

MEASURING MEDICATION ADHERENCE IN ASTHMA PATIENTS IN DEVELOPING COUNTRIES: INSIGHTS FROM NORTH MACEDONIA

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Abstract

Adherence to prescribed drug therapy is crucial in achieving disease control and better outcomes. This article aims to evaluate the current state in North Macedonia (NMK) and to address the need for establishing appropriate methods and implementing suitable tools for measuring medication adherence nationally. A literature review of available publications in scientific databases (PubMed, Scopus, Medline, and Google Scholar) was conducted to identify articles concerning the existence of methods for measuring medication adherence among asthma patients in North Macedonia, along with an evaluation of the current national legislative documentation addressing medication adherence. Our research identified a few, albeit limited, specific methods on a national level, and no available tools designed explicitly for measuring medication adherence in asthma patients in the Macedonian language. Adopting an improved legislative framework is crucial for adequately outlining the requirements for assessing adherence levels and implementing suitable monitoring methods. Raising awareness of medication adherence in asthma patients among various stakeholders requires continuous efforts. Improving adherence should be prioritised by healthcare professionals, national programs, initiatives, and guidelines that aim to regularly assess and enhance adherence levels for asthma patients.

Rezumat

Aderența la terapia medicamentoasă este esențială pentru controlul patologiilor și obținerea unor rezultate clinice favorabile. Scopul acestui articol este de a evalua situația din Macedonia de Nord și de a evidenția necesitatea stabilirii unor metode adecvate și a implementării unor instrumente corespunzătoare pentru măsurarea aderenței la medicație la nivel național. A fost realizată o analiză a literaturii de specialitate disponibile în baze de date științifice internaționale (PubMed, Scopus, Medline și Google Scholar), cu scopul de a identifica studii privind existența metodelor de evaluare a aderenței la medicația antiasmatică în Macedonia de Nord, precum și de a examina documentele legislative naționale. Rezultatele indică existența unor metode specifice, însă puține și limitate la nivel național, și absența unor instrumente dezvoltate explicit pentru evaluarea aderenței la medicația antiasmatică în limba macedoneană. Adoptarea unui cadru legislativ îmbunătățit este esențială pentru a defini clar cerințele privind evaluarea nivelului de aderență și pentru a facilita implementarea unor metode adecvate de monitorizare. Creșterea gradului de conștientizare privind importanța aderenței la tratamentul medicamentos în rândul pacienților cu astm, atât în rândul profesioniștilor din domeniul sănătății, cât și al altor actori implicați, necesită eforturi susținute. Îmbunătățirea aderenței ar trebui să constituie o prioritate pentru cadrele medicale, programele naționale de sănătate, inițiativele și ghidurile care vizează monitorizarea și optimizarea continuă a acestora în rândul pacienților cu astm.

Keywords: asthma, medication adherence, methods, healthcare, national programs

Introduction

Healthcare professionals of every profile play a crucial role in promoting patient medication adherence in their daily practice [1]. Medication adherence, defined as the degree to which patients adhere to their prescribed medication regimens, is a complex process influenced by numerous factors contributing

to increasing adherence [2]. Numerous studies indicate that medications are frequently not taken as prescribed, and this leads to poor disease control and increased healthcare expenditures related to suboptimal therapeutic outcomes. According to published data, approximately 50% of the patients do not follow their physicians' instructions when taking medicines [3-6].

Asthma is a respiratory disease that is typically managed with inhalation therapy, administered daily [5]. Medication adherence and correct inhalation therapy play crucial roles in controlling asthma disease effectively [7]. Adherence rates for Asthma and Chronic Obstructive Pulmonary Disease (COPD) patients are typically lower, with estimates varying significantly from 22% to 78% [8].

Healthcare providers treating these patients adhere to international and national treatment guidelines (GINA - Global Initiative for Asthma) and frequently updated strategy reports to make recommendations based on the latest research [9].

