs is the first of its size in Hungary, which analyzes patient specific data of a large population (430.000 inhabitants) over a 7 year period.

2.2. Data sources for pharmacoepidemiologic studies and their availability in Hungary

Pharmacoepidemiologic studies are only as appropriate and accurate as the data source they are based on. Study set up should be carefully designed, and the pros and cons of the different data sources must be taken into consideration. Every data source has its limitations, but the integration of data from different sources provides more thorough information about health events. Several types of data sources that are commonly used in pharmacoepidemiologic studies are summarized below.

2.2.1. Wholesale database

Drug wholesale data provide information on the medication – including both prescription and over-the-counter (OTC) drugs – supplied to pharmacies. If data from every wholesaler in a country are compiled, the complete medication use of the country is given. In Hungary complete drug sale information based on wholesaler data was managed and was available from PharmMIS Consulting Company until 2004, and since then IMS has been providing similar services. IMS is the leading pharmaceutical market research company present in over 100 countries worldwide.

An advantage of the above database is that it distinguishes between retail and institutional pharmacies, therefore the medication use of the general population and that of hospitals can be studied separately. However, as these data are not patient-specific, they only give a general overview of a country's drug consumption, and do not supply information on the individual drug use of patients. Wholesale database is a slight overestimation of a nation's medication use, as it measures the amount of drug shipped to the pharmacies, but does not take into consideration the fact that some medication is discarded by the pharmacy and does not reach the patients. Moreover, some of the medication bought in Hungary is actually used by patients in neighboring countries.

2.2.2. Pharmacy database

In several countries pharmacies maintain Patient Medication Record (PMR), with the purpose of supplying the dispensing pharmacist with valuable information on the patients'

medication history, and, consequently, aiding the delivery of high level pharmaceutical care. The International Pharmaceutical Federation (FIP) recommends the maintenance of the PMR, because it is an essential requirement for the implementation of pharmaceutical care as described in the FIP Statement of Professional Standards on Pharmaceutical Care issued in 1998 [22]. With the introduction of computers in pharmacies these databases became electronic.

These databases are usually limited to prescription only medication, but in some cases they also include OTCs. Some PMRs do not only provide information on the mediation use of the patients, but may also include data on the patients' health history, diseases and allergies. The pharmacy based PMRs are unable to capture any medication acquired in other pharmacies, and, consequently, impair the quality of pharmaceutical care. Recognizing the limitations arising from the fragmentation of information on patients' medication use, some countries (e.g. Canada) set up centralized pharmacy databases which can be accessed by every pharmacy [23].

In Hungary pharmacies do not maintain such databases, although some pharmacy softwares are able to store the information on the dispensed prescriptions.

The manual review of prescriptions accumulated at pharmacies is also an optional data source for pharmacoepidemiologic studies, although manual reviewing is a very time consuming process.

2.2.3. Medical database

General practitioners (GP) maintain a detailed medical history of their patients. A great advantage of these databases is that, beside the prescribed medication, thorough information on the patients' health status is also available. These databases supply the prescribed daily dose (PDD), which provide very useful information for some types of pharmacoepidemiologic analyses. The completeness of these databases is limited by the fact that they may not include medication prescribed by other doctors. A further limitation is that they do not necessarily represent the actual medication use of the patients, because they record only the fact of prescribing, but it is well known that patients do not always claim their prescriptions.

In 2005 the UK launched its new centralized patient record database to which every GP is connected, and supplying medical data on their patients [24]. This is the first database of its kind in the world which will provide comprehensive medical information on a nation's health status, and thus, among several other functions, it will become a precious source for health statistics.

2.2.4. Patient interview

Directly interviewing the patients about their medication use does not only give valuable information on the prescription and OTC drugs, but also on any supplements and herbal remedies. They can provide data on any medication patients use regardless of the source they acquired them from (even if they use any medication that was originally prescribed to someone else). Through direct interview data on the socioeconomic background (eg. level of education, income, housing) of the patients can be recorded, which otherwise would not be available, and which can effect and explain some of the medication use pattern. As patients may use drugs differently from how they were instructed by doctors or pharmacists, interviewing is the method that can give the closest picture of the actual medication use of patients.

Interviewing patients is generally a time consuming process, therefore it is usually not feasible to include large number of subjects. As limited number of subjects are involved, careful sampling is essential to ensure that the results are representative.

The accuracy of information collected by interviewing patients may be limited by the fact that most patients are not drug experts, therefore they tend to provide incomplete information about their medication. Also, during a face to face discussion patients may not disclose all details of their health concerns. Some patients may purposely report misleading information.

2.2.5. Insurance database

Insurance drug claims databases consist of prescriptions dispensed to their insured clients. In several countries these databases only accumulate information on prescriptions that were reimbursed at some extent by the insurance company, and therefore have no data

on non-reimbursed prescriptions. If health insurance is not mandatory in a country, then the insurance database reflects the drug use of that special segment of the population which can afford to have health insurance, so its results have to be used with caution and cannot be extrapolated to the entire population. Insurance databases collect data on the dispensation of the prescriptions, but have no information on the actual consumption of the medicine. It is also possible that the medication is taken by someone different from whom the medication was originally prescribed to. Accumulating data on a nation's drug use based on insurance databases becomes difficult if more than one health insurance company operate in a country.

In Hungary basically every citizen is covered by national health insurance, and the Hungarian National Health Insurance Fund Administration is the single national health insurance company. Its prescription claims database provides a complete history of the prescription drug use of the population at the patient level. Further details of the database are described under section 4.1.

2.3. Patient cooperation

It is well recognized that the mere prescribing of medications does not necessarily result in the desired improvement in the patients' health. Often, the failure is not due to the inappropriate selection of the medication, but rather, to the inappropriate use of the drug. The maximal beneficial effect of a treatment plan can only be achieved if patients strictly comply with the recommendations, although, in reality, they often fail to do so, which leads to suboptimal clinical benefit and complications of the disease, wastes health care resources through increased treatment cost and increased hospitalization rate, and reduces patients' quality of life [25, 26]. These serious consequences justify the necessity of extensive research of the issue.

Several terms – such as compliance, adherence, persistence – have been used during the past decades to describe the extent at which the prescribed treatment was followed. *Compliance* is defined as the extent to which the patient follows medical instructions [25]. Medical instructions refer not only to the use of medication or medical devices, but also to dietary and lifestyle recommendations. The above definition views the patient as a passive subject in the process, although active cooperation of the patient is essential. Therefore the term was redefined and the expression of adherence was introduced. *Adherence* is defined

as the extent to which a person's behavior corresponds with agreed recommendations from a health care provider as agreed upon through a shared decision-making process between the patient and the health care provider [25]. Adherence involves a mutual decision-making process between the patient and the health care provider. This definition recognized the importance of the patient's active contribution to the development of the treatment plans. While the difference between the definition of compliance and that of adherence is evident, in the scientific literature they are rarely defined clearly and they are often used interchangeably [27].

While compliance and adherence describe the quality of medication taking behavior of the patient, persistence is rather focusing on the length of the therapy. *Persistence* is defined as the time between the first and last doses taken [28]. In most persistence studies treatment cessation is defined as nonrenewal of a prescription within a grace period of a specified length (usually ranging between 30 and 180 days) after the end of the last prescription [29–31]. A gap in the course of the treatment may not actually indicate the discontinuation of the therapy, but rather a 'drug-holiday', therefore application of a grace period of any length may lead to false persistence results. Resent research strongly discourages the use of a grace period as an indicator of therapy discontinuation, and advices to use the time period between the first and the very last prescription as the persistence, regardless of any gaps in the course of treatment [28]. As persistence describes the continuity of the treatment over an extensive period of time, persistence studies are only applied in cases of long term therapies, and not in cases of acute treatments.

2.3.1. Measuring adherence

Adherence rate is the extent to which patients' behavior corresponds with the prescribed treatment plan, expressed in percentages. Adherence can vary between 0 and 100 percent, or even over 100 percent, when the patient is using more medication than prescribed. Although adherence is a continuous variable, most research use adherence as a dichotomous variable and categorize patients as being either adherent or nonadherent [32]. There is no set standard of what to be considered as adequate adherence. Many of the adherence studies apply an 80% breakpoint, and consider rates over 80% to be adequate [7, 33], while lower breakpoint value can be found in the literature, as well [34]. Some

research do not only set the accepted low level, but an upper limit is also defined (110 or 120%), above which patients are also classified as nonadherent, recognizing that not only the underuse, but also the overuse of the medication can result in undesired health outcomes [35, 36]; although the underuse of medications is much more common than the overuse [37]. The level of the acceptable adherence rate should be carefully considered for each research study individually, and should be based on how much the therapeutic outcome is affected by the decreased adherence. In studies focusing on the treatment of cancers or HIV/AIDS, where extremely strict adherence is crucial in achieving desired outcomes, the level of good adherence is set at 90 or 95% [36, 38, 39].

Although there are several methods available for the assessment of adherence, it is difficult to obtain accurate measurements, and the techniques are rather estimating than precisely measuring adherence rate. Methods should be carefully selected and the results should be evaluated with caution. The application of more than one adherence measuring methods in a study may compensate for the weaknesses of the different approaches and can provide a more realistic result. In precisely designed clinical trials adherence can be exceptionally high, due to the strict patient inclusion criteria and the high level of attention patient receive [40]. Therefore, the results of such studies cannot be extrapolated to the general population in everyday setting.

The techniques of measuring adherence ranges from patients' self report to highly sophisticated electronic monitoring devices [25].

