Policy report

Unlocking the potential of therapeutic adherence as a priority for a forward-looking approach to healthcare policies

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Executive Summary

Twenty years ago, the World Health Organisation identified poor adherence to treatment as a "worldwide problem of striking magnitude." Twenty years later, and despite the WHO's findings, the global healthcare system has still not undergone a necessary increase in the effectiveness of therapeutic adherence interventions. The following policy report will provide an evidence-based outline of both the causes and the impact of low therapeutic adherence, particularly in relation to non-communicable diseases (NCDs) - the leading cause of death worldwide[1]. It will address three key areas for policy action: patient-healthcare professional relationships and treatment governance; technology and innovation, and future-proofing regulations.

The analysis will also demonstrate the clear benefits of improving therapeutic adherence for both patients and the healthcare industry. Such improvement should be a priority for policymakers seeking to build resilient healthcare systems, especially considering current socio-demographic trends.

There is substantial room for improvement in current levels of therapeutic adherence across the EU, and the challenge is significant enough to warrant immediate attention and action from policy makers. Coupled with the European institutions' increased activity on healthcare and the upcoming EU elections in 2024, there is real momentum to enable policy makers to act.

This report aims to spark debate about therapeutic adherence and its effects among policymakers and translate it into policy action. Its findings confirm that, despite widespread acceptance of therapeutic adherence as a metric of treatment success, challenges remain in encouraging incremental innovation, patient empowerment and uptake of digital technology. To support increased therapeutic adherence, it is essential to establish a comprehensive policy framework – at national and European level. This provides policymakers with a timely opportunity to improve health outcomes in a way that works for local people living with non-communicable diseases and the health systems that serve them.

Introduction

The WHO defines therapeutic adherence as "*the extent to which a person's behaviors – taking medication, following a diet, and/or executive lifestyle changes, corresponds with agreed recommendations from a healthcare provider*"[2] – a definition that involves the patient as an active participant in their own treatment, and not simply a follower of medical instructions.

The case for action on therapeutic non-adherence is based on its widespread occurrence in the healthcare sector, impacting every country and healthcare system. Non-adherence contributes to an increase in unmanaged chronic diseases, comorbidities, and costs for the healthcare sector, as well as exacerbating the burdens health systems face. It is particularly challenging for non-communicable disease (NCD) management, as these are high prevalence, chronic diseases with high mortality rates which require substantial expenditure on the part of health systems.

Despite awareness of these issues within the industry, there is an unmet need for evidence-based, targeted policies supporting the sector to increase therapeutic adherence for better care. This report aims to fill the gap through an overview of best practices and recommendations based on them, providing guidance to policymakers who seek to tackle low therapeutic adherence.

[1]World Health Organization. (2019) Global Health Estimates: Life Expectancy and leading causes of death and disability https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates

[2]World Health Organization. (2003) Adherence to long-term therapies: evidence for action. https://iris.who.int/handle/10665/42682

Section I: Reducing the burden of NCDs by boosting therapeutic adherence

Therapeutic adherence in the NCD context

As healthcare systems worldwide face enormous challenges, social and economic sustainability is crucial for making them fit for the future. One of the main challenges systems are faced with is the growing trend of chronic diseases - the leading cause of mortality and morbidity in Europe – with knock-on consequences for healthcare expenditure.

As chronic diseases develop slowly, are long-lasting and often incurable, effective, and safe therapies are a key factor in improving patient outcomes, avoiding adverse events and mortality, while reducing their impact on health systems. Improved therapeutic adherence has the potential to help achieve these goals, starting from early intervention and comprehensive management of the diseases, given that it has been shown to contribute positively to clinical outcomes[3], in a context where universal adherence to long-term medication remains to be achieved.

The high prevalence of therapeutic non-adherence exacerbates its impact on the management of non-communicable diseases, given that non-adherence affects up to 50% of patients with conditions such as diabetes and hypertension[4]. This, in turn, prevents patients and health systems from getting the full benefits of NCD treatment in terms of health outcomes and reduction of disease burden.

Cardiovascular medications alone are estimated to be responsible for half of the 50% reduction in mortality from coronary heart disease over the past 20 years.[5] This is an outstanding achievement which has a transformative impact on people's lives – however, high rates of non-adherence in real-world settings[6] likely limit the potential impact of these medications.

Chronic diseases are by no means rare, with over one third of the EU population[7] reporting that they live with a chronic condition. Once people living with chronic illnesses stop taking their medication as advised, the risk of comorbidities and deterioration in their quality-of-life increases – as does the importance of returning to therapeutic adherence.

Additionally, changing lifestyles have led to a surge in cardiovascular disease risk factors, resulting in an increased burden of treating cardiovascular diseases. Taking China as an example, the increasing prevalence of overweight and obesity has led to a continuous rise in patients with hypertension, diabetes, and hyperlipidaemia.