The multiple factors influencing medication adherence emphasise the need for customised approaches and interventions to enhance adherence and improve patient outcomes [10,11]. Among all these factors, probably the most important include behaviour, belief, self-management, health literacy, the role of the health provider, the role of the caregiver, and adherence to national asthma guidelines [12].

There are several methods to evaluate patient medication adherence, including (i) self-report questionnaires or structured interviews, (ii) electronic devices, (iii) therapeutic drug monitoring, and (iv) pick-up/refill rates [13]. Each of the methods mentioned above has limitations, and none are inherently superior to the others [14].

Therefore, we aim to analyse the methods for measuring medication adherence among asthma patients in NMK, analyse the need for tools to measure medication adherence, and review the country's legislation regarding treatment adherence for regular assessment. An additional goal is to evaluate the application of appropriate methods for measuring medication adherence and present initial results on the necessity of studies to increase adherence among these patients.

Materials and Methods

A literature review limited to the Macedonian and English languages for the existing tools for measuring medication adherence and articles published in scientific databases (PubMed, Scopus, Medline, Google Scholar, Web of Science) were examined using the keywords "medication adherence", AND "asthma", AND "measuring methods" AND "tools". The review encompassed both original research articles and literature reviews that examined the application of specific tools for assessing medication adherence. These tools included self-report questionnaires, pharmacy refill records, electronic monitoring devices, pill counts, and other widely utilised adherence measurement methods. Studies were eligible for inclusion if they focused primarily on medication adherence, were published in peer-reviewed journals, contained an accessible abstract,

provided a clearly defined study design and methodology, and reported information regarding the validity and/or reliability of the employed adherence assessment tools. Exclusion criteria involved non-peer-reviewed publications, case reports, conference abstracts, opinion pieces, letters to the editor, and commentaries. Following the removal of duplicate records, a multi-stage screening process was conducted, involving title and abstract evaluation and full-text review. Ultimately, 20 studies published between 2009 and 2023 met the inclusion criteria and were retained for detailed analysis.

In this research, several national-level documents adopted in North Macedonia were reviewed to identify current standards, strategic directions, and regulatory requirements related to medication adherence assessment and improvement tools. The documents included: the Good Pharmacy Practice guidelines (2009) [15], the National Health Strategy 2021 - 2030 [16], the Guidelines for the Practice of Evidence-Based Medicine for the Treatment of Asthma Patients at the Primary Healthcare Level (2023) [17], and the Law on Health Care [18].

The inclusion criteria were: official adoption by national health authorities, relevance to primary care or chronic disease management, reference to adherence or pharmaceutical care, and availability in the Macedonian language. These documents were selected to provide national context for the adherence-related practices and identify opportunities for improvement.

Results and Discussion

Literature review

Many researchers worldwide aim to improve medication adherence in asthma patients. However, this critical area of research remains under-researched in North Macedonia.

Different methods are used to measure medication adherence in asthma patients, with their limitations and strengths (Table I).

Electronic databases (pharmacy claim databases, registries) can be used to measure asthma medication adherence, either by compiling them into a single summary statistic over a long period, such as the medication possession ratio, or by analysing them as a time series, such as the continuous measure of medication gaps [26].

Pharmacy records are a reliable source for measuring the first initiation phase, especially when connected to clinical electronic monitoring records. However, they need to accurately capture the implementation of the regimen. These records can also help identify overuse of reliever medication. This is important because it may suggest poor asthma control and inadequate adherence to controller medications.