Patient self-report is a convenient and inexpensive method, but its reliability is jeopardized by the fact that patients tend to overestimate their own adherence, as they may inaccurately recall their medication taking behavior, or they simply want to please the health care provider and avoid possible conflicts with him [37].

Doctors' estimation of their patients' adherence has been used in some clinical trials, and could also play an important role in everyday practice in the identification of patients who require intervention to have their adherence improved. Unfortunately, doctors tend to overestimate patients' cooperation and they are inadequately detect poor adherence [41].

Pill count technique is based on counting the remaining number of doses on the next clinic or pharmacy visit. Adherence is often overestimated as patients may remove remaining pills before the visit. Data can be distorted if patients take pills that remained from a previous refill.

The analyses of *pharmacy records* can be used as a simple and cheap way of assessing adherence. From the amount of dispensed drugs and the refill frequency adherence can be calculated, therefore this method is applicable only in cases of chronic health concerns that require long term continuous treatment. The accuracy of this approach is limited by the lack of information on whether the patient actually ingested the medication or not. Also, patients may obtain medication from other sources, which could not be detected. The advantages of the method are the relatively large number of subject that can be easily studied, and as the patients are not aware of the study, their behavior is not modified in the research setting, rather reflects their usual medication use.

Biochemical analyses measure the concentration of the drug or its metabolites, or of an added inactive trace chemical from blood or urine samples. These methods are expensive and may only be used in clinical settings. Although biochemical analyses are the only methods that can definitively prove the ingestion of the medication, they can only give information about the drug use for a short period of time, which is less than the elimination time of the drug.

Electronic devices, such as the Medication Event Monitoring System (MEMS), were developed to ensure an accurate monitoring of medication use. MEMS is a special pill box, containing a microchip in its cap, which records the exact time and date of each opening of the bottle, and, consequently, the time of the medication taking, assuming that the medication is taken at the time of opening [42]. This technique allows the detection of even minor deviations from the recommended therapeutic plan, and the exact time frames of nonadherent periods can be identified. However,their high price greatly limits the use of such devices.

2.3.2. Improving adherence

Improved adherence results in positive health outcomes and, consequently, in lowered health care expenditures [43–45]. There are several intervention methods available aiming at increasing patients' adherence, and, consequently, optimizing health outcomes. Improving short-term adherence is relatively successful, but improving adherence in long-term chronic diseases is difficult and not very effective [46]. Patients with acute health problems usually have higher adherence rates than those who are treated for chronic health

conditions [40]. Although nonadherence cannot be simply overcome by quantifying the level of adherence, factors that lead to poor adherence must be identified and addressed. Nonadherence can be attributed to one or more of the following reasons: socioeconomic-related factors, health system-related factors, disease-related factors, therapy-related factors and patient-related factors [25]. Until the actual cause of nonadherence is understood and dealt with on an individual level, long term success cannot be achieved. It is common belief that nonadherence is mainly the result of forgetfulness, but it has been revealed that only one fourth of nonadherence can be attributed to forgetfulness, but in the majority of cases patient deliberately chose not to take the medication [47]. Deliberate nonadherence can be the result of one or more of several factors: having fear of or experiencing side effects; not believing that medication is necessary or effective; not being able to afford to purchase the medication; not knowing how to use the drug properly.

Numerous adherence improving approaches are targeted to compensate poor memory [48]. Such methods include simple checklist reminder, special calendar blister packs, daily pillbox, or even reminding telephone calls or SMS. Other methods should be employed when addressing deliberate nonadherence. Patient education and motivation usually lead to improved adherence [40]. The education should be focused on both the health condition and the treatment, including basic information about the medication, proper timing, possible side effects and drug interactions, and the importance of adherence should be emphasized, as well. The treatment should be tailored to the patient's lifestyle to cause the lowest possible interruption in regular daily activities, and the drug regimen should be simplified.

3. MAIN RESEARCH OBJECTIVES

1. To investigate the quantitative and qualitative changes in the utilization of oral antidiabetic drugs (OAD) through patient level data between 1998 and 2004 in Csongrád County.

2. To explore the trends in the prevalence and incidence of diabetes in Csongrád County through drug utilization data.

3. To reveal any seasonality in the onset of type 2 diabetes.

4. To analyze patients' adherence and persistence with OAD therapy, and to identify patient groups that require increased attention during a pharmaceutical care program.

5. To assess the pattern of pharmacy visits of patients with type 2 diabetes, and to explore if the degree of patients' loyalty to their pharmacy correlates with their adherence to antidiabetic therapy.

6. To investigate the complexity and the financial burden of the pharmacological treatment of diabetes and its complications.

4. RESEARCH SUBJECTS and METHODS

4.1. Research subjects and data source

The primary study population included the entire 430.000 inhabitants of Csongrád County. From this population every OAD user was identified and the final research cohort included each and every patient for whom any OAD was dispensed in Csongrád County between 1998 and 2004. 38,855 patients met the inclusion criteria, and all of their 912,620 prescriptions for OADs dispensed were retrieved from the electronic prescription drug claims database of the Hungarian National Health Fund Administration (HNHFA). The database is considered valid and comprehensive because the HNHFA is the sole health insurance company in Hungary with which every citizen is registered and with which all pharmacies have contracts. The database consists of all reimbursed and nonreimbursed dispensed prescriptions, therefore, it provides a complete history of the prescription drug use of the population at the patient level. The database consists of the following information on all dispensed prescriptions: patients' age and sex; unique IDs of the patient, dispensing pharmacy, and prescribing doctor; the town where the dispensing pharmacy is located; dispensing date; ATC code; code of the medicine (specific for trade name, pharmaceutical form, strength, and package size); number of packages; amount paid by the patient; and amount reimbursed by HNHFA. The number of dispensed DDDs is not shown in the database, but it can be calculated from the data available. The utilization of OADs in the region was expressed in defined daily doses per 1,000 inhabitants per day (DDD/TID).

Beside the OAD use of the entire population, the complete prescription medication history of 1350 patients with newly diagnosed type 2 diabetes was analyzed for a 5-year period following the diagnosis, and for a 6-month period prior the diagnosis. This cohort claimed a total of 342,854 prescriptions during the 60-month period of diabetes and 18,256 prescriptions during the 6-month period prior the initiation of antidiabetic treatment. The cohort included all patients with newly diagnosed type 2 diabetes, whose treatment was initiated with OAD between August 1998 and May 1999, and claimed at least one prescription for any type of medication in each year during the following 5-year period, indicating that the person was still alive, therefore requiring treatment. Patients without any

antidiabetic medication use during the 6 months prior the first prescription were classified as newly diagnosed [49]. It is a critical part of the cohort definition to appropriately select the necessary length of the drug free period for identifying incidence users, as the length of the drug free period can substantially influence incidence measurement and cohort characteristics [50]. The waiting time distribution (a method first described by Hallas et al. for drug utilization research [51]) of the first occurrence of an oral antidiabetic medication prescription for a given patient from the beginning of 1998 reached a steady state after 6 months in our database, which proves that the 6-month run-in period is appropriate (Figure 2).

The first prescription for OAD was referred to as the index prescription, and all analyses were performed relative to the index date in case of the 1350 patients. Conducting the study relative to an index date rather than through calendar date is often used [29, 49], which technique allows to follow the course of a treatment from the beginning, and patients with different start date can be grouped into the same cohort. Furthermore, the method can eliminate biases due to in-year initiation or discontinuation of the therapy, and seasonal variations are also leveled off if patients are selected over a longer period of time.

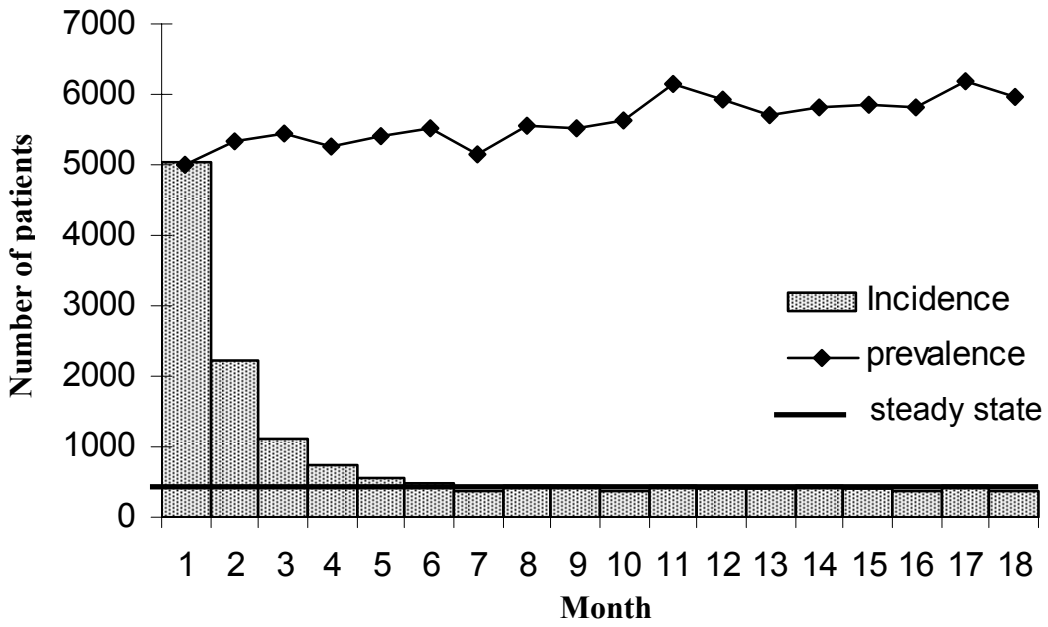

Figure 2. Waiting-time distribution. The histogram shows when oral antidiabetic drug (OAD) users appear for the first time from the beginning of 1998. The steady state indicates the real incident cases.