In this context, improving therapeutic adherence presents an opportunity for people to get the full benefit of their medications. This can improve their lives and reduce avoidable ill-health and its social costs for individuals, families, and the health system.[8]

[3]Rasmussen J.N., Chong A., Alter D.A. (2007) Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction.
[4]Kleinsinger, Fred. (2020) The Unmet Challenge of Medication Non-adherence, The Permanent Journal 22.
[5]Ford ES, Ajani UA, Croft JB, et al. (2007) Explaining the decrease in U.S. deaths from coronary disease, N Engl J Med Jun 7
[6]Bosworth, Hayden B et al. (2011): Medication adherence: a call for action. American heart journal
[7]Eurostat (2021) Self-perceived health statistics: chronic morbidity. https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Self-perceived_health_statistics&oldid=509628#Chronic_morbidity:_long-standing_illnesses_or_health_problems
[8]Institut Sapiens. (2023) Améliorer l'adhésion thérapeutique : un enjeu de santé publique https://www. institutsapiens.fr/wp-content/uploads/2023/06/Ameliorer-ladhesion-therapeutique-V1.pdf

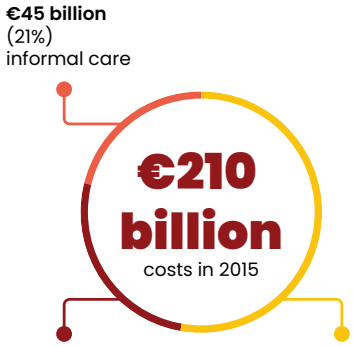
The burden of cardiovascular disease as the most impactful NCDs

NCDs represent a major challenge for public health systems in Europe, where they cause **90% of all deaths**.[9] Cardiovascular disease is the leading NCD in Europe

- hypertension
- arteriosclerosis
- heart disease
- congestive heart failure
- stroke

37%
of all EU deaths annually

Every year in the EU, more than 6 million new cases of cardiovascular disease are diagnosed and over 1.7 million people die from diseases of the circulatory system[10,11]



€45 billion
(21%)
informal care

€54 billion
(26%)
productivity losses

€111 billion
(53%)
health care

These costs will increase on a yearly basis driven by the triple threat of demographic changes, lifestyle factors, and climate change (the combined effects of extreme heat and air pollution are documented drivers of acute cardiovascular events).[12,13]

Key drivers of (non-) adherence and the challenges posed

The lack of therapeutic adherence poses significant, yet avoidable, challenges to the healthcare sector. In Europe alone, around 200,000 people die each year due to non-adherence. Apart from the large loss of life, the healthcare sector also faces financial losses and becomes burdened with avoidable illnesses. Studies estimate that around 80 to 125 billion Euros is lost annually to non-adherence in Europe.[15]

As healthcare systems worldwide face enormous challenges, social and economic sustainability is crucial for making them fit for the future.

One of the main challenges systems are faced with is the growing trend of chronic diseases - the leading cause of mortality and morbidity in Europe[16] – and its compounding effects on the healthcare system's costs.

Discussions of non-adherence generally apportion the blame predominantly to patients, whereas evidence suggests that this represents a misunderstanding of wider systemic factors[17] that affect patient behaviours and capacity to adhere to agreed treatment plans. A whole-of-government, multistakeholder approach response is essential in addressing non-adherence, involving patients, clinicians, and industry.

Patients' desire to follow their treatments plans can be derailed by various obstacles, which are different for each individual and interact in various ways – as illustrated in the OECD's[18] multi-dimensional model of non-adherence. This model includes both individual and systemic factors, such as (see infographic):

[9]WHO (2021) Monitoring noncommunicable disease commitments in Europe. https://www.who.int/europe/publications/i/item/WHO-EURO-2021-4479-44242-62494
[10]Timmis et al., 2022 https://www.eea.europa.eu/publications/beating-cardiovascular-disease#:~:text=It%20is%20the%20most%20common,2022%3B%20WHO%2C%202022).
[11]WHO, 2022, Global Health Observatory, World Health Organization, Geneva, Switzerland (https://www.who.int/data/gho).
[12]EFPIA (2022). Chronic diseases: sustainable solutions for europe powering up chronic disease management
[13]Peters Annette (2021), Cardiovascular risks of climate change. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7649889/
[14]Ibid.
[15]International Longevity Centre. (2022) Doctor's orders: Why adherence is critical to improving health outcomes across the life course. https://ilcuk.org.uk/125-billion-lost-each-year-due-to-non-adherence/.
[16]Eurostat (2020). Causes of death statistics. https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Causes_of_death_statistics
[17]World Health Organization. (2003). Adherence to long-term therapies: evidence for action. https://apps.who.int/iris/handle/10665/42682
[18]OECD Health Working Paper No. 105. (2018) Investing in medication adherence improves health outcomes and health system efficiency https://www.oecd-ilibrary.org/social-issues-migration-health/investing-in-medication-adherence-improves-health-outcomes-and-health-system-efficiency_8178962c-en

Barriers to therapeutic adherence (WHO multi-dimensional model)

healthcare system/health team barriers

condition-related factors

therapy-related barriers

patient-related factors

socio-economic factors

- Healthcare system/health team barriers: poor quality of patient-provider relationships, complicated procedures for picking up prescriptions, limited reimbursement of prescription charges; limited time available to HCPs to train patients and explain disease risks / adherence benefits; lack of training for HCPs to understand patients' barriers to adherence and design individualised approaches for improvement.

- Condition-related factors: presence of comorbidities, lack of symptoms.

- Therapy-related barriers: lack of efficacy, side effects of medication, treatment complexity, inconvenient administration routes, storage requirements.

- Patient-related factors: forgetfulness, personal and cultural norms, beliefs and attitudes, health literacy, level of trust in healthcare team; varying levels of understanding/acceptance of disease risks and benefits of treatment; difficulties in acceptance of illness, and optimism bias – the human tendency to think positive events are more likely and negative events less likely than they are in reality.

- Socio-economic factors: low incomes, lack of social and emotional support, poor social service coverage, decrease in HCP population, persistent problems in patient pathways and early diagnosis.

An urgent need for action

According to the OECD report, improving therapeutic adherence will be of benefit to the whole healthcare system and contribute to healthcare system resilience, spending efficiency, and long-term sustainability[19]. However, despite the potential gains in terms of health outcomes and public finances, therapeutic adherence is still not considered a priority in many countries[20].