Table I

Adherence methods and their strengths and limitations

Method	Strengths	Limitations	References
<i>Electronic database (pharmacy claim database)</i>	Easy to use, inexpensive, non-invasive	Suggests supply without assurance of administration	[19, 20]
	Supports retrospective adherence assessment	Could overestimate the adherence level	
	Evaluates adherence and persistence		
<i>Patient self-reported (questionnaires, visual analogue scales)</i>	Easy applicability in clinical practice	Overestimation of the level of adherence	[13, 21]
	Cost-effective and efficient	Subjective, influenced by recall or reporting bias	
<i>Digital technologies</i>	Objective	No actual evidence that the medication is being ingested	[22, 23]
	Additional information on the degree of adherence	High costs	
		They are not routinely being used in the clinical setting.	
<i>Therapeutic Drug Monitoring</i>	Provides direct evidence of drug concentration	Invasive methods and costly	[24, 25]
	Accurate, objective	Only measures adherence at a specific moment in time.	
	Can detect over- or under-dosing	Not suitable for all types of medications	
		Inter-individual differences	

Pharmacy records provide an accurate, cost-effective, and practical means for assessing adherence and persistence. The most measured parameters in pharmacy claim databases are the Medication Possession Ratio (MPR) and the Proportion of Days Covered (PDC) [20].

Patients' self-reports can also be utilised to measure medication adherence. The self-reports could be diaries, questionnaires, and psychometric scales. Whether distributed online, administered as structured interviews, or given as written questionnaires, these methods are prevalent in adherence research and can be easily adapted for various patient populations [27]. Many self-reported questionnaires are intended to measure medication adherence across multiple medical conditions. However, asthma-specific questionnaires are also available, such as the Medication Intake Survey Asthma (MIS-A) [28], Medication Adherence Report Scale for Asthma (MARS-A) [29, 30], the Test of Adherence to Inhalers questionnaire (TAI) [31], and the Inhaler technique questionnaire (InteQ) [32]. Various digital technologies have been developed to improve medication adherence in patients with respiratory diseases. Electronic monitoring devices are digital adherence technology that records the time and date when a dose is taken. For example, the Smart inhalers used for asthma can be standalone devices or attachments to existing inhalers. These devices track usage data and can transmit this information *via* Bluetooth to a connected mobile application [33]. Some inhalers can assess inhaler technique/quality of inhalation. At this point, it is straightforward to

identify unintentional poor adherence [34]. Direct methods involve more invasive interventions to detect the drug or its metabolites in the patient's body fluids, which can be detected in urine or blood. These methods can be helpful in specific contexts, but several limitations must be considered, for example, the variation in drug pharmacokinetics and interactions with other medications or food that can affect the accuracy of these measurements; measurements can vary significantly from one individual to another. Additionally, there is always a chance of obtaining false results if patients take their medication just before the measurement is performed [23].

We have not identified any study that analyses adherence specifics among asthma patients on a national level, and we have yet to find specific measuring tools available in Macedonian. The presented studies primarily focus on factors influencing diseases rather than improving medication adherence.

Legal policy

Adherence issues are not a primary concern in most national-level policy or legislative documents [15-18]. A regular assessment of adherence levels and implementation of effective improvement and monitoring methods must be adequately outlined and required [35, 36]. To contextualise the findings from North Macedonia, a comparative summary table was developed to illustrate how adherence-related policies and practices are addressed in low- and upper-middle-income countries (LMICs and UMICs) (Table II).

Table II

Comparison of Health Strategies for Asthma and Medication Adherence (MA) in North Macedonia and Other Countries

	<i>Law on Health Care</i>	<i>National Health Strategy</i>	<i>GPP Good pharmacy practice</i>	<i>Asthma Guidelines</i>	References
North Macedonia	Framework law for the entire healthcare system MA- no mention	Strategic policy document defining healthcare system goals; MA not mentioned	Implementation of advanced pharmaceutical care principles: professional strategies for pharmacists to optimise patient outcomes; MA- no mention	Guidelines for evidence-based medicine practice for the treatment of asthma patients briefly mention adherence but lack defined tools or protocols.	[15-18]
Other Countries (LMICs and UMICs)	Health laws have been established, though their content and specificity differ between systems; MA – not mentioned.	Specifying healthcare system objectives; MA not explicitly addressed	GPP aligned with WHO/EU standards; enforcement varies; MA– no mention	No official national asthma guideline in most cases; practices are largely informal or expert-driven	[36-38]

Several documents address medication adherence issues in NMK to varying extents. The Good Pharmacy Practice (2009) outlines the responsibilities of pharmacists in the treatment process but does not provide specific algorithms or best practices for assessing and improving adherence. The pharmacist plays a vital role in promoting rational prescription and medication use, especially by providing guidance on the rational use of medicines and monitoring their effects. It does not specify the pharmacist's role in determining whether the patient is taking the medication correctly and understands how to take it [15].

