



Review Article

The role of adherence in patients with chronic diseases

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ABSTRACT

In the long-term management of chronic diseases, adherence and persistence to prescribed medications are continuous challenges in order to obtain all the potential benefits of drug therapies. Suboptimal drug adherence and discontinuations of therapies remain the most frequent reasons why several diseases are poorly controlled in the population. One the main issue is that physicians are relatively limited in time and tools to detect patients with a poor adherence. The present review discusses present and future strategies that are now available or are being developed to detect and to support adherence in patients with chronic diseases and provides some simple clues to identify patients at high risk of discontinuation in the clinic.

1. Introduction

In recent decades, the prevalence of chronic non-communicable diseases and that of patients with multiple morbidities has increased steadily worldwide although with large geographical disparities [1–3]. Thus, in Europe [4], a Dutch monitoring study based on medical records of patients listed in a nationally representative network of general practices over the period 2002–2011 has reported a ~7% increase in the prevalence of chronic diseases from 34.9% to 41.8%. This increase in developed countries is due essentially, but not only, to the aging of the population, which cumulates chronic diseases, but also to improvements in health care and social environment leading to a significant reduction in premature avertable mortality from several chronic diseases [5]. Indeed, in several chronic clinical conditions such as type 2 diabetes, hypertension, dyslipidemia, newly available therapies have enabled to reduce significantly patients' morbidity and mortality [6–8]. Nevertheless, in most of these conditions, despite the variety of effective and well tolerated therapeutic approaches, the quality of the diseases control remains most of the time insufficient [9]. Thus, in a Swiss population-based cohort of 6733 subjects aged 35–75 years of the Lausanne area, only 17.2% (95% CI 13.7 to 21.5) of patients had an adequate simultaneous control of glycemia, cholesterol and blood pressure after 15 years of follow-up [9]. Even lower results were obtained among Swiss general practitioners at the national level [10].

Several reasons are usually evoked to explain why the control of most

chronic diseases is so imperfect. One of them is the patients' poor adherence to prescribed medications leading to incomplete treatments and frequently to early interruptions of drug therapies. According to the 2012 nomenclature for adherence issues, adherence is defined as “*the process by which patients take their medication as prescribed, further divided into three quantifiable phases: initiation, implementation and discontinuation*” [11]. In chronic diseases, it is assumed that patients have initiated their therapy as proposed by their physicians. Yet, non-initiation or primary non-adherence remains frequent in all chronic diseases affecting about 28% of new prescription in the US [12]. In South-East England, a longitudinal survey of new prescriptions with data collection at 10 days and 4 weeks performed on 258 patients recruited from 23 community pharmacies found that, among patients 75 years or older, 30% of patients still taking their medication at 10 days and 25% of those still taking their medications at 4 weeks were non-adherent according to a self-assessment [13]. In half of the case, non-adherence was non-intentional. However, the main issues in all chronic diseases are the day-to-day adherence and most importantly the long-term persistence [14]. Thus, in hypertension, a systematic review and meta-analyses of studies on adherence from 2010 to 2020 involving 27 million patients found that, whatever the method used to assess drug adherence, the global prevalence of anti-hypertensive medication non-adherence ranged between 27% and 40% and, as expected, non-adherence was associated with a poor control of BP, complications from hypertension, all-cause hospitalizations, and all-cause mortality [15]. Of note, a low

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adherence and persistence is not specific to “silent” diseases such as hypertension [16] or dyslipidemia [17,18] but also in diabetes [19], depression [20] or rheumatoid arthritis [21] and many other symptomatic or asymptomatic chronic diseases. Thus, a poor adherence to medications and a non-persistence should always be considered in the long-term management of patients with chronic diseases, particularly when therapeutic objectives are not achieved despite several medications. This is the case for example of apparent resistant hypertension, a clinical situation frequently due to a low adherence [14,22–24]. Another critical situation in chronic diseases is when medications are prescribed as a preventive measure, and not to suppress symptoms. In that case, adherence is low and the risk of discontinuation is high. Thus, in primary cardiovascular prevention, adherence to blood pressure lowering drugs or statins has been found to range between 42 and 61% depending on drug classes and figures are only slightly better in secondary prevention ranging between 62 and 76% [25].

2. Factors influencing adherence in chronic diseases and patients at risk

As nicely summarized by the WHO twenty years ago [26], adherence to medications is a complex process influenced by multiple factors. Thus, in addition to patient-related factors such as age, gender, symptoms and beliefs, physicians have to consider also treatment-related factors (treatment complexity, tolerability profile of drugs, dosing frequency), conditions-related factors (comorbidities, type and severity of the disease, disabilities...), the socio-economic environment and of course the health care system (access to care or drug reimbursement) including physicians’ own abilities to communicate, to establish a good physician-patient relationship and to empower their patients [14]. One major aspect to consider is that adherence to medications is a dynamic process that can vary considerably depending on life events. Thus, almost all patients can become transiently non-adherent because of personal issues. In clinical practice, the difficulty lies in the physician’s ability to detect and recognize long episodes of poor adherence or eventually treatment interruptions.

