# Clinical and pharmacoeconomic impact of patient medication adherence

Doktori tézisek

**Dr. Koncz Tamás**

Semmelweis Egyetem
Patológiai Doktori Iskola

**Témavezető:**
Dr. Gulácsi László Ph.D., Habil.
Egészség-gazdaságtani és Technológiaelemzési Kutatóközpont
Corvinus Egyetem

**Hivatalos bírálók:**

**Szigorlati bizottság elnöke:** Prof. Dr. Papp Zoltán
**Szigorlati bizottság tagjai:** Dr. Hőgye Mihály, Ph.D.
Dr. Mészáros Ágnes, Ph.D.

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## Introduction

The primary goal of health care decision making is to maximise the health care gain for the population that the interventions provide. The available resources, however, are scarce. Thus, decision makers are confined to making choices between alternative health care interventions competing for resources. Health-economic evaluation, or in the case of pharmaceuticals, pharmacoeconomic evaluation is a decision tool that compares the costs and the outcomes or health gains of these interventions. (Drummond et al.. 1997)

The comparison of health care interventions is usually based on results of clinical trials. However, since the 1960s, the introduction of clinical trials as they are known today, it has been pointed out that their results do not necessarily match those expected in routine clinical practice. (Schwartz and Lellouch 1967, Sackett and Gent 1979, Feinstein 1983, Revicki and Frank 1999) As the main goal of health economic analyses is to inform and aid decisions for routine clinical practice, it is imperative that these evaluations account for the factors that differ between clinical trials and real life practice.

The differences are due to the different conditions of clinical trials and routine practice. An important factor is the difference in patients' compliance with their prescribed treatments.

Non-compliance with prescribed medication is as old as medicine itself. (Lindström and Bingefors 2000) It has a number of causes: medical, psychological, socio-economic, the burden of co-payment, access to medication, understanding of disease and pharmacological therapies, adverse effects, ease of use, disease and medicine specific factors, or simple forgetfulness. (Cleemput et al.. 2002, Skaer et al.. 1996)

According to a Cochrane systematic review, the full benefit of pharmacological treatments can not be realised with current levels of patient compliance. (Haynes et al.. 1999) Its impact can be negative both from a clinical and an economic perspective. (Hughes et al.. 2001a, Cleemput et al.. 2002)

In spite of this, the study of patient medication compliance has been somewhat neglected by both the Hungarian and the international scientific community. This may explain the lack of universally accepted terminology and methods of measurement. The lack of consensus hinders comparability of findings from different studies; hence there is a need for an overview of current knowledge.

*Definitions*

There are a number of terms used to describe the phenomenon of "medication taking." The English language uses compliance, adherence, and persistence. The differences between these terms will be highlighted below. The Hungarian word is *beteg-együttműködés.*

The most widely used term remains compliance, which has a broader and narrower definition. According to the broader definition, compliance is „the quality of the patient's execution of the prescribed therapy". (Métry 1999) For the narrower definition of compliance, it is necessary to consider that a prescribed regimen has two dimensions: dose and time. Therefore, compliance is the extent to which a patient acts in accordance with the prescribed interval and dose. Its quantification is the comparison of two series: the dosing history and the prescribed regimen. Compliance is typically expressed as a percentage of total number of doses taken (if prospectively measured) or therapy-days available (if retrospectively measured), in relation to the time period of observation during which compliance is measured. (Hughes et al.. 2007)

There are many chronic therapies that need to be followed life-long. Therefore, the term *persistence,* i.e. persisting with the therapy has been introduced. Medication persistence is the length of time from initiation to discontinuation of therapy and is measured in units of time. (Hughes et al.. 2007, Urquhart 1997)

There is a blanket term that is used to describe the whole phenomenon: *adherence.* Adherence is defined as the quality of the patient's execution of the prescribed regimen. It is not quantifiable, it is a qualitative term. The definition of adherence by the World

Health Organization (WHO) is "the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes corresponds with agreed recommendations from a health care provider." (WHO 2003)

*Measurement*

There is also great disparity in how compliance and persistence are measured. Methods range from questionnaires and patient diaries to electronic prescription databases and electronic compliance measurement devices to therapeutic drug monitoring and directly observed therapy. The thesis compares the advantages and disadvantages of the various measurement methods and a summary is provided in Table 1.