Although the HNHFA's database is a valuable resource for pharmacoepidemiologic studies, it has some limitations. The database includes no information on the prescribed daily doses (PDD) (dosage or number of days supplied) or the patients' diagnoses (International Classification of Diseases [ICD] code). The database consists of prescriptions dispensed in retail pharmacies, but it has no information of medicines used by inpatient departments. However, data from IMS, which gathers sales information from drug wholesalers, show that in Csongrád County the institutional use of OADs was less than 1.5% of the total utilization. This small amount, the use of which could not be linked to individual patients, is very unlikely to cause considerable distortion in the results of the research. The town of residency of patients is not available, and it is possible that some patients who claimed their prescription in Csongrád County had a permanent residency outside of the county. On the other hand, some residents of Csongrád County might have claimed some of their prescriptions in other counties. This phenomenon is expected to be very marginal, as only less than 1 percent of the OAD prescriptions dispensed in Csongrád County were prescribed by doctors who were primarily registered in other counties.

4.2. Distinguishing between the types of diabetes

As the indication for the medication (ICD code) was not available from the database, it was not possible to distinguish between type 1 and type 2 diabetes based on medical diagnosis. When medical diagnosis is not available, differentiation based on age is commonly used. It is an accepted approach to classify patients as having type 1 diabetes if they are diagnosed before the age of 30 or 35, and those whose disease developed after the age of 30 or 35 are defined as type 2 diabetics [52, 53]. Since the onset of type 2 diabetes is shifting to a younger age, and type 1 diabetes can, as well, develop after the age of 30, the above method may misclassify some of the patients [54, 55].

In the present research, for the classification process, not only the age, but also the type of treatment was taken into consideration. According to the guidelines and product monographs, the pharmacological treatment of type 2 diabetes can be achieved by OADs, by insulin, or by the combination of OAD and insulin. Insulin is the basis for the treatment of type 1 diabetes, although some of the OADs may be added to the therapeutic scheme; however, OADs alone are not suitable for the treatment [56, 57]. Therefore, patients who

receive OAD treatment without any insulin can be definitively defined as having type 2 diabetes, while those being on insulin alone, or on the combination of insulin and OAD can have either type of diabetes, in which cases age should be taken into consideration. For the two endpoints of the study period (1998 and 2004) the utilization of OADs and insulins were analyzed together. Until the age of 40, the prevalence of patients using insulin (insulin alone or insulin plus OAD) remained nearly steady at each age group (splitted into 5-year categories), after which a sharp rise was evident. Those patients above the steady prevalence level were classified as having type 2 diabetes. Combining insulin with OAD is not a common practice, and under the age of 40 hardly any patient on insulin received OAD as well, indicating that OADs are almost never prescribed for patients with type 1 diabetes. In conclusion, anyone receiving OAD or the combination of OAD and insulin was classified as having type 2 diabetes. Based on the above criteria, of all patients receiving pharmacotherapy for diabetes, 6% had type 1 diabetes and 94% had type 2 diabetes. These figures are in accordance with previously published international estimations, where the ratio of type 2 diabetes was assumed to be between 85 and 95% [3].

4.3. Methods used for measuring adherence and persistence

Adherence to OAD was defined using the medication possession ratio (MPR), a method commonly used to quantify medication adherence. The MPR indicates the proportion of days for which the patient possessed a supply of medication [7]. Nonadherence was set as MPR < 80%, which has been often used in the literature in cases of diabetes and other chronic diseases. The mean MPR was calculated for patients receiving combination therapy. The prescribed daily doses (PDD) were not recorded in the database; therefore, the WHO's DDDs were applied as the assumed prescribed doses [58]. The method can be considered appropriate because its results correlated well with the outcomes of other adherence measuring method (refill frequency) executed on the same set of data. In Hungary, as a general regulation, doctors were allowed to prescribe a 1-month supply of medication (which equals 30 PDDs), so patients should have claimed their prescriptions each month. Refill frequency adherence was calculated as the number of months in a year in which the patients claimed at least one prescription for OAD, divided by 12. The results yielded by the DDD and the refill frequency methods were compared by performing Pearson

correlation after Kolmogorov-Smirnov test for assessing normal distribution ($R = 0.934$, $P = 0.006$), and paired t-test was applied to demonstrate that there were no significant differences ($P > 0.05$). This comparison proves that, on average, the DDD does not significantly differ from PDD, and also that in the HNHFA database for assessing adherence the DDD and the refill frequency methodology can be used interchangeably. In a comparative study, Merlo et al. also concluded that DDD is as suitable as PDD in pharmacoepidemiologic studies at the individual level [59].

The adherence estimation was performed on chronically treated patients to eliminate bias due to in-year initiation or discontinuation of therapy. The cohort of chronically treated patients was defined as patients who had at least one prescription filled in a 6-month period both before and after the studied year.

Persistence was defined as the length of time, expressed in months, between the date of the first prescription and the date of discontinuation (which was assumed to be 30 days after claiming the last prescription, as generally 1-month supplies are prescribed). Persistence was calculated relative to the index date (date of the first prescription). Persistence analysis included only newly treated patients, defined as subjects who have not claimed any prescription for the studied drug during the 6-month period prior the index date.

4.4. Data processing and statistical analyses

The original database files from HNHFA were converted to MS Excel and the majority of data extraction and data processing tasks were accomplished using Visual Basic scripts. Visual Basic scripts enable some degree of automation in the data processing and ensures the documentation and reproducibility of the steps of the research procedures.

Student's t-test and chi-square analysis or Fisher's exact test were applied to compare means and proportions, and linear regression over time was conducted to evaluate long term trends in monthly and annual patient number and DDD totals. Correlations were tested by Pearson correlation if data were normally distributed, and by Spearman correlation if data were not normally distributed. Kolmogorov-Smirnov test was applied to assess the normality of the distribution. Persistence calculations were performed by Kaplan-Meier survival analysis, with patients being censored at the end of their observation time if they were still on the therapy.

Seasonal patterns were identified by seasonal decomposition, and the strength of the seasonality was quantified by the coefficient of determination ($R^2_{Autoreg}$) of an autoregressive regression model [60].

A P-value <0.05 was considered significant, and all reported P-values are two-tailed. Statistical analyses were conducted in SPSS version 13.0 (SPSS Inc, Chicago, IL).

5. RESULTS

5.1. Prevalence of OAD users

The prevalence of patients using OADs steadily increased during the study period ($R = 0.970$, $P < 0.001$). The yearly prevalence of OAD users increased by 50% in 7 years, from 12,159 patients in 1998 to 18,587 patients in 2004. During the study period a total of 38,855 patients received any OAD treatments at least once. In respect of the total population, the prevalence was 2.88% in 1998 and 4.32% in 2004. Considering only the adult population, the prevalence was higher: 3.61% in 1998 and 5.51% in 2004.

While the monthly patient number was only 5006 at the beginning of 1998, by the end of 2004 it reached 10597.

5.2. Incidence of OAD users and seasonality in the onset of type 2 diabetes

While the prevalence was continuously rising, the yearly incidence cases did not display an upward trend, varying between 4204 and 4748.

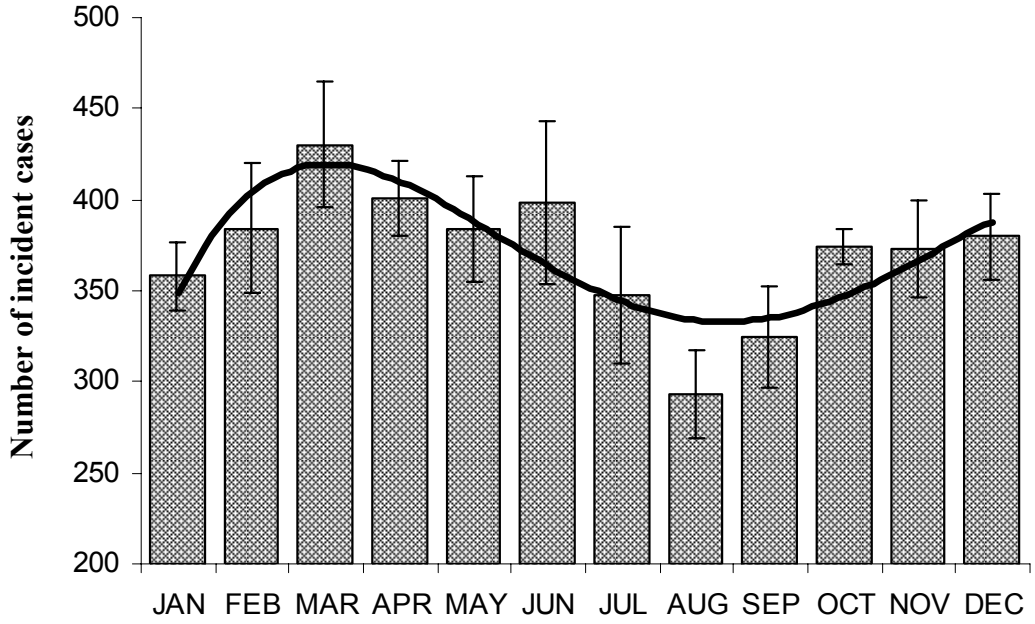

Figure 3. The monthly number (mean ± SD) of incidence cases of type 2 diabetes and a fitted polynomial trend line presenting the sinusoid seasonal pattern.