There are a variety of reasons why the scale of the problem is so easily overlooked. Firstly, it is not immediately apparent, and can be difficult to measure. Patients are the experts in their own adherence, and their healthcare team can only learn about their adherence levels by either asking them or observing them. This can be a very sensitive, potentially fraught discussion, which must be handled with respect and patience on the part of the healthcare professional. Studies also note that the complexity of current treatments for chronic disease can act as an impediment to long-term treatment adherence.[21]

The efforts of patients, clinicians, scientific societies, and other healthcare stakeholders to tackle non-adherence may therefore have gone unnoticed by policymakers. As such, policy actions that could help alleviate the risks of non-adherence have also gone unnoticed – with the regulatory environment continuing to pose barriers to improving therapeutic adherence.[22] While some in the healthcare industry do recognize that conditions have improved over the last few years, it is generally agreed that there is much more left to be done, especially in creating a holistic approach to treatment. Issues arising from the short-term view of caring for patients with chronic diseases, which leads to cost cutting measures and lack of investment in the future, are also overlooked by policymakers.

A holistic approach to treatment will reduce the impact that chronic illnesses have on families, social environments, professional environments, society overall, and the person at the centre of care. There is a real opportunity for policymakers to help people live longer, healthier lives through a comprehensive, well-resourced approach to adherence that promotes digital technologies, better regulation, and public communication campaigns facilitating access to health technologies. The success of this approach depends on the buy-in of healthcare professionals, patients, policymakers, and healthcare companies.

[19]Yfantopoulos, John, Marianna Protopapa, Athanasios Chantzaras, and Platonas Yfantopoulos. (2021) Doctors' Views and Strategies to Improve Patients' Adherence to Medication. Vol. 20. http://dx.doi.org/10.1007/s42000-021-00294-2

[20]OECD Health Working Paper No. 105 (2018). Investing in medication adherence improves health outcomes and health system efficiency (June 2018) https://www.oecd-ilibrary.org/social-issues-migration-health/investing-in-medication-adherence-improves-health-outcomes-and-health-system-efficiency_8178962c-en

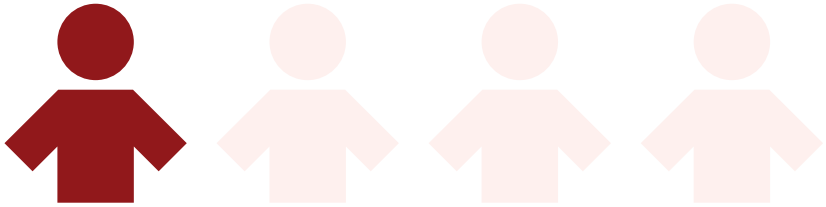
[21]Ibid.

[22]Bosworth, Hayden B., Bradi B. Granger, Phil Mendys, Ralph Brindis, Rebecca Burkholder, Susan M. Czajkowski, Jodi G. Daniel, et al. (2011) Medication Adherence: A Call for Action, American Heart Journal, Vol. 162. http://dx.doi.org/10.1016/j.ahj.2011.06.007.uploads/2023/06/Ameliorer-ladhesion-therapeutique-V1.pdf

Challenges and benefits of therapeutic adherence applied to cardiovascular diseases

Non - therapeutic adherence represents a major challenge for the treatment of cardiovascular diseases

Non-adherence to cardiovascular disease mediciation has been estimated to be higher than 60%[23]



Nearly one out of four patients is **partially or completely non-adherent** to their treatment following a discharge from the hospital.[24]

Therapeutic adherence could concretely contribute to improve patients' outcome and save resources

40%

of patients **do not properly adhere to their cardiovascular disease medications**, according to analysis of nearly 2 million patients.[25]

~9%

of **all cardiovascular disease events** in Europe could be attributed to **poor adherence** to vascular medications, and that the level of optimal adherence confers a significant inverse association with subsequent adverse outcomes.[26]

up to 50%

of cardiovascular disease **hospital admissions** may be **due to poor adherence.**[27]

[23]Kravitz RL, Hays RD, Sherbourne CD, et al. (1993) Recall of recommendations and adherence to advice among patients with chronic medical conditions. Arch Intern Med. doi: 10.1001/archinte.1993.00410160029002.
[24]Jackevicius Cynthia A, Li P, Tu JV. (2008) Prevalence, predictors, and outcomes of primary non-adherence after acute myocardial infarction. doi: 10.1161/CIRCULATIONAHA.107.706820.
[25]Laufs, Ulrich, Rettig-Ewen, Volker, Bo, Michael. (2011) Strategies to improve drug adherence. European Hearth Journal. doi:10.1093/eurheartj/ehq297
[26]Rajiv Chowdhury et al. (2013) Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. Eur Heart J doi: 10.1093/eurheartj/eht295. Epub 2013 Aug 1.
[27]Chen Chen, MD (Adherence with cardiovascular medications and the outcomes in patients with coronary arterial disease: "Real□world" evidence. Clin Cardiol. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9748759/

Section II: Policy Actions

This section will briefly set out some suggested policy actions for European policymakers that could help improve therapeutic adherence and further alleviate the burdens of NCDs, in support of the sustainable development goals target to reduce premature mortality from NCDs by 1/3 by 2030. The current political landscape presents an opportunity to introduce new goals and ideas onto the health policy agenda. The European Parliament elections, scheduled for June 2024, will breathe fresh life into a series of debates on healthcare policies and the EU's growing intervention in the sector.

In addition, the ongoing reform of the General Pharmaceutical Legislation means that policy makers remain active on health issues in the run-up to these elections. Health stakeholders, patient organisations and policymakers must seize this chance to get therapeutic adherence onto the political agenda and to tackle it as a public health, social and economic issue.