*Table 1.* Methods for assessing patient adherence

| | **Single measurement** | **Continuous measurement** |
|---|---|---|
| Not reliable | Patient interview<br>Pill count<br>Electronic database | Patient diary<br>Retrospective questionnaire |
| Reliable | Therapeutic drug monitoring | Directly Observed Therapy<br>Electronic compliance monitoring |

*Prevalence*

As for the prevalence of non-adherence with prescribed medications, there is agreement in the scientific literature that the phenomenon is ubiquitous regardless of the therapeutic area. Systematic reviews estimate general rates of 50% of compliance in developed countries and even lower in developing countries. Examples with anti-hypertensive, anti-hyperlipidaemic, anti-HIV, anti-depressive and other pharmacotherapies are quoted in the thesis. A systematic review on adherence with biological disease-modifying

antirheumatic drugs (DMARDs) in Rheumatoid Arthritis (RA) is included in this thesis. (Koncz et al.. 2010)

The clinical and economic consequences of non-adherence may be severe. Non-adherence impacts the chance of therapeutic success. (WHO 2003) The consequences range from the negligible to the catastrophic, depending on the disease, the severity of the disease, the co-morbidities and the extent of non-adherence. In particular, infectious and chronic diseases are impacted. Non-adherence delays therapeutic remission, increases disease severity, new symptoms may appear, and in the case of infectious diseases, the risk of complications and development of multiresistent strains increases. (Haynes et al.. 1999, Métry 1999) As for the economic consequences, the impact on subsequent overall health care resource utilization is determined primarily by the decrease in clinical effectiveness, and on the relationship between loss of effectiveness and increased resource utilization. Evidence that suboptimal patient adherence results in decreased clinical effectiveness, hence in increased health care resource utilization is provided in the thesis. (Koncz et al. 2008) Increased health care costs due to non-adherence are also reviewed in a number of health care settings and therapeutic areas and it is concluded that non-adherence may have severe health economic consequences. Direct medical costs of non-adherence were $735 million and $13.35 billion, respectively, in Ontario, Canada and the whole of the United States. These are 0.8 and 1.7% of the annual health care expenditure, respectively. (Iskedjian et al.. 1998, Sullivan et al.. 1990)
To assess the combined impact of non-adherence on both effectiveness and costs requires the use of economic evaluations. The thesis contains an assessment of the inclusion of adherence in pharmacoeconomic analyses.

**Objective, main aims and hypothesis**

The *objective* of this thesis is to provide evidence that patient medication adherence is below the level deemed optimal by current medical knowledge (*suboptimal adherence*) and this fact has implications on the effectiveness and economics of pharmacotherapy.

The *hypothesis* is that patient adherence is suboptimal and this will decrease the clinical effectiveness of pharmacotherapy and will increase overall health care resource utilization.

The objective will be approached through three main goals:

*Goal #1:*
Evidence on patients' level of adherence with pharmacotherapy will be explored through a systematic literature review of adherence with biologic DMARDs.

Goal # 2:
In a second literature review, pharmacoeconomic studies that considered medication adherence will be assessed.

*Goal #3:*
An example of evidence when suboptimal patient adherence results in decreased clinical effectiveness will be provided.

**Methods**

The first goal of the thesis was to provide evidence on patients' level of adherence with pharmacotherapy and it was explored through a systematic literature review of adherence with biologic DMARDs. (Koncz et al. 2010) A MEDLINE search between 1 Jan 1997 1 Feb 1 2010 was conducted for English language articles that assessed adherence, compliance, and persistence with biologic DMARDs in RA. Two investigators reviewed the titles and abstracts of all citations identified by the literature search independently. Potentially relevant studies were retrieved and the inclusion criteria were applied. The two investigators reviewed the eligible articles independently, disagreements on scoring on the evaluation criteria were resolved by consensus and information was extracted for each selected study. Given the large variations in methods and patient samples of the studies included, no attempt was made to perform a meta-analysis or to stratify studies.

The second goal of the thesis was to perform a literature review to assess if recent pharmacoeconomic studies considered medication adherence. The literature was searched for pharmacoeconomic evaluations published in the period between January 1997 and March 2009. Articles were included if they explored the dependence of cost-effectiveness results on varying levels of some form of adherence-related measure. The different methodologies used were reviewed and articles were appraised critically.