The monthly incidence cases displayed a seasonal pattern. The results of the autoregressive regression model fitted to the monthly data revealed a strong seasonality ($R^2_{Autoreg}$ = 0.632). Seasonality followed a sinusoidal pattern; the peak month was March, with a monthly incidence of 430.3 ± 34.0 (mean ± SD) cases, and the trough month was August, with a monthly incidence of 293.2 ± 23.8 cases (Figure 3). Similar patterns were found in both sexes.

5.3. Patient demography

There was a slight female majority of patients: 56% of patients were females and 44% were males, which remained constant during the study period. The average age for males was significantly lower ($P < 0.001$) than for females in each year, and gradually decreased in both genders. In 1998 the average age was 64.48 years for females and 61.81 years for males, which decreased to 63.37 and 61.16 years by 2004.

No significant difference was found in the average age of the two genders at the initiation of the OAD therapy. The average age of incidence users was 59.12 years in 1999 and 57.39 years in 2004.

The demographic characteristics of the 1350 patients, who met the inclusion criteria for detailed analyses, (including 621 males and 729 females) did not differ statistically ($P > 0.05$) from the characteristics of the total study cohort of incident users, indicating that the sample is representative.

5.4. Utilization of OADs

The overall consumption of OADs increased by 76% from 20.85 DDD/TID in 1998 to 36.83 DDD/TID in 2004 (Table 2).

The selection of OADs to prescribe from became much wider over the years: in 1998 there were seven active ingredients formulated in 15 products (different brand name, strength, package size), which increased to 11 active ingredients and 42 products by 2004.

	ATC code	1998	1999	2000	2001	2002	2003	2004
metformin	A10BA02	0.161	1.363	3.883	5.768	7.449	9.559	11.200
buformin	A10BA03	5.016	4.335	3.266	2.597	1.943	1.446	1.056
glibenclamide	A10BB01	11.351	10.085	10.455	9.302	7.998	6.855	5.538
glipizide	A10BB07	0.603	0.750	0.999	1.135	1.175	0.770	0.452
gliquidone	A10BB08	0.557	0.541	0.624	0.588	0.507	0.473	0.401
gliclazide	A10BB09	3.001	4.268	6.171	7.343	8.587	10.391	11.702
glimepiride	A10BB12	N/A	0.017	0.351	0.788	1.165	2.324	3.939
acarbose	A10BF01	0.161	0.447	0.702	1.245	1.660	2.043	2.492
rosiglitazone	A10BG02	N/A	N/A	N/A	0.000	0.001	0.004	0.028
repaglinide	A10BX02	N/A	N/A	N/A	0.001	0.006	0.013	0.025
nateglinide	A10BX03	N/A	N/A	N/A	0.000	0.003	0.002	0.003
Total		20.850	21.805	26.451	28.768	30.493	33.880	36.835

Table 2. Utilization of oral antidiabetic agents in defined daily doses per 1,000 inhabitants per day (DDD/TID) in Csongrád County 1998-2004, N/A = product not available.

The patient level data from HNHFA allow for the assessment of the prescribed drug scheme, and, consequently, it can be revealed if medications are used as a single agent or in combination with other OADs, which cannot be studied on wholesalers' data. During a 12-month period 56.5% of patients received only one type of drug regime, with no changes, 23.7% of patients had one change, and 19.8% of patients had two or more changes in their oral antidiabetic treatment. As the therapeutic scheme of a patient may be changed during a year, for the analysis of therapeutic schemes, the treatments received in the month of July in each year were used. (The month of July was chosen, because the values of this month fit best the linear regression fitted to the monthly patient numbers.) The analysis disclosed that in 1998 monotherapy was prescribed for 74% of the patients, and the combination of 2 or more OADs was used by 26% of the patients. The ratio of subjects receiving combination therapy slightly increased over the years, and reached 31% by 2004. In 1998, biguanide monotherapy was prescribed for 9.9% of patients, while 63.3% used sulfonylurea monotherapy and 25% received a combination of biguanide and sulfonylurea. In 2004, 21.5% of patients were treated with biguanide only, 40.5% received sulfonylurea monotherapy, 6.8% received acarbose only, 22.0% received a combination of biguanide and sulfonylurea, 4.5% got acarbose and sulfonylurea, and the combination of 3 drugs from different therapeutic groups was taken by 3.2% of the patients. The prescribing of irrational combinations (drugs from the same therapeutic class) happened in some rare cases.

The initial OAD treatment of new users was assessed, as well. The vast majority of patients started with monotherapy: in all the studied years 91% of patients were prescribed a single agent, and 9% received combination therapy as an initial treatment. In 1999 32.0% of patients received biguanides (18.0% metformin and 14.0% buformin), 66.5% took sulfonylureas (35.4% glibenclamide, 25.6% gliclazide, 2.7% glipizide, 2.2% gliquidone, 0.6% glimepiride) and 10.0% used acarbose as an initial therapy. In 2004 43.9% received biguanides (42.6% metformin, 1.3% buformin), 48.5% of patients were prescribed sulfonylureas (7.3% glibenclamide, 26.2% gliclazide, 0.7% glipizide, 0.5% gliquidone, 13.8% glimepiride) and 17.5% started with acarbose.

5.5. Adherence and persistence

During the study period the adherence rate did not show any changing tendency, varying between 47.9% and 49.2%. Women had a significantly better ($P < 0.001$) adherence rate than men, 51.3% vs. 45.5%. The adherence rate peaked in patients between 60 and 79 years and was lowest in patients in their 30s (Figure 4). The adherence rate of patients on monotherapy was 40% and of those on combination therapy was 67%.

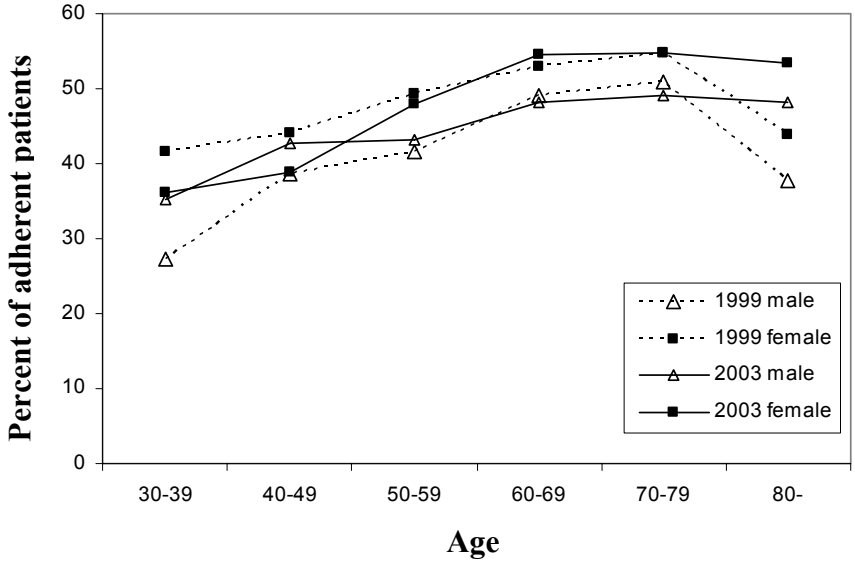

Figure 4. Percentage of adherent patients in 1999 and 2003, broken down by age and gender.

The long term follow up of patients revealed that soon after the initiation of OAD therapy many patients discontinued the treatment. After the first month one third of patients stopped taking the OADs, and after 12 months only 58.7% of them remained on the OADs. Persistence was found to be highly different regarding each active ingredient: it was highest in case of metformin (one year persistence: 62.4%), which was followed by gliclazide (60.2%), glimepiride (55.9%), glipizide (52.4%), acarbose (52.0%), gliquidone (37.6%) and buformin (34.3%) (Figure 5). Males had slightly better persistence rate than females did. Persistence rate was highest in patients between 50 and 69 years, and was lower in both younger and older age groups.

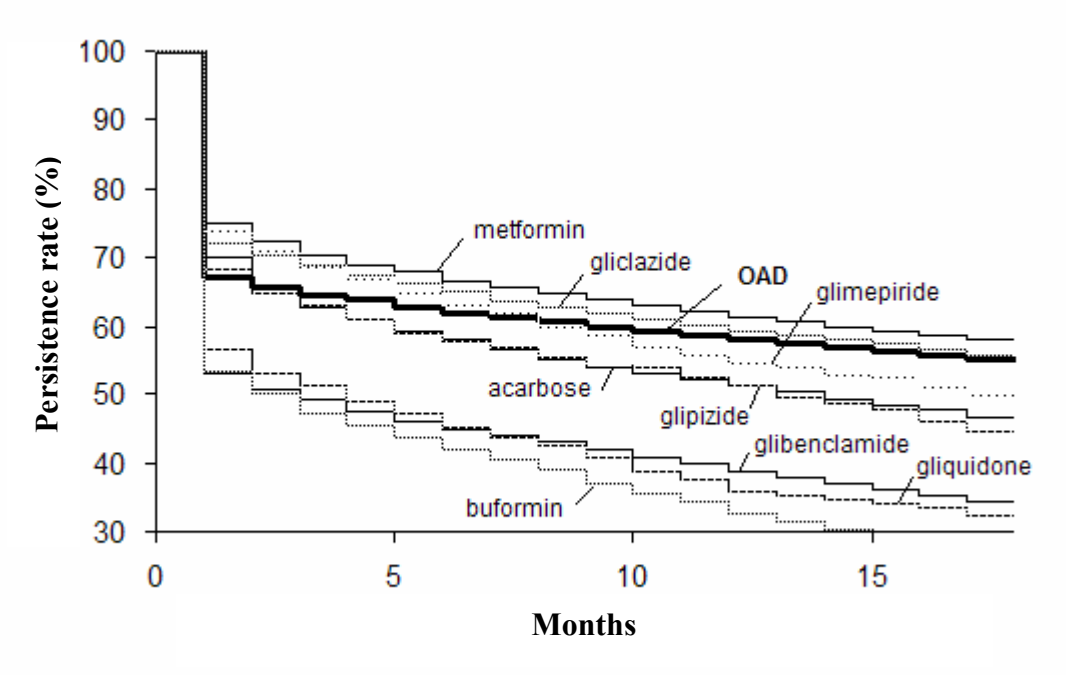

Figure 5. Persistence with oral antidiabetic therapy (OAD), and with individual drugs.