The methodology of this report included a broad literature review and analysis of various study results, recommendations, and best practices and will incorporate stakeholder input collected through a questionnaire. The areas covered include the patient-HCP relationship and treatment governance, the role of technology and innovation, and future-proof and agile regulation, with a spotlight on the use of Real-World Evidence and Fixed-Dose Combination medicinal products (FDCs).

Patient-HCP relationships, coordination between HCPs, and treatment governance

THE ROLE OF HCPS

Insight: Good relationships between patients and healthcare professionals are vital in the treatment process, as are collaboration, coordination, and communication among healthcare professionals.[28] For as long as there have been doctors, they have had to wait for patients to come to them for treatment. This has limited their capacity for early intervention, comprehensive monitoring, and influence over the patient's treatment outcomes and future disease progression, making it harder to build long-term cooperation and trust. Over the years, models of medicine that bring professionals closer to citizens have been developed to address these challenges.

Community-based healthcare professionals, including nurses and pharmacists, are often well-placed to discuss therapeutic adherence with their patients, due to the trust they have developed with their communities[29], and good relationships between HCPs and patients helps deliver improved therapeutic adherence.[30] Pharmacists, in particular, have repeated interactions with patients over a period of time and can learn about their needs and concerns surrounding treatment. Other good practices in this field include the empowerment of clinicians[31] and patients themselves through information provision, and recognition of the role of patient advocacy groups as the experts in their own unique treatment needs and expectations.

Best practice: Community pharmacists

→ Several countries, including the United Kingdom, Canada, Japan, and Australia, have implemented pilot programs delivered by pharmacists to improve medication adherence. These projects have the common goal of creating a relationship between patients and their pharmacists that extend beyond prescription dispensing into treatment follow-up and information sharing. In Japan, for example, patients have access to electronic medication notebooks for recording their medication history. Additionally, pharmacists receive additional payments as an incentive to provide patients with guidance on medications.

PATIENT EDUCATION AND HEALTH LITERACY

Insight: Low health literacy is also an oft-cited reason for non-adherence[32] and low health literacy skills are common across developed countries.[33] Health literacy is usually viewed as a shared responsibility between patient and HCP, as the latter has control over length of consultations, the kind of information provided, and the responsibility to provide sound healthcare advice. Relevant factors from the patient perspective include lack of knowledge about the treatment and disease, the complexity of treatment, and fears surrounding treatment.[34]

[28]Manthey, Marie. (2012) Foundations of Interprofessional Communication and Collaboration," Creative Nursing, Vol. 18. http://dx.doi.org/10.1891/1078-4535.18.2.64.
[29]OECD Health Working Paper No. 105 (2018). Investing in medication adherence improves health outcomes and health system efficiency https://www.oecd-ilibrary.org/social-issues-migration-health/investing-in-medication-adherence-improves-health-outcomes-and-health-system-efficiency_8178962c-en
[30]Kevin Cheung, PharmD, Jacob Hicks, PharmD, Brian McEwen, and Gregory Cianfarani (2012) Strong Healthcare Provider-Patient Relationship Improves Patient Adherence and Lowers Healthcare Costs: A Meta-Analysis.
[31]Haskard, Kelly B., Summer L. Williams, M. Robin DiMatteo, Robert Rosenthal, Maysel Kemp White, and Michael G. Goldstein. (2008) Physician and Patient Communication Training in Primary Care: Effects on Participation and Satisfaction. Health Psychology, Vol. 27. http://dx.doi.org/10.1037/0278-6133.27.5.513.
[32]Baryakova, Tsvetelina H., Brett H. Pogostin, Robert Langer, and Kevin J. McHugh. (2023) Overcoming Barriers to Patient Adherence: The Case for Developing Innovative Drug Delivery Systems. Nature Reviews Drug Discovery, Vol. 22. http://dx.doi.org/10.1038/s41573-023-00670-0.
[33]Nutbeam, Don (2008) The Evolving Concept of Health Literacy, Social Science & Medicine, Vol. 67 http://dx.doi.org/10.1016/j.socscimed.2008.09.050.
[34]Kvarnström K, Airaksinen M, Liira H. (2018) Barriers and facilitators to medication adherence: a qualitative study with general practitioners, BMJ Open. doi: 10.1136/bmjopen-2016-015332

In addition to training for HCPs, patient empowerment is essential in securing improved therapeutic adherence – as recognized in the European Society of Hypertension's 2023 Guidelines[35] and the International Society of Hypertension's 2020 Global Hypertension Practice Guidelines[36], which is one of the first practice guidelines to recognise the importance of therapeutic adherence. In particular, patient beliefs about medications and their side effects strongly influence adherence to treatment. Additional potential benefits of increased health literacy include improved understanding of which HCP is the most suitable to visit for a particular situation, and easier navigation of care pathways.

Of course, such educational measures will require improved financing. More funds should be dedicated to educational therapy, both within and outside of hospitals. Such a measure is seen by the healthcare community as a long-term investment that requires dedication and commitment from policymakers, and not as a short-term solution.

Best practice: Patient Therapeutic Education (PTE)

- Patient Therapeutic Education (PTE) is a technique that was developed for the purpose of enabling health care professionals to pass on their knowledge and expertise to patients so that patients can become partners in their own care.[37] Such educational programs have been shown to improve health behaviours, disease outcomes, and quality of life among different patient populations.[38]

  Different countries have implemented their own models of PTE, giving healthcare providers the skills and tools to educate patients and enable them to manage the treatment of their conditions. In Switzerland, remuneration of HCPs depends on the time spent on PTE, while in Germany, the Netherlands and Belgium, PTE is required as part of HCP education.

