

REVIEW

Adherence in severe asthma

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Summary

Adherence in asthma is an important cause for concern. Although nearly 50% of asthma patients are considered poorly adherent to therapeutic advices, adherence is still difficult to assess, understand and improve despite major medical consequences. In this review, we revisited the literature of the last 10 years related to adherence in severe asthma. The concepts have changed and “compliance” is usually replaced by “adherence”. Assessment of adherence is addressing ethical issues, but provides important insight into difficult-to-treat asthma. Different tools have been used but none is routinely recommended. Health-related outcomes (poor control, exacerbations, hospitalizations, lung function decline), which are clearly associated with severe asthma, are often worsened by non-adherence with consequences also on patient related outcomes (quality of life). The potential behaviour associated with non-adherence and all other related factors including easy-to-recognize psychological traits can help for patient's future management. Therapeutic educational interventions have been recognized with a scientifically proven efficiency even though evolution and improvements are needed. A multidisciplinary approach is required in severe asthma. Therapeutic adherence for a given patient is always a prerequisite to any other aspects when addressing severe asthma phenotypes. Severe asthma should be considered only in those who still experienced poor asthma outcomes despite optimal adherence. At a glance, poor adherence and severe asthma should be considered antinomic. Better understanding of the causes and customised management are potential future directions.

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Introduction

Severe asthma is a heterogeneous disease. It has been nowadays better defined. Guidelines and expert panel reports accurately described the need for an extensive assessment securing the diagnosis, establishing and managing co-morbidities, environment and appropriately addressing the concern of therapeutic adherence [1]. This rigorous clinical pathway is required to describe not only a common natural history of the disease that will lead to permanent uncontrolled symptoms, recurrent exacerbations with the potential need for hospitalization and/or the risk of near-fatal/fatal episodes, chronic airflow impairment with an accelerated decline in lung function but also the potentially unacceptable weight of treatments. A follow-up of 6 months at least is then required (Fig. 1). Interestingly, this definition of severe asthma (Table 1) is mainly

based on the level of medication required to gain control – if control can be achieved and ideally sustained. Before advising for important drug interventions (long-term maintenance with oral steroid, anti-IgE subcutaneous administration, or enrolment in a clinical trial testing innovative drugs), optimal therapeutic adherence is a pre-required condition for considering the three following key points: that the natural history of the disease is not sufficiently affected by optimal inhaled therapies using high doses of inhaled corticosteroid (ICS), long acting b2 agonist (LABA) and other controllers (LTRA, LA theophylline), that the biological pathway involved in this resistance has been sufficiently assessed according to the best current standards of care and that environment and therapeutic education were optimized.

In this review, we will discuss new definitions of therapeutic adherence in the scope of severe asthma,

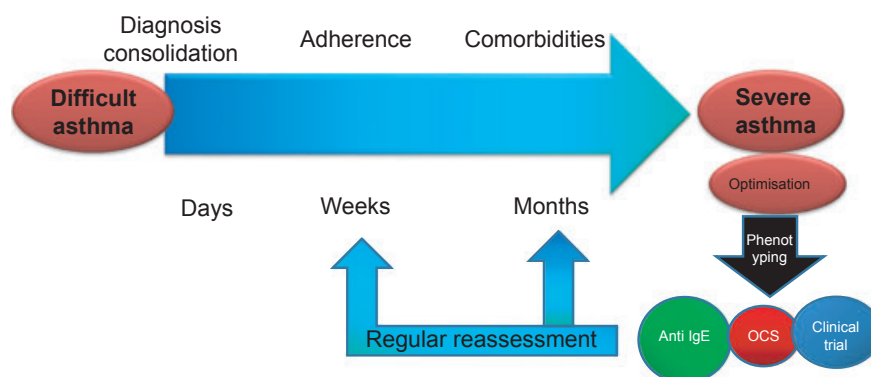


Fig. 1. Place of adherence assessment in difficult-to-treat asthma.

Table 1. Adherence to treatment

Acceptation	Patient agrees to take medication
Understanding	Patient understands the role and conditions of treatments use (dosage, time, and technique)
Observance	Treatment intake according to recommendation
Perseverance	Persistence of adequate treatment during the period recommended

how worth the assessment is and how to do it before discussing the reason for poor therapeutic adherence and potential helping solutions.