5.6. Co-medications

The complete prescription medication history of the 1350 patients (inclusion criteria are described in section 4.1.) gives the chance to study not only the antidiabetic medication of the patients, but all of their other medicines, as well. 18.0% of all prescriptions dispensed during the 5-year period were for medication treating diabetes (ATC A10 = OADs and insulins), and 82.0% were for drugs treating other health concerns. The majority of medication, 42.1%, were from the ATC C main group (drugs for the cardiovascular system);

26.1% were from ATC A main group (drugs for the alimentary tract and metabolism) which include the 18.0% antidiabetic medication; 11.9% were from the ATC N main group (drugs for the nervous system); 6.1% were from the ATC M main group (drugs for musculo-skeletal system); each of the other ATC main groups had a less than 3% share (Figure 6).

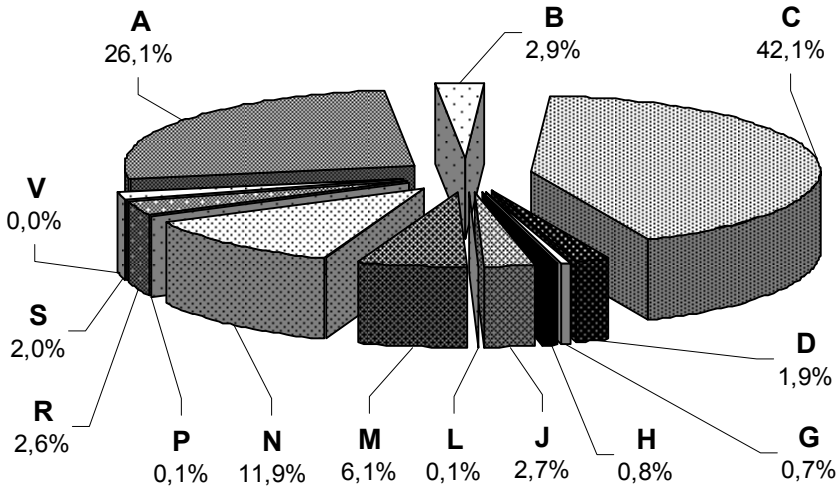

Figure 6. Percentage of prescriptions over the 5-year period according to the ATC main groups. (Capital letters refer to the ATC main groups, see Table 1 for the coding)

ATC main group	Yearly number of prescriptions per		
	inhabitants	prediabetics	diabetic patients
A	4.08	2.80	13.25
B	0.81	0.80	1.49
C	4.25	12.40	21.37
D	0.03	1.04	0.97
G	0.98	0.30	0.37
H	0.23	0.29	0.40
J	0.36	1.33	1.35
L	0.06	0.02	0.06
M	1.02	2.51	3.08
N	3.03	4.32	6.06
P	0.01	0.05	0.04
R	1.25	1.06	1.34
S	0.28	0.57	1.00
V	0.00	0.01	0.01
Total	16.40	27.50	50.79

Table 3. Comparison of the yearly average number of prescriptions – categorized by ATC main groups – claimed by average inhabitants, prediabetics (patients prior the diagnosis of diabetes) and by diabetic patients. For diabetic patients, the yearly average of the 5-year study period is given. For average inhabitants, estimation is based on reference [2] and [61].

During the course of diabetes – with the progression of the disease – a significant increase was found in the number of patients using drugs from ATC C main group ($P < 0.001$), drugs from ATC B main group ($P = 0.001$), drugs from ATC M main group ($P = 0.021$), and drugs from ATC N main group ($P < 0.001$). No statistically significant changes could be detected in cases of other medication groups.

Diabetic patients used much more medication than the average population: they claimed 3 times more prescriptions than the average citizen, and nearly 2 times more than what they had claimed just prior their diagnoses of diabetes (Table 3). Although diabetic patients used more medication from most of the drug groups than the average population, the increase in the number of prescriptions for cardiovascular drugs (ATC C main group) was the most striking one.

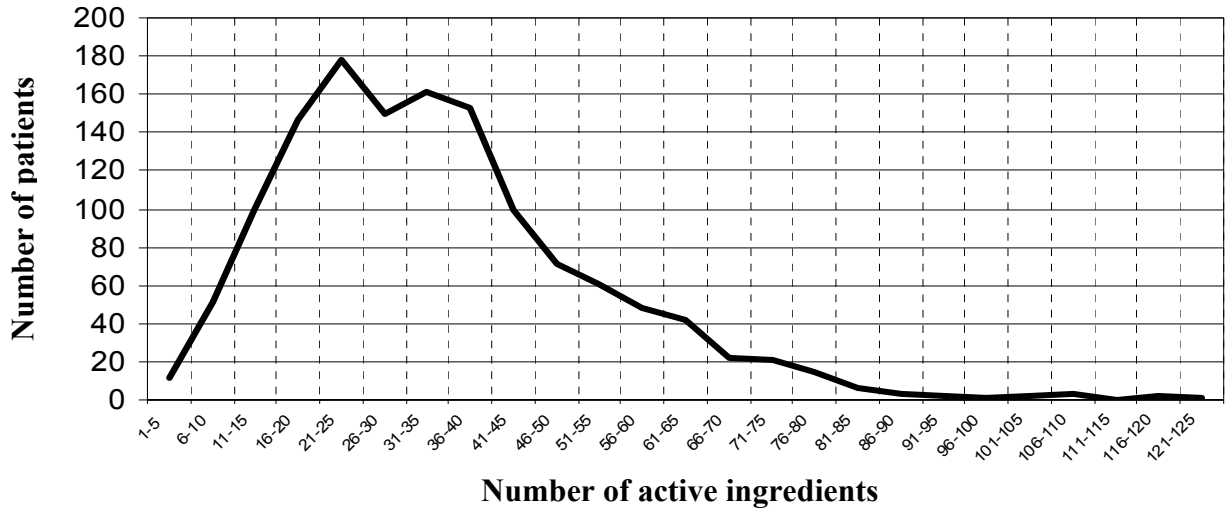

Figure 7. Number of active ingredients patients (n = 1350) used over a 5-year period.

During the first year of diabetes males claimed 40.0 prescriptions and females collected 48.3 prescriptions on average. By the fifth year this increased to 54.8 and 62.3 prescriptions, respectively. During the first year males used an average of 10.8 different active ingredients which increased to 12.9 in the fifth year, and females used 13.2 active agents in the first year and 14.5 in the fifth year. During the 5-year period males were treated with 30.9 active ingredients, and females received 37.2 on average, but the maximum was 122 different active ingredients prescribed for a single patient (Figure 7). The number of products patients were treated with is even higher if the different strength, package size

and brand names are also taken into consideration: males received 39.9 different products, and females were prescribed 48.4 products during the 5-year period.

In one third of patient–pharmacist interactions patient claimed only one prescription, but in nearly 20% of the pharmacy visits patients presented 5 or more prescriptions. During the first year of diabetes, 5 or more prescriptions on a single visit were claimed at least once by 57% of patients, which increased to 72% by the fifth year.

5.7. Pharmacy visit pattern

Pharmacy visit pattern analysis included 1350 patients for whom 342,854 prescriptions were dispensed during 116,850 patient–pharmacist interactions in a 5-year period. Males made significantly less pharmacy visits than females did ($P < 0.001$).

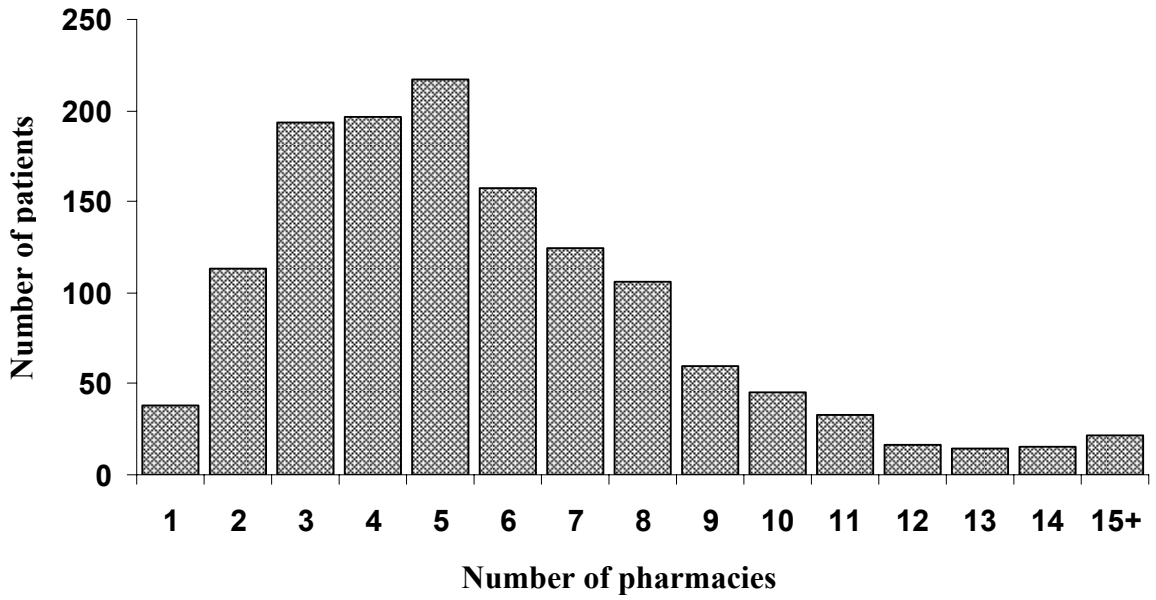

Figure 8. Number of pharmacies patients (n = 1350) visited over a 5-year period.