The third goal of this thesis was to provide evidence when suboptimal patient adherence results in decreased clinical effectiveness and increased health care resource utilization by assessing the rate of gastrointestinal (GI)-related hospitalizations occurring with varying levels of gastroprotective agents (GPA) use when co-prescribed with non selective non-steroidal anti-inflammatory drugs (nsNSAIDs). (Koncz et al. 2008) It was a retrospective, observational, database study conducted in the United Kingdom. The DIN-LINK primary care database contains longitudinal data for more than 800 000 currently registered patients in the United Kingdom drawn from a representative panel of 100 primary care practices. The DIN-LINK database contains details on all elements of a patient's medical history, such as diagnoses, test results, prescriptions, referrals, and hospitalizations, as entered by general practitioners. (Doctors' Independent Network (DIN-LINK) database, 2010)

GPA co-prescription, the proxy for GPA use, was calculated as the percentage of days with a GPA prescription within a rolling 3-month period of nsNSAID use:

$$\text{GPA use (\%)} = \left( \frac{\text{Days on GPA}}{\text{Days on nsNSAID}} \right) \times 100$$

Patients were stratified according to the following levels of GPA use: 100% (i.e., full gastroprotection), 80–99%, 60–79%, 40–59%, 20–39%, and 0–19%.

To evaluate the effect of varying GPA use on the risk of hospitalization, rates and odds ratios (OR) of GI-related hospitalizations were calculated for the different subgroups (by GPA use level) of the total high GI-risk patient population and for frequent nsNSAID users with GI risk.

## Results

### Adherence with biologic DMARDs in RA

The systematic literature review found that compliance rates with biologic DMARDs in RA are well below 100% and persistence rates decrease steeply over time. No studies were found that reported on adherence with biological DMARDs other than TNF-alpha inhibitors. Thirteen of the sixteen included studies looked at persistence only, two studies assessed compliance only and one study assessed both. Compliance data were available from studies based on US claims databases with relatively large sample sizes and the method of compliance measurement was the calculation of the medication possession ratio (MPR). The MPR with infliximab (INF), etanercept (ETA) and adalimumab (ADA) ranged between 63 and 90% and trends were reported on differences between compliance rates for the three tumour necrosis factor (TNF)-alpha inhibitors. One study suggested that combining the above agents with MTX, which is a frequently used therapeutic strategy may reduce compliance rates. Conclusive compliance results, nevertheless, can not be drawn due to the small number of studies and lack of statistical significance in the original reports.

Persistence decreased steeply over time. The findings for differential persistence rates between individual drugs were contradictory as there was evidence both for and against greater persistence with INF versus ADA and ETA. Comparisons between ETA and ADA were also inconclusive, although a greater number of studies indicated longer drug survival with ETA than with ADA. Some of the studies showed no differences between the three agents at all. There was also a trend in favour of greater compliance and lower persistence with TNF-alpha inhibitor monotherapy in comparison with use in combination with methotrexate (MTX).

Incorporating adherence in pharmacoeconomic evaluations

An explicit definition of adherence (or compliance or persistence) was not given in most studies. However, the measure of compliance or persistence was provided in most cases; therefore, an implicit definition could be obtained. The data sources for compliance or persistence rates were based on randomized controlled studies or observational data. The reliability of the methods showed great variance.

The most important assumptions of these studies are those relating non-compliance or non-persistence to the effectiveness and the costs of treatment. A few studies had some supporting evidence for the link between non-adherence and effectiveness, but others relied on simple assumptions, e.g. non-adherent patients incurred no health benefits. (Haby et al. 2004, Donnelly et al. 2004, Suarez et al. 2002, Jasmer et al. 2000) The impact of non-adherence on costs, if accounted for at all, was derived indirectly from the assumed changes in effectiveness.

These limitations make it challenging to draw valid conclusions on the impact of non-adherence on the cost-effectiveness of treatments, and to compare this across different therapeutic areas.

