

Primary nonadherence: the forgotten component of medication adherence?

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Hippocrates (400 BC) was the first to note that some patients do not take their prescribed medicines and many later complain that the treatment does not help.¹ Since then the World Health Organisation (WHO) has called nonadherence to medication “a worldwide problem of striking magnitude” and “one of the 2 largest unsolved gaps in healthcare” (the other being suboptimal prescription of medication).² In the past few decades, new and efficacious medications with positive benefit-to-risk profiles have been developed and we have seen an increased focus on improving health outcomes for people and reducing costs (eg, reducing healthcare utilization).¹ However, we have made less progress in monitoring and improving adherence to medication.

Recently, a taxonomy of adherence has been developed in an effort to standardize adherence-related terminology for clinical and research use and to enable benchmarking of existing adherence enhancing strategies at the European level.³ The taxonomy defines medication adherence “as the process by which patients take their medication as prescribed” and subdivides medication adherence into 3 essential components: 1) initiation (taking the first dose of prescribed medication); 2) implementation (taking medication as prescribed); and 3) discontinuation (stopping treatment).⁴

Much of the research done to date on the prevalence of nonadherence has measured the implementation and discontinuation components of the taxonomy. Less is known about the frequency with which patients fail to fill prescriptions for new medications (initiation).⁵ This may be due to a lack of available data to measure initiation in a cost-effective way. Data are readily available worldwide to measure the implementation and discontinuation components of adherence in large-scale pharmacy claims databases.³ In contrast, there is a lack of necessary data linkage between what is prescribed by the physician and what is dispensed by the pharmacist

to measure initiation and data that do exist, outside of a small number of integrated healthcare systems, are often insufficient to draw any valid conclusions.⁵

Initiation is the first component in the taxonomy and the first step to understanding why patients do not take their prescribed medications. Measuring medication initiation provides important baseline rates of primary nonadherence in acute and chronic conditions. Reported rates of noninitiation have been shown to vary between 2.3% and 50% (weighed average [SD], 5.1% [1.3%]) across studies.⁶ This large disparity in rates may reflect the multiple definitions of initiation and methods of measurement applied in studies, with different time frames used to identify prescribing and dispensing events.⁵

In this issue of *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*), Kardas et al⁷ aimed to address this lack of research on medication initiation and analyze the extent of primary nonadherence in Poland. The recent implementation of a nationwide eHealth system in Poland and the introduction of electronic prescriptions (e-prescriptions) enabled primary nonadherence (initiation) to be measured through the comparison of e-prescription rates to dispensation rates for 47 drugs from 6 major therapeutic areas (diabetes, antithrombotic agents, cardiovascular system, lipid modifying agents, anti-infectives for systemic use, psychoanaleptics). In line with previous research, primary nonadherence was defined as an e-prescription not being dispensed within a period of 30 days.⁶ In total, out of 119 880 e-prescriptions issued in Poland in 2018, 24 967 e-prescriptions were not dispensed, resulting in a primary nonadherence rate of 20.8%.

Similar to studies on the prevalence of nonadherence, much of the research to date on the risk factors associated with poor adherence has focused on the implementation and discontinuation components of the taxonomy.^{8,9} A systematic review of the psychosocial and behavioral factors

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associated with initiation identified only 24 studies and the factors identified were the same as for implementation and discontinuation, for example, patient characteristics, comorbidities, and healthcare provider relationships.⁶ Kardas et al⁷ aimed to identify the major drivers of primary nonadherence and found that primary nonadherence was lower in drugs covered by the Polish “Leki 75+” program, which allows patients aged 75 years or older to obtain certain medications for chronic conditions free of charge in community pharmacies (16.87% vs 19.89%; $P < 0.001$). Drugs are normally subject to an out-of-pocket copayment which varies within drug classes.⁷ This finding adds to the growing body of evidence that cost and economic considerations impact medication initiation.¹⁰ However, there is also some evidence that over time as patients become more engaged in their treatment, cost-related adherence problems may decline and other factors may become more influential, for example, side effects.¹¹ It is quite feasible that the strength of the association between a risk factor and nonadherence may vary per adherence component, with some factors having a greater influence on initiation than implementation or discontinuation; this requires further exploration.

Initiating a medication regimen can also be the beginning of a series of complex health behaviors that may have a long-term effect on a patient’s health and wellbeing. This is especially relevant for patients with multimorbidity who use multiple self-management strategies, for example, taking medication, following dietary guidelines, and physiotherapy. There is some evidence of a threshold effect for the relationship between number of concurrent medications and medical conditions and adherence.¹² Adherence has been shown to initially increase, followed by a decrease as the number of morbidities and/or medications increases. There is also some evidence that not only the number of morbidities but the types of morbidities influence medication adherence.¹² Kardas et al⁷ found significant variability in primary nonadherence across therapeutic areas, drug classes, and individual drugs. In recent years, there has been a rapid increase in the prevalence of multimorbidity and polypharmacy, presenting significant challenges for monitoring and supporting medication adherence.¹² There is a need for new innovative approaches to be developed to detect potential medication adherence problems when new medications are initiated in patients with multiple chronic conditions.

Initiation is influenced by a complex interplay of multiple risk factors, including individual patient and healthcare provider risk factors as well as the external influences of the healthcare system, policy, and media.¹³ More rigorous methodological studies are needed to understand the magnitude of the effects of these risk factors on initiation and the relationship between risk factors; some factors may have an indirect effect on initiation via others.⁹ A more thorough

understanding of the factors that influence medication initiation will enable healthcare providers to identify more targeted interventions and develop support systems for patients at the outset of their treatment process.⁶ To date, the existing adherence interventions have not distinguished between the different components of the adherence taxonomy and successful interventions that target all components may not be cost-effective.^{14,15} Some intervention strategies may be more effective at addressing particular adherence components. For example, addressing medication concerns before the treatment commences (initiation), rather than later in the treatment process, may be more beneficial to the patient and lead to better adherence and long-term health outcomes.

The recent implementation of the nationwide eHealth system in Poland also highlights how utilizing and triangulating several digital health solutions can yield interesting insights into population-level real-life adherence patterns, enabling clinical and health policy decisions to be informed by data. It also highlights the critical need for further data integration at the European level. Database networks provide an opportunity to develop a better understanding of medication adherence patterns, determinants of nonadherence and associated health and cost outcomes. They may also provide the ability to compare and evaluate the impact of different healthcare management systems and healthcare policies on health behaviors, including adherence and outcomes across countries. Medication adherence is a critical element of chronic disease management and a major public health concern. Therefore, more effort needs to be made to measure, understand, and ultimately improve it.

ARTICLE INFORMATION

DISCLAIMER The opinions expressed by the author are not necessarily those of the journal editors, Polish Society of Internal Medicine, or publisher.

CONFLICT OF INTEREST None declared.

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