The Health Strategy of the Republic of North Macedonia (2021-2030) outlines the direction and pathways for modernising and advancing the country's healthcare system. Its primary objective is to enhance the healthcare experience for every citizen and improve the population's health status [16].

In contrast, the Guidelines for Evidence-Based Medicine Practice for the Treatment of Asthma Patients at the Primary Healthcare Level (Ministry of Health, 2023) include certain elements related to medication adherence. These guidelines, developed by GINA 2019 and 2020, aim to maintain the quality of treatment and management of asthma patients in primary care by improving the quality of clinical services, enhancing professional practice, and increasing the cost-effectiveness and efficiency of services. The "Medication Check" section emphasises the importance of recording the medications the patient is using and inquiring about any side effects. It also highlights the necessity of clearly explaining to the patient which medication acts as a controller, which medication to use and how to use it, in case of

exacerbations (reliever). The need for healthcare workers to regularly check the inhalation technique of inhaled medications and ensure adherence to instructions is also stated. A very important part is to encourage patient motivation for adequate treatment and minimise risk factors. Additionally, the guide suggests that patients should have a written asthma control plan [17].

The Law on Health Care regulates the system and organisation of healthcare and the provision of healthcare services. It guarantees rights and outlines the state's needs and interests in ensuring healthcare. Additionally, it addresses healthcare institutions and their functions [18].

Medication adherence is not mentioned in documents except in the Guidelines for Evidence-based Medicine Practice for the Treatment of Asthma Patients at the Primary Healthcare Level (Ministry of Health, 2023).

The documents from the national level highlighted in the results section provide only a minimal legislative foundation for the regular assessment and improvement of adherence levels across different patient groups. This differs from the NICE (National Institute for Health and Care Excellence) guidelines, which provide detailed recommendations for medication adherence and optimisation across different patient groups and healthcare settings [40]. This guideline does not include specific recommendations for assessing medication adherence for diseases. The increased need for continuing development and adoption of national policies supporting medication adherence is emphasised, given the significant role pharmacists play in delivering services to patients [41].

National policies on the appropriate use of medications are established in Australia, the US, and Finland. In some instances, countries such as Switzerland and England have reimbursed pharmacists for providing cognitive behavioural pharmaceutical services to improve adherence. Monitoring and supporting adherence are often integrated into broader initiatives, such as medication reviews in Australia, Spain, Denmark, and Finland, as well as medication checks in Denmark.

Notably, in England, the US, and Switzerland, programs that emphasise medication adherence include motivational initiatives and consultations led by pharmacists, which play a crucial role in enhancing patient adherence and improving health outcomes [42]. Regarding the results of the Guidelines for Evidence-based Medicine Practice for the Treatment of Asthma Patients at the Primary Healthcare Level (Ministry of Health, 2023), in the next 3 - 4 years, an indicator must be employed to evaluate whether a patient adheres to at least 80% of the prescribed therapy. In practice, North Macedonia needs more specific policy documents on adherence that have been developed, published, or implemented. Adherence issues are critical for effective disease management, patient health, and the overall efficiency of the healthcare system. At that point, the current state is a situation that calls for more discussions, research, and debates.

Adherence to treatment regimens is crucial for achieving optimal disease control and enhancing the quality of life, underscoring its importance as a primary factor in managing asthma effectively [43]. North Macedonia has implemented a nationwide e-health system called "My Appointment," which was initially created to facilitate hospital appointments.

The system has expanded to offer a wide range of services in both public and private institutions. It is centrally managed and cloud-based, featuring multiple modules that can integrate with other healthcare applications. These modules cover digital scheduling, electronic health records, e-referrals, lab and imaging service orders, and e-prescriptions.