*Database analysis on the impact of adherence on clinical effectiveness*

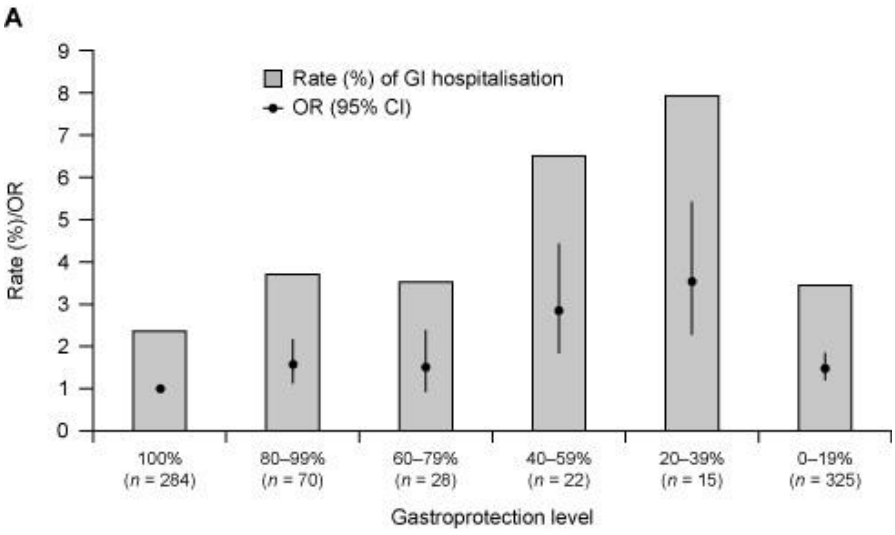
The results reveal low levels of GPA co-prescription among nsNSAID users with more than 70% of patients receiving little or no gastroprotection, and significant under-utilization of GPAs among high-risk patients.

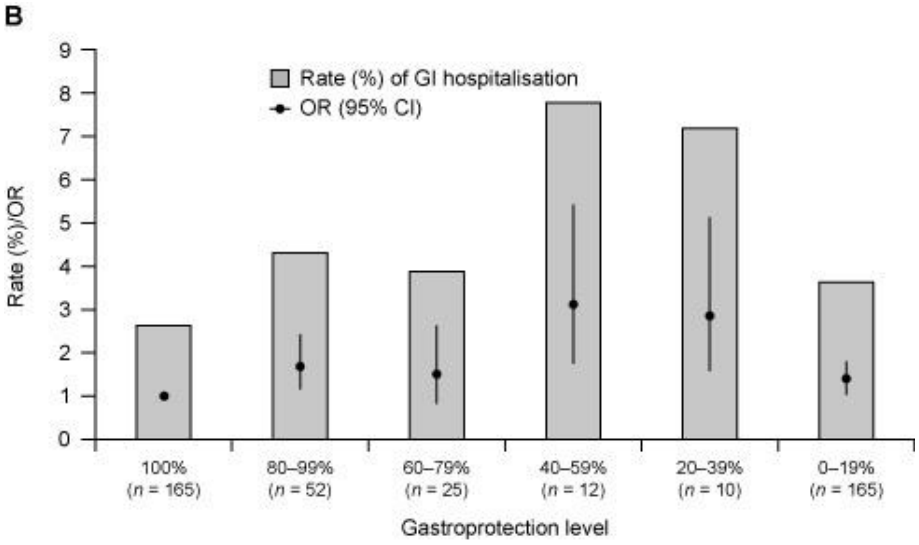
The study also illustrates that the risk of GI-related hospitalization among high-risk nsNSAID users increases considerably with lower levels of GPA use:

Lower levels of GPA use were associated with an increased rate of GI-related hospitalization. Overall, the rate of hospitalizations for the total patients with a GI history during the analysis period was 2.4% with 100% GPA use, rising to 8.0% with less frequent (20–39%) GPA use. For frequent nsNSAID users with a GI history, hospitalization rates increased from 2.6% with 100% GPA use to between 7.2% and 7.8% with low to moderate GPA use (20–39% and 40–59% co-prescription, respectively).

Compared with patients with 100% GPA use, the OR for hospitalization also increased statistically significantly in cohorts with decreasing levels of GPA use. For the total patient population with GI history, high but not full levels of GPA use (80–99% use) were associated with 1.57-fold higher odds of a GI-related hospitalization compared with patients having 100% GPA use (OR 1.57), whereas the odds of a GI-related hospitalization were up to 3.5-times higher for nsNSAID users with levels of 20–39% GPA use (OR 3.52). The odds increased only moderately in patients with 0–19% GPA use (OR 1.47) (Figure 1).