Interestingly, in a survey undertaken amongst healthcare professionals managing hypertension in the European Society of Hypertension (ESH) Centres of Excellence, only 23% of physicians considered that the identification of non-adherent patients is really difficult and 53% found it moderately difficult [27]. These answers are surprising when we know the low reliability of the techniques used for detecting sub-optimal adherence in the medical office, mainly patient’s interview [28,29], and the little time dedicated by physicians to discuss prescribed treatments (between 1 and 5 min) [27]. In fact, there is no gold standard method for assessing medications adherence in clinical practice, which could provide simultaneously a proof of the drug ingestion and a dosing history between two medical terms. Today, in treated patients with uncontrolled hypertension, it is becoming increasingly popular to measure drug concentrations in plasma or urine to monitor adherence [30]. Chemical adherence testing using new mass spectrometry platforms has become more accessible and cheaper and can provide pertinent information when there are doubts about medication adherence. However, this interesting approach has its own limitations including the lack of dosing history, the cost and the fact that patients tend to increase their adherence before clinical terms (white coat adherence). Thus, only the total absence in blood or urine of a prescribed compound can ascertain non-adherence.

In clinical practice, interviewing patients about missed doses, reduced doses or changes in medications remains the most common way to assess adherence despite the poor reliability of this approach because patients want to please their physicians [27]. In fact, during a consultation, physicians have no other choice than to rely on the recognition of the few clinical clues or “warning signals” associated with a higher risk of poor adherence as reported by Mackenzie and MacDonald [31] (Table 1). They may also take into account the results of some

Table 1

Clinical warning signals that may be associated with an increased risk of poor adherence to therapy (adapted from Ref. [31]).

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- Patient expressing:
 - > a lack of belief in benefits of treatment
 - > concerns about adverse effects of medications
 - > tiredness of taking medications
 - > a fear of lifelong treatment
 - Poor understanding of their disease and the benefits of treatment
 - Unexpected increase in clinical parameters (blood pressure, glycemia, cholesterol)
 - Inadequate response to treatment
 - Complex treatment regimen or multiple co-morbidities
 - Poor attendance at planned review appointments
 - Communication difficulties
 - Previous unsatisfactory clinician encounters
 - Depression or other psychiatric illness
 - Significant competing priorities (Caring responsibilities for other family members, financial issues ..)
 - Poor social or family support network
-

epidemiological data showing that some subgroups of patients are clearly at higher risk of treatment discontinuation. Thus, in a large Swedish cohort of patients with hypertension followed during two years, among patients with a first prescription, 26% discontinued treatment during the first year, and a further 9% discontinued during the second year and discontinuation was more common in men and in younger patients (30–49 years) [32]. Older people with minor cognitive troubles and patients with multiple comorbidities and depressive patients may also be at high risk of poor adherence and persistence.

3. Consequences of poor adherence in chronic diseases

As expected, drugs that are not taken do not work and one cannot anticipate major clinical benefits from therapy in patients with a low adherence. Several studies have confirmed that a low adherence to therapy is associated with adverse health outcomes that go beyond the poor control of clinical parameters. Thus, in the cardiovascular field, a low adherence has been associated with an increased incidence of target organ damages (left ventricular hypertrophy, albuminuria ...) and cardiovascular events (stroke, myocardial infarction, angina pectoris or heart failure) in patients with hypertension, diabetes or dyslipidemia [14,33,34]. In nephrology, a suboptimal adherence is associated with an increased risk of kidney function decline [35]. However, many other aspects of diseases management are negatively affected by a low adherence including exacerbations of diseases resulting sometimes in acute hospitalizations, increased health costs and of course a reduction of patients’ quality of life [36–38]. The multiple negative impacts of low adherence to medication in chronic diseases further emphasize the need for an effective early recognition of the problem in clinical practice.

4. What can be done to improve adherence?

Owing to the multiplicity of potential causes of low adherence to medications, there are almost as many strategies or potential interventions to improve adherence as causes. Interventions are generally focused on the patient and on the quality of the prescribed treatment but also on the socio-economic environment. However, despite the numerous options, meta-analyses and systematic reviews on interventions to ameliorate adherence conducted until 2014 were rather disappointing, current methods of improving medication adherence for chronic health problems being mostly complex, not very effective, of short duration and with a minor effect size [39]. This is also true for educational and behavioral interventions (motivational interviewing, cognitive-behavioral therapy) for example in older patients taking multiple medications [40]. These approaches are certainly effective [41] but the level of evidence remains low because there is a lack of carefully conducted trials in this field. Therefore, firm conclusions on the efficacy of these approaches cannot be drawn. Finally, the choice of the strategy

will depend on local availabilities considering that whatever the intervention, adherence will improve by about 20% and that most of the time several different interventions are needed to achieve a good long-term adherence and persistence.