Definition of the problem, facts about adherence in the real world

Asthma affects an estimated 300 million people worldwide and is estimated to account for one of 250 deaths and 15 million disability-adjusted life years lost annually [2–5]. Suboptimal adherence to medication regimens is a recognized, but incompletely understood problem seen in all severities of asthma and contributes to poor asthma control, increased mortality and hospitalization rates, decreased quality of life (QoL) and reduced lung function [6–9]. Poor adherence by itself affects asthma control and often led to an overestimation of asthma severity.

The key study GOAL disseminated the idea that 85% of asthma patients could be at least well-controlled using low dose combination of ICS and LABA when adherence was good. One year later, nevertheless, 35% of patients who were uncontrolled after the first step of the study remained uncontrolled. This study mimicked real life data where control is achieved in about half of the patients. Despite treatment with high-dose therapy, ~5% of adult patients remain difficult to control, with persisting symptoms and frequent exacerbations. This subgroup of patients is a cause for concern because of the potential consequences of uncontrolled disease, including fatal or near fatal asthma [10]. Non-adherence is a potential

key aspect linked to patients, for this permanent poor control.

Definitions and facts

Initially, Haynes introduced the term of “compliance” as “the level of coincidence or ad equation between medical prescriptions and recommendations and patients’ behaviour” [11]. A high risk of misinterpretation or overlap with the concept of submission and obeisance led to its progressive replacement by more appropriate concepts of adherence [12–14]. Indeed, adherence is a three step component comprising acceptance, observance and persistence, closely correlated. Different patterns of poor adherence have been described: suboptimal (lower dose taken than prescribed), therapeutic gaps (behavioural variability over time), non-persistence and to the most, primary poor adherence (Table 1).

Adherence is opening the way for collaborative supports between patients and health care professionals in the perspective of a common therapeutic project [15]. This concept fulfils the partnership between patients and health care providers advocated by most of the current guidelines and recommendations. In the field of social psychology, adherence is defined as “the ability to take medication accordingly”. This ability is influenced by cognitive, emotional, social and behavioural factors. At a glance, the most appropriate and accurate word in the field is “therapeutic adherence”.

Therapeutic adherence might be qualified of erratic, clever, not intentional or intentional, objective, subjective, etc. [16]. It is noteworthy that these words are important and should be used appropriately.

In the real world, all studies reported adherence levels rarely exceeding 50% of the patients, depending on chosen timescales and tools considered. Although intuitively adherence should improve with disease severity, objective measurements demonstrated that observance,

for example to OCS in “OCS-dependent” patients, was not exceeding 50% [17].

Consequences: is it worth assessing therapeutic adherence? Health consequences of non-adherence in severe asthma

Usually, the initial situation is described as a “difficult-to-treat asthma”. Very clear reports identified the need for a clinical pathway aiming to identify the cause and associated factors with this frequent situation [1]. Checking the diagnosis and the adherence to treatment are the first two critical steps of this procedure. “Refractory asthma” is a potential cause for difficulty, but it is not the most common. Gamble *et al.* [17] reported in a population of 182 difficult-to-treat asthma patients referred to their centre a prescription filling for inhalers below 50% in 63 patients. In the 51 treated with oral corticosteroids, prednisone could be detected in their plasma in only 26, whereas cortisolaemia was normal in the remaining 23 with no detected plasma concentration of prednisone, and three had both but declared intermittent use of the drug.

Interestingly, these non-adherent patients (who were mainly female) had worst medical indices: a poorer quality of life and a higher admission rate in the previous 12 months. The use of short-acting bronchodilator nebulization was frequent in these patients.

Large trials in adults reported adherence to ICS rating between 30% and 50% in adults, where poorer adherence was related to poorer asthma-related health outcomes (emergency room attendance, OCS bursts, hospitalizations) [9, 18–21]. Of note, these outcomes are often related to the natural history of severe asthma, making the distinction between difficult-to-treat, including non adherent, and severe asthma, which are complex and uneasy to discriminate.