*Figure 1.* Rate and OR of GI-related hospitalizations in (A) total patients with GI history and (B) frequent nsNSAID users with GI history






**Discussion**

As with other chronic conditions, RA patients' adherence "rates" to prescribed pharmacological regimens are low, "ranging between 30 and 80%", depending on the definition and methodology of measurement of adherence. (van dem Bemt and van Lankfeld 2007) These low rates raise concerns that the efficacy of the biologic DMARDs shown in RCTs may be reduced to lower effectiveness in routine clinical care due to poor adherence. It may also be a waste of the limited health care resources available for biologic therapies. It was concluded that compliance rates with biological DMARDs in RA are well below 100% and persistence rates decrease steeply over time. These findings are in line with what was seen in other therapeutic areas and highlight that non-adherence is a ubiquitous issue in medicine. (Koncz et al. 2010)

The second goal of the thesis was to perform a literature review to assess if recent pharmacoeconomic studies considered medication adherence. To assess the combined impact of non-adherence on both health outcomes and costs requires the use of economic

evaluations. In spite of its potential impact on clinical and economic outcomes, adherence is not routinely included in pharmacoeconomic analyses.

Hughes et al. and Cleemput et al.. reviewed the literature for pharmacoeconomic evaluations that considered non-adherence and identified a need for better methods for integrating measures of adherence in economic evaluations. (Hughes et al. 2001, Cleemput et al. 2002) Later, Hughes et al. performed a review in 2007 to investigate the empirical evidence whether approaches of incorporating non-adherence into pharmacoeconomic evaluations had improved since the original publications of Hughes and Cleemput. (Hughes et al. 2007) The conclusion of all three review papers was that patient adherence with pharmacotherapies is usually not included in pharmacoeconomic evaluations and even when it is, the definitions and methods used to describe it are not standardized. The review in the thesis is an update of Hughes et al.'s latest review and it found that patient adherence with pharmacotherapies was usually not included in pharmacoeconomic evaluations and even when it was, the definitions and methods used to describe it were not standardized.. (Hughes et al. 2007)

The third goal of this thesis was to provide evidence when suboptimal patient adherence results in decreased clinical effectiveness and increased health care resource utilization by assessing the rate of gastrointestinal (GI)-related hospitalizations occurring with varying levels of gastroprotective agents (GPA) use when co-prescribed with non selective non-steroidal anti-inflammatory drugs (nsNSAIDs). (Koncz et al. 2008)

The use of GPAs is recognized as an effective strategy for limiting or preventing GI damage and ulcer complications associated with nsNSAID treatments. This retrospective study aimed to discuss the extent of GPA co-prescription among nsNSAID-treated patients in the UK general practice, including patients considered at high risk for developing GI adverse events. Levels of GPA co-prescription alongside ns-NSAIDs were used as a proxy for adherence with GPAs in the absence of an appropriate database measuring adherence directly. This study also evaluated the impact of varying GPA use levels (the proxy for adherence) on the risk of GI-related hospitalization. It was shown that lower levels of GPA co-therapy with nsNSAIDs, used as a proxy for adherence with

GPA co-therapy, were associated with increasing rates of GI-related hospitalization, hence increasing health care resource utilization. (Koncz et al. 2008)

## Conclusions

This thesis addresses what is considered to be an important, but often neglected aspect of clinical evaluation of medicines and pharmacoeconomic analyses.

The *objective* of this thesis was to provide evidence that patient medication adherence was below the level deemed optimal by current medical knowledge (*suboptimal adherence*) and this fact had implications on the effectiveness and economics of pharmacotherapy. The *hypothesis* was that suboptimal patient adherence would decrease the clinical effectiveness of pharmacotherapy and would increase overall health care resource utilization.

The first goal was to explore the evidence on patients' level of adherence with pharmacotherapy through a systematic literature review of adherence with biologic DMARDs. It was concluded that compliance rates with biological DMARDs in RA are well below 100% and persistence rates decrease steeply over time. These findings are in line with what was seen in other therapeutic areas and highlight that non-adherence is a ubiquitous issue in medicine.