During the first year males made an average of 15.3 pharmacy visits, and females made 18.0 visits. By the fifth year this increased to 17.5 and 19.7 visits, respectively. Each year patients visited an average of 3 pharmacies, and over the 5-year period 5.7 pharmacies (Figure 8). No statistically significant differences were found between the two genders.

Patients' loyalty to the pharmacy they most often visited was 73.5% on average. Strong inverse correlation ($R = -0.929$, $P < 0.001$) was found between the number of pharmacies in a town and patients' loyalty. In towns where only one pharmacy operates loyalty rate was 85.5%, while in Szeged, where 34 pharmacies are located, the loyalty rate was only 67.1%.

Adherence rate over the time span was found to be very low: only 16.4% of males and 19.1% of females were adherent to the antidiabetic therapy (including both OAD and insulin treatments). Increased patient loyalty resulted in significantly better adherence rates in females ($R = 0.881$, $P = 0.004$), but not in males ($R = 0.381$, $P > 0.05$). Only 8.6% of females with less than 40% loyalty were adherent, but the adherence rate increased to 24.5% among females with over 80% loyalty (Figure 9).

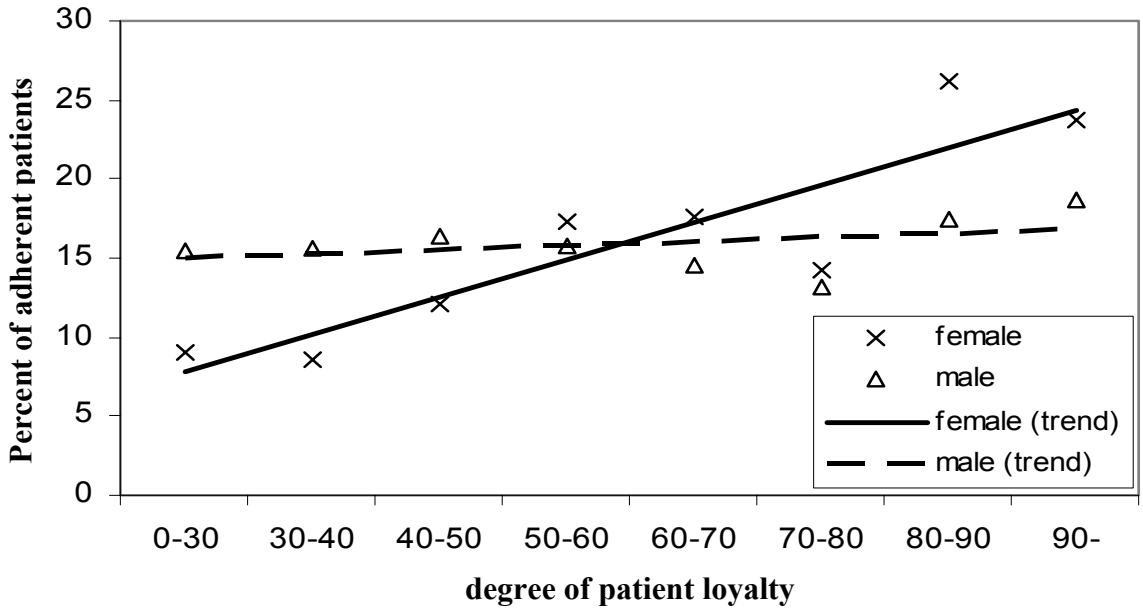

Figure 9. Correlation between the degree of patient loyalty (to the pharmacy they most often visited) and the adherence rate.

5.8. Cost of treatment

While the utilization of OADs showed a 76% increase between 1998 and 2004, the expenditure increased by nearly 250%; the annual cost rose from 82.9 million Forints (HUF) in 1998 to 283.6 million HUF in 2004 in Csongrád County. Some of the increase in cost

was due to inflation, but a greater part of the increase can be attributed to the higher price of newer products. The financial burden on patients increased more dramatically, by over 550%. The average reimbursement on OADs was 85% at the beginning of 1998, which gradually decreased to 65% by mid 2000, and remained steady since then. In 1998 copayment varied between 1.28 and 80.40 HUF/DDD. The most often used product (Gilemal 5 mg) had a 2.00 HUF/DDD copayment. In 2004 copayment ranged between 1.30 and 204.38 HUF/DDD. The largest quantity was prescribed from Diaprel, which had a copayment of 12.13 HUF/DDD, and the second largest quantity was prescribed from Merckformin 850 mg, for which patients had to pay 7.69 HUF/DDD (Table 4).

	1998		2004	
	copayment	total cost	copayment	total cost
metformin	25.88–30.51	25.88–30.51	7.49–77.33 (F)	29.24–77.33
buformin	2.30 (F)	23.00	18.00 (F)	52.80
glibenclamide	2.00 (F)	20.33	12.07 (F)	39.93
glibenclamide micro	1.28–1.67 (F)	12.78–16.40	1.30–10.93 (F)	15.25–35.33
glipizide	12.00	40.07	15.80	52.53
gliquidone	11.48	38.28	11.72	45.88
gliclazide	12.20	40.67	12.13	47.40
gliclazide MR	N/A	N/A	14.50	56.50
glimepiride	N/A	N/A	24.87–30.87	58.12–72.73
acarbose	48.88–80.44	97.75–161.00	49.60–82.00	115.55–193.00
rosiglitazone	N/A	N/A	149.95–204.38	348.62–472.50
repaglinide	N/A	N/A	107.47	126.42
nateglinide	N/A	N/A	129.71	259.46

Table 4. The cost of oral antidiabetic drugs in 1998 and 2004. The copayments and the total costs are expressed in Forints per defined daily doses (HUF/DDD). (F) indicates that medication was available free of charge for eligible patients. N/A = product not available

Financial support on medication was further reduced by making less people eligible for free medication (a form of social support). At the beginning of 1998 one fifth of the prescriptions were free of charge, but at the end of 2004 this number decreased to 6.4%.

The expenses of the OADs are only part of the total medication cost of patients with diabetes. A total medication cost analysis was performed on the complete prescription medication record of the 1350 newly diagnosed diabetic patients. The analysis revealed that

antidiabetic medications (including OADs and insulins) were responsible for only 15.7% of the total prescription medication costs over the first 5 years of diabetes, while drugs for the treatment of cardiovascular diseases (ATC group C) accounted for 42.5% of all expenses. There were no statistically significant differences ($P > 0.05$) between the expenses of males and females during the five years, but the medication cost prior the diagnosis of diabetes was significantly ($P = 0.001$) higher for females than for males. The overall prescription medication cost (copayment and insurance reimbursement) for the 5 years was, on average, 429,448 HUF per patient. With the progression of the disease the annual cost rapidly increased, and by the fifth year it was more than the double of the costs of the first year (Figure 10). During the first year the average medication expense was 60,366 HUF per patients, which increased to 124,206 HUF by the fifth year.

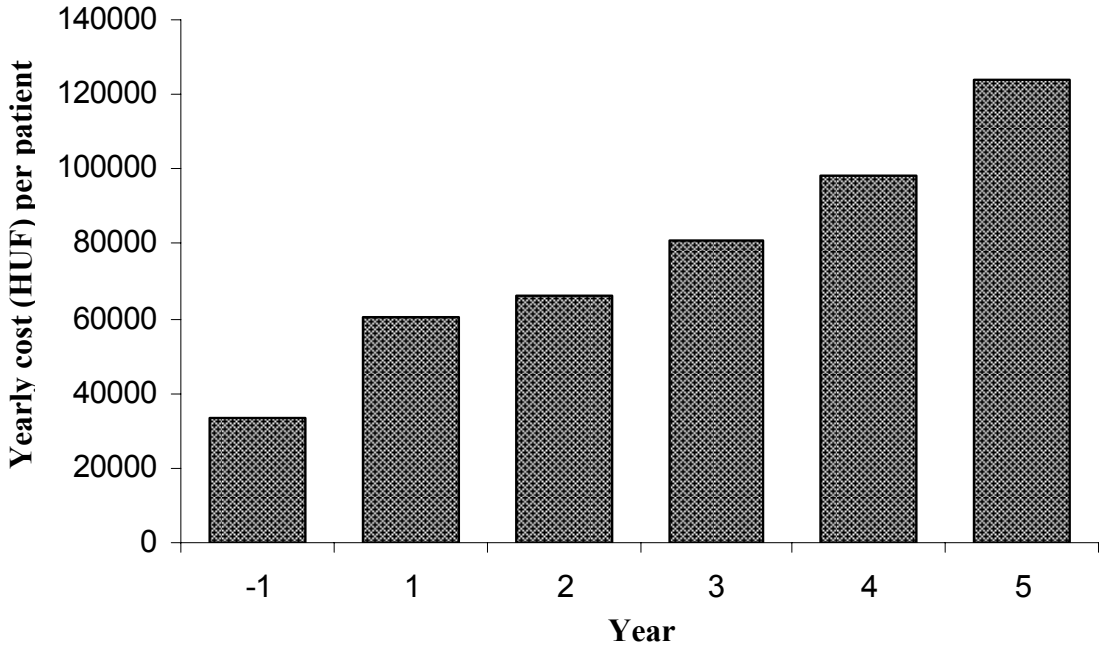

Figure 10. The increase of the average yearly prescription medication cost (copayment and insurance reimbursement) in Forints (HUF) per patient as diabetes progresses. Year -1 represents the period prior the initiation of antidiabetic treatment.