Nevertheless, more recent analyses have suggested that some specific interventions are particularly effective. Thus, in the secondary prevention of cardiovascular events in patients with atherosclerotic cardiovascular diseases, three distinct interventions were found to result in improvements in both adherence and clinical outcomes: a short message service, the use of fixed-dose combinations and a community health worker-based intervention [42]. In this context, the use of fixed-dose combinations or single-pill combinations appears to be most effective strategy to recommend today. Indeed, the use of single pill combinations that associate two or even three pharmacological entities is now possible in several chronic diseases including hypertension, dyslipidemia, diabetes. They enable to simplify the patient's treatment by reducing the number of pills and to avoid some degree of medical inertia. The use of single pill combinations has been shown in meta-analyses to increase adherence and persistence in hypertension and hence to improve blood pressure control [43]. More recent data have even shown a reduction in all-cause mortality and cardiovascular events when antihypertensive therapy was provided as single pill compared to identical drugs as multipills [44]. Another striking example is the management of HIV patients. The significant reduction of the pill burden in HIV treatments has led to a considerable increase in drug adherence and to significant decreases in morbidity and mortality [45]. As shown in Table 2, other useful approaches include: reducing the administration frequency, avoiding drugs with frequent side effects, stopping unnecessary medications, linking drug intake with regular daily activities and also empowering patients, prescribing drugs based on a shared decision process and involving other health care providers such as nurses, psychologists or pharmacists [46] (Table 2).

5. Challenges and future directions

In recent years, a great interest has focused on the development of technology-based approaches to improve adherence. These include text messaging, mobile apps, telemedicine and social media. With the use of telemonitoring, mobile health tools (mHealth) and digital health, improvements in medication adherence and clinical endpoints have been reported for example in patients with diabetes or hypertension and also in other chronic diseases [47–50] but the impact on morbidity and mortality remains to be demonstrated using carefully conducted prospective randomized controlled trials in order to assess their real added value. Although well accepted by some patients, there are still some barriers to a wider use of these technologies in clinical practice [51]. One of them is the ability to manage these techniques by general physicians in their clinical setting. Other open questions are linked to the accessibility of the techniques by older patients and to the confidentiality of data. Nevertheless, new systems will continue to be developed and they will probably represent an interesting complementary approach to behavioral and motivational interventions supporting the patient-physician relationship, this latter remaining the basis of a good adherence.

Another interesting development that may positively influence drug adherence in patients with chronic diseases is the availability of new drugs administered only once every 3–6 months or even once a year using new pharmacological approaches such as small interfering RNA. Such drugs can now be prescribed to patients with osteoporosis [52] or hypercholesterolemia [53] and perhaps also in the future to hypertensive patients [54]. With these compounds, the treatment scheme is maximally simplified, and it is generally assumed that the problem of suboptimal adherence should be markedly improved or even solved. This is perhaps true, but real-world data tend to attenuate the initial enthusiasm. Indeed, in the Austrian survey among patients treated for osteoporosis with denosumab, long-term persistence decreased

Table 2

Some interventions that may improve adherence at the physician and patient levels.

Physician level
1. Take time to talk about adherence
2. Measure adherence whenever possible
3. Simplify treatment as much as possible using single pill combinations
4. Use preferentially long-acting drugs (“forgiving drugs”)
5. Stop unnecessary drugs
6. Assess individual barriers to adherence and try to solve them
7. Empower the patients
8. Provide positive feedback on behavioral and clinical improvements
9. Collaborate with other healthcare providers, especially nurses and pharmacists
10. Repeat information on the risk of risk of the disease and benefits/risks of treatments
11. Increase the frequency of medical terms in severe cases
Patient level
1. Do not hesitate to discuss adherence issues
2. Monitor home parameters when possible
3. Couple drug intake with regular home activities
4. Use reminders or week organizers
5. Have a provision of drugs at work
6. Use family, nurses, pharmacist, or social support whenever possible
7. Self-management with simple patient-guided systems
8. Eventually participate to group sessions if available

progressively, 73% of patients remaining under treatment after 7 years [52]. In patients with hypercholesterolemia, figures are even lower. Indeed, in a cohort of patients receiving high doses of statins or a PCSK9 inhibitor approximately one third of PCSK9-treated patients filled only one or two claims, and 33.3% became non-persistent with treatment after 60 days [55]. In the secondary-prevention sub-cohort, mean duration of PCSK-9 inhibitor treatment was 69 days, and 44.4% were treated for 60 days or less. These observations further emphasize that the patients' motivations and willingness to stay on therapy do not only depend on drug characteristics and on the burden of taking several medications but also on several other non-pharmacological parameters.

6. Conclusion

In patients with chronic diseases, long-term adherence and persistence are significant challenges on which depends not only the quality of diseases control, but also, and more importantly, the prevention of their complications, including mortality. Physicians usually recognized that adherence is an important issue in the management of chronic patients, but they are relatively limited in terms of capacities to detect and to diagnose a poor medication adherence. Moreover, they have often no time to dedicate to this issue. Thus, there is an urgent need to develop new strategies to support adherence and this may be done through the implementation of modern technologies but also to a greater involvement of other healthcare providers such as nurses, psychologists, or pharmacists, who may have more time and competences to assess the barriers and the pharmacological issues that impair adherence and persistence. They may also contribute to obtain a more in-depth analysis of patients beliefs and motivations in partnership with physicians.

Declaration of Competing Interest

The author declare he has no conflict of interest.

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