In our experience in a prospective 1-year follow-up study, nocturnal awakening, exacerbation and hospitalization were more frequent in the poor adherent group [22]. Salmeron *et al.* [23] observed in patients with asthma admitted in the emergency room that the lack of treatment (especially inhaled steroids) was extremely frequent and a risk factor for near-fatal asthma.

Improving adherence led to better control and lung function associated with a better quality of life in a prospective trial comparing two strategies of decision (clinician vs. shared with the patient).

One can tell that therapeutic adherence in severe asthma is not important. If the disease is not adequately controlled by the treatment, there are no reasons for continuing with it, in particular because of potential unacceptable side effects.

In fact, consequences of poor adherence in severe asthma – if we consider that asthma can be categorized

as severe when adherence is poor – can be dramatic. ED visits and hospitalizations – ICU requirement and deaths to the worst – are surrogate outcomes that fully justify the cause for concern. The cumulative annual dose of OCS received during two to three exacerbations in a year treated for 10 days with 1 mg/mg of systemic steroids is equivalent to 5 mg every day. Long-term secondary effects, such as osteoporosis or diabetes mellitus, are also justifying this cause for concern.

However, not all severe asthma patients will follow the dramatic natural history of the disease encompassing acute episodes of severe exacerbations and accelerated decline of lung function. A large proportion will respond to best efforts engaged comprising environmental and triggers/precipitating factors management, education and optimal pharmacological prescription.

How to measure adherence?

For clinicians, the therapeutic adherence might ideally be presented as a dichotomous variable and perfectly constant over time to avoid the requirement of any subsequent reassessments.

Therapeutic adherence is assessing all factors potentially associated with a poor control and/or the severity of the disease (Table 2).

There are numerous tools to assess adherence and a single one does not reflect the reality of the situation. There are attempts to define pre-specified threshold chosen to transform a continuous variable into a dichotomous one. In the literature, different thresholds have been used and validated, such as peak flow meter use in a pre-defined period of time (between 50% and 85% of the expected use) [4, 17, 24].

According to this specific tool, therapeutic adherence estimation ranged from 30 to 70% [6, 25–27], with extreme values ranging from 0 to 100% [28–30]. Using electronic devices connected to an inhaler and/or a peak flow meter may help to quantify the compliance (rather than adherence) to the prescription (frequency, date, time, etc.). These technologies can be inserted in

Table 2. Factors assessed by therapeutic adherence: any precipitating or triggering factor

Smoking and other at-risk behaviour
Absence of any preventive strategy
Inappropriate inhaler use
Auto-adjustment of doses below or above the prescription
Selective choice of non-observed medications
Erratic and/or intermittent therapeutic adherence
Unscheduled visits including hospitalization, emergency room attendance
Missing visits, health care nomadism

the devices. The patients can obtain the information or not with a potentially different conclusion. In a previous trial where patients with severe asthma were asked to fulfil an electronic peak flow during 15 days at the beginning of the study and during the last 15 days of the year of the trial, we observed a significant stability of this pattern. This finding was in discrepancy with previous reports, not targeting severe asthma, suggesting that this behaviour was largely variable over time. [22–31].

Other available tools to directly assess observance are summarized in Table 3. There is no easy and pragmatic way to assess adherence in the clinic at present.

Simple Morisky's questionnaire is weaker than direct interrogation and its use in clinical routine might not be recommended. In routine practice, physicians are likely to assess therapeutic adherence in all patients as a synthesis of subjective criteria more or less pre-specified, such as the assessment of patient ability to handle

inhaler devices, knowledge about disease and action plan in case of asthma exacerbations, knowledge about treatments including doses and potential side effects, regular attendance to physician's clinics, regular prescriptions renewal, symptoms and success of treatments, expressed beliefs and concerns about treatments, professional absenteeism, etc.

Most of the severe asthma patients overestimate their level of observance because of memory recall, defence or desire to please their health care provider. As a result, most of the physicians tend to overestimate their severe asthma patients adherence too [6].