6. DISCUSSION

6.1. Prevalence

The yearly prevalence of OAD users only reflect the number of patients using OADs and not the total number of people having diabetes, as it did not include patients who use insulin only, and therefore the number of people receiving any type of medical treatment for diabetes is expected to be about 20% higher. According to the official health statistics, 6.51% of the adult population of Csongrád County was registered as having diabetes in 2003, which was slightly higher than the national average of 6.28%. (Figure 11) [2].

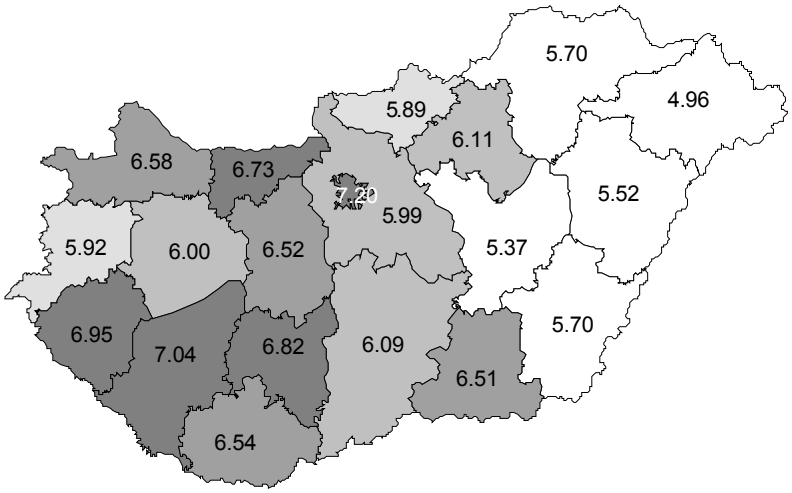

Figure 11. Prevalence of diabetes among the adult population in 2003 (map is based on official national health statistics [2])

Although there was a continuously rising tendency in the monthly patient numbers, some distinct fluctuations were evident, which could be contributed to price changes of the medication patient claimed. Just before any increase in the copayment of drugs, the number of patients claiming their medication increased, after which transient declines of up to 15% in the number of patients were noted.

6.2. Incidence and seasonality

The incidence cases of OAD users can be considered as the incidence cases of type 2 diabetes. The onset of type 2 diabetes is difficult to identify and study from the point of view of pharmacoepidemiology, as in the earliest stage of the disorder, mostly nonmedical approaches are applied that are not always recorded in the medical profile. In the progression of type 2 diabetes the initiation of treatment with oral antidiabetic drugs is the stage at which all patients can be definitively recognized as having the disorder.

The seasonal pattern in the onset of type 1 diabetes has been described [62], but seasonality in the onset of type 2 diabetes has not been previously reported. Some studies revealed seasonal changes in glycemic control in selected cohorts of patients with type 2 diabetes [63–65]. The months of peak and trough coincide with the peak and trough periods in the seasonality of HbA_{1c} values previously reported [63]. Although the exact mechanism causing the seasonality is not yet known, it is thought that seasonal changes in weather, eating habits and physical activity may be contributing factors [63].

6.3. Patient demography

The female majority of patients diagnosed with diabetes in the studied population is the result of the demographic structure of the general population. Females have a longer life expectancy than males (76.5 years for females, and 68.2 for males [66]). Therefore, at an older age there is a marked female majority. The age- and gender-specific prevalence reveals that males have a slightly higher prevalence of diabetes than females do.

The decline in the average age of incidence users suggests that the onset of type 2 diabetes is shifting to a younger age.

The gap between the average age of prevalent users and the average age of incident users is getting wider, indicating that patients are now treated for a longer period of time, but this can be rather contributed to the earlier initiation of the treatment than to any improvement of life expectancy of diabetic patients. Between 1999 and 2004 the gap increased from 3.01 to 4.04 years for males, and from 4.36 to 5.77 years for females, which indicates that after the diagnosing of diabetes females live much longer than males do.

6.4. Changes in the utilization of oral antidiabetic drugs

Along with the escalating patient number, the total utilization of OADs increased, as well. Although the use of each therapeutic group increased, a marked restructuring was evident.

The extensive increase in product number is not only the result of the broader selection of active ingredients, but rather due to the availability of generic drugs. By 2004 over one third of the total metformin use was in the form of generic products (Merkformin was considered as the original product which was the first metformin marketed in Hungary).

The use of biguanides increased by 136%, but the share of the available active ingredients – metformin and buformin – fundamentally changed. Buformin was the only biguanide on the market for two decades after its licensing in Hungary in 1967, and metformin was licensed only in 1996, and became available from early 1998. In 1998 the vast majority of biguanide use was due to buformin, which gradually decreased, and in 2000 the ratio switched in favor of metformin, and by 2004 metformin was responsible for over 90% of biguanide utilization. This is a positive change as guidelines recommend the use of metformin, and the application of buformin is considered to be out of date [56]. Metformin was prescribed, either alone or in combination with other OADs, for only 4.2% of the patients in 1998, whereas in 2004 it became the most often used OAD, received by 43.0% of patients. Its widespread use can be justified by the fact that metformin is the first choice of drug in overweight patients and that in Hungary half of the adult population is overweight or obese [67]. Phenformin, an other representative of the biguanide group, that had been available in several other countries, was never marketed in Hungary.

The use of sulfonylureas increased at a much lower scale than the use of biguanides, undergoing a 42% raise. While in 1998 glibenclamide was the most often used sulfonylurea (and the most often used OAD, as well) with 11.35 DDD/TID, in 2002 gliclazide took the lead, and in 2004 only 5.54 DDD/TID glibenclamide was consumed. In 1998 only 17% of the glibenclamide use was in the form of micronized glibenclamide, which gradually increased, and in 2004 the share of the micronized form was two thirds. During the same time frame the utilization of gliclazide increased from 3.00 to 11.70 DDD/TID. The modified release formulation of gliclazide became available in 2003, and in 2004 already over 20% of the gliclazide was used in that form. Glimepiride was first marketed in 1999,

and by 2004 its use reached 3.94 DDD/TID. The use of the other two available sulfonylureas (glipizide and gliquidone) remained subsidiary during the study period. In the case of elderly people, the choice of sulfonylurea should be one of the short-acting ones, such as gliclazide, and the prescribing of the long-acting sulfonylureas, such as glibenclamide, should be avoided [56, 68]. Among patients 65 years of age or older, glibenclamide was the most often prescribed OAD in 1998, taken by 71.6% of the elderly patients, but in 2004 only 15.3% of the patients were using it. In 1998, gliclazide was prescribed for 21.9% of the elderly patients, and in 2004 it was the most often used sulfonylurea, received by 40.8% of them.

Acarbose is the only representative of the alfa-glucosidase inhibitors available on the Hungarian market, which was licensed in 1991. In 1998 its use was still marginal (0.16 DDD/TID), which only slowly increased, and reached 2.49 DDD/TID in 2004. Its relatively high price (see Table 4) may explain its limited use for the several years following its launch. Until the introduction of rosiglitazone and the meglinides (repaglinide, nateglinide), acarbose had been the most expensive OAD. Miglitol, an other alfa-glucosidase inhibitor, was license in Hungary in 2000, but it has not been marketed since.

The meglinides and rosiglitazone, even after being available on the market since 2001, still could not gain ground. Their high price compared with other OADs was the likely reason that caused their use to remain marginal. Although by the end of 2003 these newest OADs were accepted into the reimbursed category, their copayments were still exceptionally high.

Calculation was performed in order to estimate the proportion of patients with type 2 diabetes who were treated with insulin. Patients were classified as described under section 4.2. During the study period the use of insulin did not change considerably among patients with type 2 diabetes. In 1998, 16.53% were treated with insulin alone, 2.27% with the combination of OAD and insulin, and 81.20% with OADs. In 2004, 16.05% were treated with insulin alone, 3.63% with the combination of OAD and insulin, and 80.31% with OADs. The proportion of patients on combination therapy is extremely low compared with that of other countries. In France, 18% were treated with insulin plus OAD, 9% with insulin, and 71% with OAD; in Sweden, 23% used insulin plus OAD, 3% received insulin, and 74% received OADs [69, 70].