However, legal and operational challenges are still preventing the system from being more widely adopted [44].

In NMK, pharmacy dispensing and electronic medical records can be utilised to measure medication adherence; however, some limitations exist.

According to the Law on Health Care, the state provides primary, secondary, and tertiary health care. According to the scope of work, the detection and treatment of diseases and injuries, the provision of health and midwifery care, and the implementation of medical rehabilitation for patients all belong to the primary level, which includes prescribing medication by general practitioners [18].

Specialist-consultative health services at the secondary level include outpatient examinations with a referral from the selected doctor or another specialist, health treatments performed at the secondary level, and day-hospital activities. At the secondary level, asthma patients are evaluated by a pulmonologist. Based on their condition, the specialist provides a report and recommends the appropriate therapy. The report is given to the general practitioner, who then prescribes the medication as recommended by the specialist.

Measuring medication adherence often presents difficulties because the pharmacy's e-prescribing system is linked only to the general practitioner's system. Consequently, the specialist pulmonologist cannot determine whether the patient is taking the medication.

The pharmacy dispensing records can be used for research purposes, as a method for measuring medication adherence.

Self-report measures are commonly used to assess medication adherence, offering practicality in clinical practice and research settings.

These tools typically involve patients completing scales or questionnaires to provide insight into their adherence behaviours. While self-report tools have some limitations, such as patients' tendency to overestimate their adherence, they remain valuable due to their ease of use [45].

When selecting a self-report tool, it is essential to consider its psychometric properties and predictive validity [46]. It is necessary to recognise that many tools have been created and validated for various medical conditions and diverse patient groups. Researchers should prioritise tools with strong psychometric characteristics, paying attention to their reliability, internal consistency, and their ability to accurately predict clinically relevant outcomes.

Currently, there are no available self-report questionnaires for measuring medication adherence among asthma patients in NMK. The final goal is to introduce and make available two specific questionnaires in the Macedonian language for use in this context.

In a review published by Khoiry *et al.*, it was found that nearly half of the included studies demonstrated insufficient evidence for cross-cultural validation and internal consistency in existing self-reported adherence instruments in low- and middle-income countries. Additionally, fees were applied for using these instruments in 70% of the studies conducted in Low and Middle-Income Countries (LMICs). Despite this, due to the methodological shortcomings observed in some of the studies included, there is a need to develop a well-validated self-reported adherence instrument that can be universally adapted to the contexts, health systems, and resources of LMICs [47]. When discussing digital adherence technologies, such as smart inhalers, we have found no available

data in North Macedonia. Consequently, this method of measuring medication adherence should be evaluated by authorities, stakeholders, and pharmaceutical companies, with efforts focusing on ensuring that this technology is accessible to patients nationwide. To address the identified legislative and policy gaps, a Macedonian guideline on medication adherence could be modelled after international standards, such as the NICE Medicines Adherence guideline [40]. A contextually adapted version should include structured protocols for adherence assessment in primary care, formal involvement of pharmacists in patient education and follow-up, and integration of adherence monitoring into electronic health records. It should also promote shared decision-making, the use of validated self-report tools, and ongoing training for healthcare professionals on adherence-supportive practices. Furthermore, the guideline could propose mechanisms for monitoring adherence outcomes and promoting good practice. Providing such normative guidance would not only help standardise adherence support across the health system but also bridge the current gap between policy and practice.

Although medication adherence is recognised as a key determinant of treatment success, our analysis shows that national-level monitoring and policy implementation remain limited in North Macedonia, consistent with broader European trends. Recent studies have found that most European countries do not assess medication adherence at the national level, despite the increasing use of electronic medical records and e-prescription systems that could facilitate such assessments [48, 49]. North Macedonia, for instance, has implemented the "My Appointment" e-health system, which includes components such as e-prescriptions and electronic health records; however, these tools are not fully leveraged for adherence tracking.