The medical outcomes in severe asthma are clear. The patient related outcomes are less well defined. The perspectives of the patients with severe asthma are heterogeneous. Some of them are keen to participate actively in medical decisions when some are rather or totally passive [32,33]. In most cases, the objectives are rarely discussed in a real concerted partnership but can be

Table 3. Potential ways to assess therapeutic adherence

Tool	Strengths	Weaknesses
Peak flow and paper survey	Easy Low cost Ethical Lot of additional information	Uncontrolled Not directly assessing medication intake
Electronic peak flow	Controlled Objective Ethical?	Not directly assessing medication intake
Hidden counter inserted in the inhaler device	Objective Direct and accurate assessment	Unethical Assess compliance rather than adherence Not directly securing medication intake Expensive Unavailable in routine
Questionnaires (patient, related)	Easy Repeatable Ethical Low cost	Uncontrolled, memory recall Lack of accuracy Not directly securing medication intake
Written diary card	Easy Low cost	Missing or falsified data Not directly securing medication intake
Drugs measurements	Directly related to medication intake Objective Accurate	Expensive oral steroids only ¹⁷ No clear validated thresholds (usually Yes/No) Ethical?
Weighting inhalers	Repeatable Relative low cost	Not easy Not directly securing medication intake
Blisters counters	Easy Ethical Accurate Repeatable Relative low cost	Not directly securing medication intake
Pharmacists reports	Accurate Objective Low cost	Not directly securing medication intake Ethical
Doctor's appreciation	Repeatable Routinely performed Low cost	Not so easy Subjective Mostly Inaccurate Training

overtaken by different mechanisms, usually hidden and silent. In a local team's study, we observed that patients who voluntarily agree to fulfil a diary blowing in an electronic peak flow meter for the next 2 weeks when being asked by their physicians were not necessarily those who will really do it at the end [22]. This example illustrates the discrepancies between compliance to the doctor and overall therapeutic adherence in severe asthma [33]. In clinical trials, adherence is usually assessed by combining two criteria: the rate of e-diary cards fulfilling and the count of emptied canisters returned. Accepted percentages are highly variable over trials and no clear threshold has been demonstrated as more relevant than others. Encouraged adherence by indemnity is newly proposed but may increase the gap between trials and real-life studies.

Ideal tools to develop are currently in progress. They combine adherence measurement and help for improvement: electronic alarms, counters, inhalation efficacy and strength. Telemedicine offers new perspectives for adherence home-monitoring. Information highways led by the Internet can overtake adherence assessment and include educative and information support, airway function monitoring and personalized action plans [34–38]. This will be further discussed elsewhere in the article.

In conclusion, measuring adherence is not an easy task and is usually not neutral for the patient and her or his physician. It may involve many other specific aspects such as social affiliation, psychological traits including pain, societal costs and beliefs in health care system. All these items are associated with medical outcomes in severe asthma including exacerbation rate, hospitalization, health-associated costs and disability. It is then important that this approach does not impair the alliance between patient with severe asthma and the healthcare provider, which is the bottom line for the future management. We locally use at the moment, a combination of direct interview in a collaborative-mind, associated with a scoring of device handling and treatment knowledge. A specialized and dedicated nurse in therapeutic education is routinely conducting a supervised interview where adherence is formally assessed. Psychologist intervention is additionally required in all difficult asthma cases, partly for adherence assessment.

Why do patients are so poorly adherent?

Unintentional poor adherence

The easiest poor adherence to assess in routine practice is unintentional: devices handling usually require some basic but essential competences. Treatments are often complex and easily not adapted to any given patient. In many countries, costs and access to health care services are critical limiting factors. Other factors are usually

Table 4. Putative factors associated with non-adherence

Associated with severe asthma features	Early onset/late onset Chronicity – daily symptoms/exacerbations Severity Perception of symptoms
Associated with the treatment	Duration Regimens, number of daily doses Route of treatments, complexity Potential Side effects –(systemic steroids) Time to significant symptom relief Alternative medicines Polymedication due to other comorbidities (some linked to asthma tt)
Associated with the physician	Frequency and duration of outpatient visits Quality of human relationship Quality of the team (especially for therapeutic education) Interest for therapeutic adherence Professional satisfaction Social and institutional status Coherence with other health care professional (primary care)
Miscellaneous	Complexity of medical communication Knowledge of the disease and treatments Personal history and experiences Forgetting, troubles of the memory, Acceptation of the disease, Beliefs in health
Sociodemographics	Age (adolescence) Gender (female) Marital status Education level/social status Incomes
Psychopathological	Anxiety, depression, panic/chronic psychiatric disorders
Psychological traits	Extraversion, low social desirability Coping Locus of control, perceived control

related to memory, understanding and neurological and/or psychiatric disorders.