Comparing the utilization of antidiabetic drugs in Hungary to that of some other European countries, it is notable that the use of OADs versus insulin was high in Hungary: 73.7% of all antidiabetic drugs were OADs, whereas in Sweden their share was only 48.5% in 2003 [71] (Table 5). The theoretical exposure of each patient to antidiabetic drugs (calculated from the total utilization of antidiabetic drugs and from the estimated prevalence of patients [3, 71]) was 0.47 DDD/day in Hungary, which was similar to that of Norway (0.48 DDD/day). Finland and Iceland had exceptionally good exposure rates (0.80 and 1.05 DDD/day). The low rate for Hungary suggests that many patients remained untreated and/or undermedicated.

	Iceland	Denmark	Norway	Finland	Sweden	Hungary
Diabetes prevalence (%)	2.0	6.9	6.9	7.2	7.3	9.7
Insulins (DDD/TID)	5.9	11.3	16.5	20.2	21.7	12.11
OADs (DDD/TID)	15.1	17.2	17.2	37.8	20.5	33.88

Table 5. Estimated prevalence of diabetes in the adult population and utilization of antidiabetic drugs in some European Countries in 2003 [3, 71]. (DDD/TID defined daily doses per 1,000 inhabitants per day, OADs oral antidiabetic drugs)

Considering the number of patients treated with OADs and the fact that about one fourth of them received combination therapy, the utilization of OADs should have been above 50 DDD/TID in 2004. Comparing this number with the actual consumption of 36.83 DDD/TID further supports the hypothesis that some patients did not take the desired amount of medication.

6.5. Adherence and persistence

The crude adherence rate did not change considerably over the study period. Women had a better adherence rate than man. This fact suggests that female patients tend to manage their disease better and take better care of their health. The National Health Survey of 2000 revealed that women were 30% more likely than men to have appointments with their general practitioners [67]. The results of the present research show that younger age groups are more likely not to adhere to therapy. The adherence rate was found to be lowest in patients in their 30s, although tight glycemic control would be essential from the earliest stage of diabetes to reduce a patient's risk of developing chronic complications. At younger

age, patients are less likely to have developed chronic complications of diabetes; therefore they may perceive their disease to be less serious than it is.

The results showed that people on combination therapy had a much better adherence rate (67%) than those on monotherapy (40%). This result contradicts with the general belief that the adherence rate decreases with the complexity of the therapy, although some studies support the above findings [72, 73]. It is possible that those on combination therapy had worse health conditions with possibly higher rates of complications, which made them take their situation more seriously and, consequently, made them adhere to therapy much better. In order to tests the hypothesis that the adherence of patients should improve with the progression of the disease, the adherence rate was assessed for those patients who were present during the entire study period. This cohort consisted of 3771 patients, and their adherence was followed for a 5-year period, between 1999 and 2003. The adherence showed a constantly rising tendency with the progression of time: in 1999 48.4% of males and 54.8% of females were adherent, which increased to 66.3% and 70.5% in 2003, respectively; therefore, these results support the above hypothesis.

The rate of treatment discontinuation was high, most strikingly soon after the initiation of the therapy, suggesting that a considerable portion of diabetic patients find it difficult to accept the fact that their condition would require long term medical treatment. In order to achieve long term success in the treatment, special attention should be paid to the patients during the early months of the therapy.

6.6. Co-medications

Previous studies have proven that diabetic patients take significantly more medication than nondiabetic subjects [74]. The use of many drugs by a patient is referred to as polypharmacy, which is often defined as taking 5 or more drugs at the same time [75]. The increased number of medication prescribed is often the result of treating common comorbidities of diabetes, such as hypertension, dyslipidemia, depression, and coagulopathies [76].

The large share of drugs from the ATC C main group can be justified by the fact that cardiovascular diseases are over 3 times more common among diabetic patients than in nondiabetic ones, and it has been reported that more than 90% of diabetic patients over the a

age of 65 have hypertension [77]. In the present research in the last half year of the study period 89.5% of the patients were taking some medication for cardiovascular diseases.

The concurrent use of several drugs not only increases the complexity of the treatment and results in higher health care cost, but also raises the risk of adverse drug reactions and drug-drug interactions [75]. As polypharmacy is almost inevitable in diabetic patients, regular reevaluation of the therapy is essential to minimize the risk arising from polypharmacy.

Over the 5-year period the number of products patients used was 30% higher than the number of active ingredients, which points out that subjects had used the same active ingredients in products of different packaging and brand name or strength. This may further increase the risk of medication errors, as patients may not be aware of the fact that drugs with different appearance can contain the same active ingredients.

6.7. Pharmacy visit pattern

Community pharmacies can play an important role in the management of chronic disorders by offering pharmaceutical care to their patients. Numerous studies have proven that pharmaceutical care programs focusing on diabetic patients can result in improved glycemic control [78–81]. Periodical assessments and long term follow up of patients are key elements of the care programs [82, 83], the benefit of which can be experienced to the full extent only if patients regularly visit the same pharmacy.

Although diabetic patients made a pharmacy visit once in every 20 days on average, the pharmacy visit pattern study demonstrated that in a setting where patients are free to claim their prescription at any community pharmacy, patients do not consistently use the services of a single pharmacy, but they rather tend to visit several ones. In case of females the results clearly prove the beneficial effect of higher patient loyalty, resulting in better adherence rate, although similar effect could not be detected in case of males.

The actual number of pharmacy visits can be higher than it was measured, as due to the limitation of the data source, only those patient–pharmacist interactions could be counted where prescription medication was claimed. A further limitation is that the person visiting the pharmacy may not be the patient himself or herself, but the patient's family member or caregiver.

The irregular pharmacy visit pattern disrupts the continuity of the care process, and, consequently, reduces the effectiveness of pharmaceutical care initiatives.

6.8. Pharmacoeconomic aspects

Diabetes and its complications put a high financial burden both on patients and the society. A cost analysis study on diabetes revealed that over 10% of the total health care expenses are attributed to diabetes in the U.S. [84]. The expenses of the disease are not limited to health care spendings, but they are attributed to both direct and indirect costs. The direct costs of a chronic disease include medication, outpatient services, medical devices, inpatient care and long-term care [85, 86]. The indirect costs are more difficult to define and measure, and studies vary in methodology. The indirect costs may include present and future non-medical costs, such as disability, productivity loss, or premature mortality [85]. Diabetes and its complications result in nearly 30% loss of productivity [87]. A substantial amount of diabetes-related costs arise from the complications of the disease, of which macrovascular problems have the largest share [88]. During the first 5 years of treatment, 85% of the costs arising from the complications are related to macrovascular complications [88]. European and American studies report that the direct health care expenditures are nearly 100% higher for diabetic patients than for non-diabetic counterparts matched by age and gender [84, 86]. Studies widely vary on estimating the magnitude of direct and indirect costs related to diabetes, the estimated share of direct costs from the total expenses ranges between 30 and 75% [84, 85]. Data from HNHFA allow for the cost analysis of the prescription drug treatment, but other components of direct and indirect costs could not be assessed.

The substantial increase in the copayment could have negatively effected patients' medication taking behavior, but as it was described in section 5.5., the adherence did not decrease over the study period.

Although the annual total medication cost of patients more than doubled from the first year to the fifth year, the cost increase attributed to the progression of diabetes was 69%, taking into consideration the 22% price increase during the 5-year period.

There was no non-diabetic control group to compare the expenses to, but the medication records of the study subjects were available for the 6-month period prior the

initiation of antidiabetic treatment. During that period subjects were not medicated as diabetic patients, therefore they could represent non-diabetic patients. The expenses of the 6-month period were extrapolated to 12 months to get a yearly value, which is easier to compare to the costs of the treatment during the diabetic period. The yearly medication costs prior the diagnosis of diabetes were nearly half of the costs spent during the first year of the disease (there were no price changes during this period that should be taken into consideration), and by the fifth year the treatment of diabetic patients became almost 4 times more costly than it was before the diagnosis of diabetes. Prior the diabetic period the average yearly medication costs were 29,217 HUF for males and 37,226 HUF for females ($P = 0.001$).

7. SUMMARY

During the 7-year study period the overall utilization of OADs significantly increased, and it showed clearly positive and considerable changes, which were in concordance with national and international guidelines; although the newest additions to the group of OADs have not been able to gain ground.

While the number of patients receiving treatment was consistently increasing at an alarming scale, unfortunately, their therapeutic cooperation remained low, which can result in suboptimal clinical outcomes. The rate of early treatment discontinuation was high, and the adherence of patients who continued the therapy was low, and did not change during the study period. With increased age and progression of diabetes, patients tended to better adhere to the treatment plan.

The drug treatment of patients was not limited to diabetes, but due to the high prevalence of comorbidities and complications of diabetes, they used 3 times more medication than the average population, making their treatment rather complex and costly.

The present pharmacoepidemiologic study does not only provide data on drug utilization patterns, but it also revealed a new pathophysiologic aspects of diabetes, namely that not only type 1 diabetes has a seasonal pattern in its onset, as it has been previously published, but type 2 diabetes has it, as well.

To improve patients' therapeutic cooperation and, consequently, improving clinical outcomes and reducing the development of complications of diabetes, the long term care of diabetic patients is essential through a joint effort of health care providers. Pharmacists can play an active role in the care process by the implementation of a pharmaceutical care program targeting diabetic patients.

The benefits of such program could be experienced to the full extent only if patients would regularly visit the same pharmacy. Although diabetic patients often make pharmacy visits, unfortunately, most of them are not loyal to a single pharmacy and they tend to visit several ones, which can disrupt the care process and reduce its effectiveness.

The results of the present thesis support the importance of the implementation of a pharmaceutical care program in Hungary in the near future, and provide detailed data on the medication use pattern and therapeutic cooperation of patients with type 2 diabetes, which information can serve as a resource for the design of a long-term care program.

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