The second goal was to identify and assess pharmacoeconomic studies that considered medication adherence. It was found that patient adherence with pharmacotherapies was usually not included in pharmacoeconomic evaluations and even when it was, the definitions and methods used to describe it were not standardized. This results in health technology appraisals that may provide biased estimates of the true value of medicines.

The third goal was to provide evidence when suboptimal patient adherence resulted in decreased clinical effectiveness using a health care database. It was shown in a large retrospective study that lower levels of GPA co-therapy with nsNSAIDs, used as a proxy for adherence with GPA co-therapy, were associated with increasing rates of GI-related hospitalization, hence health care resource utilization.

These findings support the hypothesis that patient adherence is suboptimal and this decreases the clinical effectiveness of pharmacotherapy and increases overall health care resource utilization.

*Health care policy implications*

Suboptimal compliance and failure to persist with drug treatments are important determinants of therapeutic non-response and are also of potential pharmacoeconomic significance. However, the work in this field lacks methodological rigour. The terms compliance and persistence have been variably and unclearly specified with a lack of consensus on their quantitative measurement in particular. Therefore, research on the effects of compliance and persistence on real-life clinical effectiveness and cost is inherently difficult.

This thesis calls for a standardization of definitions and an improvement in measurement methods so that findings of studies analyzing medication adherence can be compared. The thesis also provides recommendations on how to incorporate adherence in pharmacoeconomic evaluations. When the clinical and economic impact of non-adherence is so clear, consideration of the effects of non-adherence should be an integral part of pharmacoeconomic evaluations and in the health care decisions these evaluations inform. This will eventually allow for designing interventions to improve patient adherence which will allow for better clinical and economic outcomes with pharmacotherapy.

*Tamas Koncz's publications*

**Peer-reviewed articles related to dissertation**

**Koncz T**, Pentek M, Brodszky V, Ersek K, Orlewska E, Gulacsi L. Adherence with biologic DMARDs in Rheumatoid Arthritis. Exp Opin Biol Ther, 2010;10(9): 1367-78.
IF: 3.215

**Koncz TA**, Lister SP, Makinson GT. Gastroprotection in patients prescribed non-selective NSAIDs, and the risk of related hospitalization. *Curr Med Res Opin*. 2008;24(12):3405-12.
IF: 2.596

Hughes D, Cowell W, **Koncz T**, Cramer J. Methods for Integrating Medication Compliance and Persistence in Pharmacoeconomic Evaluations. Value in Health 2007;10(6):498-509
IF: 3.387

**Peer-reviewed articles not related to dissertation**

Emery P, **Koncz T**, Pan S, Lowry S. Analgesic efficacy of celecoxib and diclofenac in patients with osteoarthritis of the hip requiring joint replacement surgery: Results of a 12 week randomized, double-blind, noninferiority study. *Clinical Therapeutics* 2008; 30(1): 70-83
IF: 3.064

Muszbek N, **Koncz T**, Hajdu P, Adany R. Economic evaluation of population based mass screening for the early detection of cancer: a systematic review. *Hungarian Oncology* 2002; 46 (2):119-29

**Book chapters**

**Koncz T.** Health economic significance of patient adherence. In: Gulacsi L (ed). Health Economics, Medicina, Budapest, Hungary, 2005 (A beteg-együttműködés jelentősége az egészség-gazdaságtanban. Egészség-gazdaságtan; Medicina Könyvkiadó, 2005)

Brandtmuller A, Gulacsi L, **Koncz T**, et al.. Modelling in economic evaluation. In: Gulacsi L (ed). Health Economics, Medicina, Budapest, Hungary, 2005 (A modellezés szerepe az egészség-gazdaságtani elemzések során. Egészség-gazdaságtan; Medicina Könyvkiadó, 2005)

David T, Bidlo J, **Koncz T**. Cost-containment in health care and pharmaceutical finance. In: Gulacsi L (ed). Health Economics, Medicina, Budapest, Hungary, 2005 (Költség-kontroll technikák az egészségügyben és a gyógyszerfinanszírozás, in: Gulacsi L. (szerk) Egészség-gazdaságtan; Medicina Könyvkiadó, 2005)