Best practice: Counselling

- The UK's NHS previously offered a pharmacy-based service, the Medicines Use Review, free of charge to patients suffering from certain long-term conditions, until 2021. It consisted of a planned consultation between the pharmacist and the patient to discuss their medicines, with the aim of educating patients and agreeing on a treatment plan.[39] It has been replaced by structured medication reviews, carried out by clinical pharmacists working in primary care networks (PCNs).[40]

- The International Society of Hypertension's 2020 Guidelines also point to a combination of counselling, self-monitoring, and supervision as one of the most effective methods for management of non-adherence when working with

[35]Giuseppe Mancia (Chairperson), Reinhold Kreutz (Co-Chair), Mattias Brunström, Michel Burnier, Guido Grassi, Andrzej Januszewicz, Maria Lorenza Muiesan, et al. (2023) 2023 ESH Guidelines for the Management of Arterial Hypertension The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA)," Journal of Hypertension. http://dx.doi.org/10.1097/HJH.0000000000003480.

[36]Unger, T., Borghi, C., Charchar, F., Khan, N. A., Poulter, N. R., Prabhakaran, D., Ramirez, A., Schlaich, M., Stergiou, G. S., Tomaszewski, M., Wainford, R. D., Williams, B., & Schutte, A. E. (2020). 2020 International Society of Hypertension Global Hypertension Practice Guidelines. In Hypertension (Vol.. 75, Issue 6, or. 1334–1357). Ovid Technologies (Wolters Kluwer Health).

[37]Vargas-Schaffer G, Cogan J. (2014). Patient therapeutic education: placing the patient at the centre of the WHO analgesic ladder. Can Fam Physician. Mar;60(3):235-41. PMID: 24627377; PMCID: PMC3952757.

[38]Correia, Jorge César, Ahmed Waqas, Isabelle Aujoulat, Melanie J. Davies, Jean-Philippe Assal, Alain Golay, and Zoltan Pataky. (2022) Evolution of Therapeutic Patient Education: A Systematic Scoping Review and Scientometric Analysis, International Journal of Environmental Research and Public Health, Vol. 19. http://dx.doi.org/10.3390/ijerph19106128.

[39]Medicines use review (MUR), Lawley Pharmacy (n.d.). https://lawleypharmacy.co.uk/services/medicines-use-review-mur

[40]Everything you need to know about the 5-year pharmacy funding deal. C+D. (n.d.). https://www.chemistanddruggist.co.uk/CD005137/Everything-you-need-to-know-about-the-5-year-pharmacy-funding-deal#3

[41]Unger, T., Borghi, C., Charchar, F., Khan, N. A., Poulter, N. R., Prabhakaran, D., Ramirez, A., Schlaich, M., Stergiou, G. S., Tomaszewski, M., Wainford, R. D., Williams, B., & Schutte, A. E. (2020). 2020 International Society of Hypertension Global Hypertension Practice Guidelines. In Hypertension (Vol.. 75, Issue 6, or. 1334–1357). Ovid Technologies (Wolters Kluwer Health). https://doi.org/10.1161/hypertensionaha.120.15026

patients with hypertension.[41]

ROLE OF PATIENT ASSOCIATIONS

Insight. In addition to healthcare professionals and patients, organisations representing patients and clinicians can also play a valuable role in co-creating policies to improve therapeutic adherence. They connect health systems to patients' needs and are well distributed across countries.[42] Moreover, patient organisations have a vital contribution to make in helping policymakers understand patient priorities and experiences of living with a disease and in supporting care coordination processes.

ROLE OF SCIENTIFIC SOCIETIES

Insight. Scientific societies can also contribute to improved therapeutic adherence in an indirect way through information and best-practices sharing among HCPs and scientists working on therapeutic adherence tools and technologies. Involving the relevant societies in the efforts towards therapeutic adherence can act as a way to pool all resources and skills together for one goal, acting as a sort of multi-stakeholder health platform. Potential results of these societies is the identification of emerging research areas that tackle therapeutic adherence, and the reduction of research barriers for scientists, and the creation of scientific guidelines such as the ESH Guidelines for the management of arterial hypertension[43].

Best Practice: Multi-stakeholder health platforms

- The European Federation of Pharmaceutical Industries and Associations (EFPIA) Cardiovascular Health Platform brings together 10 companies working on cardiovascular diseases and allows them to partner with key stakeholders (i.e., HCPs and patients) to co-create evidence-based health policies and innovative solutions in CVD such as secondary prevention, early detection, and screening, and improve treatment.[44]
- The European Society of Hypertension (ESH) conducted a survey, alongside patients' associations, demonstrating that patients consider the reduction of the pill

[42]Chaudri, Naeem Arshad. (2003) Adherence to Long-Term Therapies Evidence for Action World Health Organization. Annals of Saudi Medicine, Vol. 24. http://dx.doi.org/10.5144/0256-4947.2004.221.
[43]Mancia, G., Kreutz, R., Brunström, M., Burnier, M., Grassi, G., Januszewicz, A., Muiesan, M. L., Tsioufis, K., Agabiti-Rosei, E., Algharably, E. A. E., Azizi, M., Benetos, A., Borghi, C., Hitij, J. B., Cifkova, R., Coca, A., Cornelissen, V., Cruickshank, J. K., Cunha, P. G., … Kjeldsen, S. E. (2023). 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension. In Journal of Hypertension (Libk. 41, Issue 12, or. 1874–2071). Ovid Technologies (Wolters Kluwer Health). https://doi.org/10.1097/hjh.0000000000003480
[44]Transforming the lives of people living with cardiovascular diseases. EFPIA Homepage. (n.d.). https://www.efpia.eu/about-medicines/use-of-medicines/disease-specific-groups/transforming-the-lives-of-people-living-with-cardiovascular-diseases/
[45]Burnier, Michel, Alexandre Persu, Michel Azizi, Aleksander Prejbisz, Vitoria Cunha, Pankaj Gupta, Jan Vaclavik, Jorie Versmissen, Reinhold Kreutz, and Sverre E. Kjeldsen. (2003) PATIENT PERSPECTIVES ON TREATMENT ADHERENCE IN HYPERTENSION: PRELIMINARY RESULTS OF AN ESH SURVEY IN FIVE COUNTRIES, Journal of Hypertension, Vol. 40. http://dx.doi.org/10.1097/01.hjh.0000835756.15202.e5.