The European Health Data Space (EHDS) initiative, which aims to integrate health data across EU member states, presents a significant opportunity for standardising and enhancing the assessment of medication adherence [50]. While North Macedonia is not part of the EU, the EHDS serves as a model for how countries might build infrastructure for cross-country comparability and evidence-based policymaking.

However, the absence of country-level data on adherence to chronic treatments in North Macedonia and many LMICs limits the ability to assess the effectiveness of existing policies and interventions. This aligns with findings from an Organisation for Economic Co-operation and Development (OECD) report, which indicates that many European countries neither routinely monitor adherence nor take sustained actions to improve it [51].

Therefore, North Macedonia should consider developing national adherence indicators and invest in the

systematic collection and use of electronic adherence data. Doing so would enable the country to track trends, evaluate the impact of interventions, and guide reforms. Moreover, context-specific interventions are critical, as policies or tools effective in one country may not be directly applicable in another [52]. Therefore, any imported adherence-enhancing strategies (*e.g.*, from NICE or EHDS models) should undergo transferability assessments and local contextualization to ensure relevance and sustainability.

In addition to policy and system-level gaps, patient-level factors must also be taken into account. According to the Health Belief Model [53, 54], patients are more likely to adhere to their medication if they perceive asthma as a serious condition and believe that adherence will lead to positive health outcomes, provided barriers such as cost or complexity are minimised. The Theory of Planned Behaviour [55, 56] emphasises the significance of patients' intentions, which are influenced by their attitudes, perceived social norms, and perceived control over their medication-taking behaviour. Meanwhile, the COM-B model emphasises that adherence depends on having the capability (knowledge and skills), opportunity (access and reminders), and motivation (beliefs and goals) to engage in regular medication use [57].

International experience shows promising strategies aligned with these frameworks. For example, the New Medicines Service (NMS) offers pharmacist-led consultations to support newly prescribed patients, particularly those with chronic conditions like asthma, with evidence showing improved adherence [58]. Through structured medication reviews and motivational interviewing, pharmacists help drive behavioural change and enhance health outcomes [59, 60]. Additionally, digital adherence technologies have demonstrated real-world success in improving medication-taking behaviour by tracking usage patterns and providing feedback to both patients and healthcare providers [61, 62]. These technologies leverage COM-B by enhancing both motivation (through feedback and rewards) and opportunity (by sharing data with providers).

Currently, there is no evidence of smart inhaler use in North Macedonia, and awareness of such technology is limited among healthcare providers. It is essential that pharmacists' roles in adherence monitoring be supported by digital tools, educational programs, and reimbursement mechanisms. The integration of validated self-report tools is also lacking in the Macedonian context. As such, a comprehensive adherence strategy in NMK should not only address policy and infrastructure gaps but also incorporate behavioural science principles and evidence-based tools to change both provider and patient behaviour.

Conclusions

Adhering to prescribed therapy is very important for achieving the desired treatment outcomes and ensuring the effectiveness of the therapeutic process. Appropriate tools need to be developed, adopted, and provided to conduct future research on medication adherence at the national level, particularly among asthma patients. Medication adherence interventions must be implemented in all national programs, guidelines and legal frameworks as a relevant issue needing improvement. In addition, all healthcare professionals must be involved in these efforts to achieve better disease control and improve patients' quality of life. Collaboration among doctors, nurses, pharmacists, and other healthcare providers is essential to developing effective ways to monitor and enhance medication adherence.

Due to insufficient awareness and training among healthcare professionals (general practitioners, pharmacists, nurses, and pulmonology specialists), as well as limited resources for enhancing and consistently evaluating medication adherence among asthma patients in NMK, immediate and relevant actions are necessary. A strategic approach that incorporates a national legal framework, organised research, and collaboration among healthcare professionals and other stakeholders could lead to significant progress in managing chronic conditions and enhancing patient outcomes in North Macedonia.

Conflict of interest

The authors declare no conflict of interest.

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