burden – the number of pills they must take – as a priority to increase their adherence.[45]

LANGUAGE AND PATIENT-PROVIDER COMMUNICATION

Communication barriers and the quality of care are tied to the quality of communication between patients and healthcare professionals, as well as the language used[46]. Also, miscommunication between patients and healthcare professionals is regarded as an impediment to medical care and the patient's quality of life[47]. Communication in this sense is considered as the amount of clarity provided by a healthcare professional when explaining conditions to patients, and the clarity used by patients in explaining their symptoms to healthcare professionals. If a doctor, for example, finds one treatment beneficial, that doctor must

be able to clearly communicate to the patient why such a treatment is recommended as well as explain the other available treatments.

DETECTION AND MONITORING – THE CASE OF ANTIHYPERTENSIVE TREATMENTS

Insight: Among people living with chronic diseases like hypertension, the risk they will stop taking their medications increases over time. It is challenging for clinicians to accurately identify and assess medication adherence, and there is no one 'best' method of doing so.[48] Despite the increasing use of direct methods to measure antihypertensive drugs in body fluids, non-adherence remains an obstacle to effective antihypertensive treatment. Measured levels of non-adherence among people living with hypertension vary considerably, largely depending on the particular method of assessment (direct or indirect, subjective or objective) used.
However, there is a lack of standardisation and consistency in measurement method selection. Reliance on patient self-reporting risks overestimating adherence level. Other methods (e.g. prescription records, pill counting, electronic monitoring) seem to have efficacy, especially regarding unintentional non-adherence. Directly observed therapy, or witnessed intake of medications, removes a source of bias but requires supervision by an HCP and therefore diverts resources away from routine care.

Best practice – chemical adherence testing

→ New adherence measurement methods are emerging, such as chemical adherence testing. According to the European Society of Cardiology and European Society of Hypertension guidelines, this is a promising tool but is not widely available. Chemical adherence testing involves using liquid chromatography–tandem mass spectrometry to detect levels of medication in patient samples. This can demonstrate the presence or absence of medication in a patient's system, as well as the levels of the substance(s) in question, providing an objective measure of adherence. Recent studies suggest it is feasible to implement in primary care, cost-effective to carry out, and perceived as acceptable by patients. However, low awareness and availability of chemical adherence testing are possible reasons for low uptake of the technology.[49]

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POLICY RECOMMENDATIONS

When reforming the structure and governance of care delivery, strengthen tools and skills of health institutions and professionals as a first touchpoint for patients (e.g., pharmacists, GPs, nurses, psychologists, behaviouralists).

Make the involvement of patient associations in assessing patient needs and in supporting patients in care coordination the cornerstone of well-funded policymaking on therapeutic adherence.

Replicate best practices to promote training of healthcare providers on patient therapeutic education, considering the opportunity of funding doctors and patients as an incentive.

Integrate courses on psychology and communication skills in HCP training and curricula, aimed at increasing adherence.

Consider patient adherence as a performance measure for healthcare systems, to optimise investment in medicinal products as a way of improving patient outcomes while reducing healthcare costs.

Consider including secondary prevention strategies, targeted at populations who fall through the gaps in primary prevention strategies, in all policy documents.

Replicate models of successful co-creation, engagement, and discussion for chronic illnesses, like the Cardiovascular Health Platform, to support patients, caregivers, and healthcare professionals.

Develop a common approach to therapeutic adherence that includes GPs, pharmacists, nurses, and patient organisations to identify and implement methods of optimal care coordination.

Accelerating technology and innovation

DIGITAL TOOLS TO GO BEYOND THE PILL

Insight: Although some doubts persist among the patient community, digital tools and new technologies are increasingly being used to support therapeutic adherence, including mobile apps, health data, AI, and tele-monitoring. One such example, gaining attention in both research and in practice, is chatbots. These bots can support patients in their home treatments and encourage adherence and are increasingly being investigated as tools for improving the latter[50]. Monitoring devices are also seen as useful for cardiovascular risk assessment and cardiovascular disease prevention.[51] However, barriers persist in the uptake of digital technology as there is little available data and further research is needed into the impact of app usage on medication adherence among people living with chronic disease.[52] Such tools should also be co-created with patients, in order to ensure that they work for the target audience and to maximise their efficacy in practice.

Best practice: e-prescribing infrastructure

→ Several countries, for example, Norway, Denmark, Finland, Sweden, England, Estonia, and the United States use e-prescribing infrastructure. Such a system permits prescribers to view a patient's medication regimen and identify non-adherence and could also notify prescribers and pharmacists about refills – potentially flagging potential gaps in medication use and allowing for intervention before they happen.[53] One US-based study from 2010 demonstrated an approximate 50% reduction in daily staff time spent on medication refills, and reported approval from clinicians and staff.[54]

Best practice: monitoring mobile health interventions

→ A quality improvement project conducted at Cleveland Clinic showed that non-surgical cancer patients who received a phone call follow-up within 48 hours of hospital discharge and had a follow-up appointment with a provider within one week of discharge were less likely to have an unplanned readmission.[55]

Best practice: monitoring devices

→ In the Netherlands, national health insurance provides coverage for adults with asthma or COPD to use the Enerzair smart inhaler, a drug-device combination. The inhaler device[56] comes with an electronic sensor that can record usage data and send it to the patient's phone.

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INNOVATION TO TACKLE THE "PILL BURDEN"

Insight: Medication management contributes to the burden treatment places on people living with multiple health conditions. Additionally, there is an association between the complexity of a medication scheme and an increased number of errors – which, in turn, puts these people at a higher risk of hospitalisation.

Older people have notably high rates of non-adherence, which may be due to their likelihood of undergoing complex treatment plans and experiencing impairments that make it harder to take certain treatments – such as difficulty swallowing oral medications.[57]

There is emerging evidence suggesting that, for older people, complexity of medication regime is associated with non-adherence. Ways to tackle this problem include reducing the number of different dosage times and administration methods the person has to manage, preferring long-acting medications over shorter-acting ones, and usage of combination products instead of multiple single pills.[58]

To go into detail, there is evidence to support the concept of a negative correlation between dosing frequency and adherence and a subtle difference between adherence rates for drugs taken multiple times per day.[59,60]

Fixed-dose combinations (FDCs), single medications or dosage forms that contain a combination of two or more active ingredients, are becoming more frequently used - especially when required to control a condition such as diabetes, or hypertension.

Scientific literature suggests they have shown efficacy in improving therapeutic adherence and patient outcomes, while reducing healthcare costs - especially among patients who live with chronic conditions such as hypertension and dyslipidaemia.[61,62,63,64]

In fact, some experts consider blood pressure control rates in some countries to be low due to the low uptake of FDCs. If the majority of patients eligible for FDCs were actually prescribed them, it would improve patients' adherence and in turn lead to higher control rates for blood pressure. FDCs attempt to reduce the number of pills a patient has to take, making the treatment process simpler and easier to maintain. Innovation in delivery methods to reduce the pill burden can also go beyond FDCs. For example, the medical community has found that the delivery method of once-a-month injections for HIV treatment offers patients much-needed relief.

[57]Baryakova, Tsvetelina H., Brett H. Pogostin, Robert Langer, and Kevin J. McHugh. (2023) Overcoming Barriers to Patient Adherence: The Case for Developing Innovative Drug Delivery Systems. Nature Reviews Drug Discovery, Vol. 22. http://dx.doi.org/10.1038/s41573-023-00670-0.
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Best practice: heart attack patients treated with polypill

- The SECURE trial[65], whose results were presented at the European Society of Cardiology Congress in Barcelona in 2022, aims to study the impact of a polypill on recurrent cardiovascular events in heart attack patients. It was funded by the European Union's Horizon 2020 research and innovation fund, enrolling 2,500 patients six months after a myocardial infarction. The study compared polypill treatment outcomes with regular care and concluded that, three years later, the number of deaths from heart and circulatory conditions, along with the number of further heart attacks or stroke, was lower in the group of patients that had taken the polypill. Patients in the polypill group also had higher levels of adherence compared with those in the usual care group.

Best practice: Vaccinations

- A less common method of reducing the "pill burden" is vaccination. In the field of hypertension, which can be controlled by available medication, non-adherence remains an issue. Vaccination is of increasing interest in such cases and could complement - or potentially replace - medication. Despite the challenges involved in developing such a vaccine, securing one would have far-reaching implications for health systems.[66]
- Clinical trials of vaccinations for individuals living with HIV have proven successful in achieving undetectable levels of the virus without any regular antiretroviral therapy.[67]

[65]Castellano, Jose M., Stuart J. Pocock, Deepak L. Bhatt, Antonio J. Quesada, Ruth Owen, Antonio Fernandez-Ortiz, Pedro L. Sanchez, et al., "Polypill Strategy in Secondary Cardiovascular Prevention," New England Journal of Medicine, Vol. 387, Massachusetts Medical Society, September 15, 2022. http://dx.doi.org/10.1056/NEJMoa2208275.
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POLICY RECOMMENDATIONS

Invest in research into the use of innovative treatment methods for chronic illnesses like cardiovascular diseases, such as Fixed Dose Combinations and vaccinations.

Adopt guidelines that help HCPs use innovative treatment methods, such as Fixed-Dose Combinations, by recognising and highlighting the benefits of their use, including the improvement of patient welfare, ease of treatment, and improved adherence rates.

Consider the benefits of therapeutic adherence when making pricing and reimbursement decisions on technologies that facilitate adherence, and adapt regulatory frameworks to facilitate uptake of incremental innovations that promote adherence.

Integrate training on digital tools into medical education through a general framework to be adopted at European level, which will also serve to increase patient uptake.

Consider the creation of a legal framework that facilitates the use of e-prescribing infrastructure by ensuring data security and quality, ease of access, and availability of a user-friendly digital infrastructure for healthcare.

Future-proof and agile regulations

ACCELERATED APPROVAL PROCEDURES AND FOLLOW-UP

Insight: People living with chronic illnesses experience significant unmet needs. This situation can be the result of slow regulatory processes, or a significant backlog in approval procedures. The accelerated approval pathway has demonstrated considerable success for patients facing serious or life-threatening diseases and provided earlier access to treatments for illnesses with unmet medical needs.[68]

However, with accelerated approval procedures, it is vital that the appropriate follow-up is conducted where all stakeholders (patients, physicians, sponsors of the medical treatment being developed, regulatory authorities and payers) are consulted and understand how the new product performs for patients for whom the product is indicated.[69]

To promote regulatory innovation and measure its impact, alongside reliable scientific evidence during trials, clear, up-to-date data on the status and impact of therapeutic adherence must be available to all interested stakeholders.

Best practice: Accelerated approval procedures

→ Regulatory agencies around the world have procedures in place for accelerated approval, with varying methods of evaluation. A key example is the European Medicine Agency's decision to put in place fast-track procedures for treatments and vaccines for COVID-19.[70] The US Food and Drug Administration permits earlier approval of medicines that treat serious conditions, and fill an unmet medical need based on a surrogate endpoint.[71] On the other hand, India has specific (but not fast-track) policy guidelines for the approval of Fixed-Dose Combination medicinal products.[72]

[68]Three things to know about the accelerated approval pathway. PhRMA Org. (n.d.). https://phrma.org/blog/three-things-to-know-about-the-accelerated-approval-pathway
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THE USE OF REAL-WORLD EVIDENCE

Real World Evidence (RWE) to support health technology assessments (HTA) can be used to contribute to a positive HTA outcome, because it is an effective way of measuring adherence (given that it cannot be measured in randomised clinical trials) and its impacts on patient outcomes and healthcare costs. This method has proven to be helpful in reducing payer uncertainties and providing patients with faster access[73]. RWE can also assist with regulatory decision-making because of its ability to demonstrate outcomes and value, thus reducing uncertainties that can delay reimbursement decisions. However, acceptance of RWE in HTA evaluations and its impact on HTA outcomes remains limited and highly variable among countries.

Best practice: Real-World Evidence for HTA procedures

→ Different countries consider the use of RWE to provide valuable information during regulatory processes.[74]

- Australia: In 2021, the Therapeutic Goods Administration (TGA) released the review on RWE and patient reported outcomes (PROs), establishing a central point of information on RWE and PROs in Australia.[75]
- Japan: the Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have been guiding RWE use since 2014 with the release of the Guidelines for the Conduct of Pharmacoepidemiologic Studies in Drug Safety Assessment with Medical Information Databases.[76]
- Spain: the Ministry of Health launched a shared information system within the National Health System, that collects real-world data to measure treatment outcomes.
- Canada: In September 2022 Canada announced a post market evaluation program to answer questions of decision-makers based on RWE.
- UK: In June 2022, NICE published a real-world evidence framework, outlining where RWE could inform appraisals.
- Italy: AIFA considered a RWE study[77] for FDCs in Cardiovascular Diseases.

Best practice: measuring and reporting in different contexts

→ At national level: the United States' Centers for Medicare and Medicaid Services (CMS) uses its Medicare STAR program to measure adherence to drugs that manage cardiovascular diseases. The responsibility falls on the health-plan insurers to monitor and improve medication adherence.[78]

→ At primary care level: In Israel, Slovenia, and Turkey, primary care physicians monitor adherence regularly.

[73]Impact of RWE on HTA decision-making. IQVIA. (n.d.). https://www.iqvia.com/insights/the-iqvia-institute/reports/impact-of-rwe-on-hta-decision-making
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POLICY RECOMMENDATIONS

Consider adherence rate as a healthcare system performance indicator.

Advocate for every intervention on therapeutic adherence to undergo a cost-effectiveness evaluation.

Require HCPs to monitor patients' therapeutic adherence, and facilitate the use of digital innovation to help in monitoring patients' therapeutic adherence.

Consider the role and the potential value of RWE and other emerging technologies to support regulatory processes.

Simplifying the registration process of Fixed-Dose Combination medicinal products.

Section III: Conclusion

As this report has shown, alongside the many efforts made by other HCPs, researchers, and the scientific society in the health sector, therapeutic adherence can bring a wide range of benefits to patients, health care systems and the industry. There are many barriers to therapeutic adherence that stem from multiple sources, including but not limited to patient behaviours, HCPs and their attitudes and training, and the wider environment in healthcare systems. The scientific evidence proving the existence of these barriers is constantly evolving, and this necessitates a comprehensive, patient-centric, evidence-based multi-stakeholder approach, where all the concerned parties can cooperate to improve understanding on therapeutic adherence, and share insights and best practices.

If properly implemented, the above measures have the potential to unleash the power of therapeutic adherence and lift a significant burden off the shoulders of the healthcare system, HCPs, and patients by facilitating treatment and reducing resource use. The best practices in this field were successful because of their comprehensive, patient-centric, and multi-stakeholder approach. Moreover, their fundamental aim was essentially to empower patients to adhere to their treatments.

Looking forward, the medical community should also lead by example through embracing technologies that help with therapeutic adherence. Researchers, engineers, HCPs, and scientific and patient organizations all contribute significantly to the development of new tools that continuously prove to be efficient and revolutionary for the medical sector. These tools, such as gene editing, RNA technologies, and the use of artificial intelligence in a wide variety of patient monitoring and follow-up methods can serve to facilitate therapeutic adherence and simplify procedures for doctors and patients alike.

Such an endeavour requires significant efforts from all those involved. As long as one piece of the puzzle is missing, be it patients, the medical community, or politicians, high rates of therapeutic adherence will always be difficult to achieve. Also, in sectors that are advancing as quickly as medicine, it is very important to maintain a degree of technological openness and neutrality. Now, as our societies age and chronic illnesses and NCDs increase in prevalence, is the time to act quickly and decisively to ensure therapeutic adherence remains on the agenda of policy makers and receives the regulatory attention it deserves.

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