Psychosocial determinants of adherence in severe asthma

Many factors can affect therapeutic adherence. Table 4 summarizes most of them [6, 11, 39–49].

All these factors have been evoked and discussed. None of them per se, if considered individually, fully explained the adherence situation. The chronic psychiatric disorders are clearly the exception and most of the authors agree on their real impact on adherence. As an example, anxiety is a well-known risk factor for emergency room visits and unusual large consumption of short-acting bronchodilators. These factors are associated with a poor asthma control and therefore potentially misleading to severe asthma. By some nosological aspect, adherence issues should be addressed at the

highest currently available level before considering asthma as severe.

In front of poor adherence to treatments, most of us dream of a specific pattern related to any non-adherent phenotype in severe asthma. However, this dream never came true and we should investigate a composite scoring system to better approach the different situations in severe asthma.

"The locus of control" in psychology is referring to a personality trait. There have been several questionnaires aiming to discriminate on locus of control in subjects with various chronic diseases. Several studies have described an association between an external locus of control with a poor therapeutic adherence in asthma. In this situation, the patients do believe that nothing could really affect the natural history of the disease. This trait was significantly associated with severity, hospitalization and emergency room visits and poor quality of life [22, 50–52].

The rate of patients considered as adherent to treatment seems to be stable over years. This observation suggests that despite increasing efforts worldwide [53–55] for therapeutic education programs, some changes are still required.

How to improve adherence, and does it work?

Physician behaviour and partnership between health care providers and patients

Effective communication between patients and health care providers is imperative for promoting adherence. Frequent repetition and overall caregivers homogenization of the discourse are required. Cultural beliefs potentially including religious belonging can be an important part of the relationship with important consequences in terms of adherence to self-management recommendations, including medications.

Devices improvement

In a 24-week randomized controlled study of adult/adolescent patients with asthma, twice-daily reminders for missed doses improved controller adherence by 18% in favour of reminders, although there were no significant differences in clinical outcomes [56]. In adults with asthma, automated interactive voice response telephone calls which inquired about symptoms, delivered education and encouraged prescriptions refills resulted in a 32% improvement in controller adherence compared to the control group, but no differences in clinical outcomes were found [57].

Reminders maintain adherence in asthmatic children [58], as does feedback to patients on their adherence to medication. When patients are aware that their adher-

ence is being monitored it improves in the short-term (e.g. 4 months) but studies with long-term monitoring and feedback are needed [59, 60].

Education as a solution to poor therapeutic adherence in severe asthma

The large gap between clinical trials and real life in terms of asthma control is the highest support for promoting therapeutic educative program development especially in mild and moderate asthma [61–64]. Severe asthma patients are mostly permanently uncontrolled despite regular optimal therapy, otherwise they should rather be considered as difficult asthma [1, 7, 65]. Thus, conflicting data exists on the subject but most authors claimed that severe asthma patients were not necessarily the best candidates for education. Meta-analyses published since 2000 are summarized in Table 5. Few of these studies addressed specifically the question of severe asthma and asthma population was largely heterogeneous. Conclusions are spread and not always focusing on clear medical and/or patient-related outcomes.

Despite these contrasting results, education programs are scientifically proven to be worth efforts in asthma and should be encouraged even though modalities and pathways are likely to progress and to be specifically developed in each centre and potentially outside. All health care providers can be part of the process but pluridisciplinary labelled teams are still required [55, 66] with a common and concordant message. In a partnership climate, adherence monitoring, increased follow-up visits frequency, shared decision process are interesting health care providers behavioural decisions. Specificities, superiority and details of different types of programs more or less specifically designed for individuals are described elsewhere but rarely extensively detailed, which is another source of questioning.

Education comprises many different aspects, but not all interventions proposed to improve adherence are considered as belonging to education.

Internet and home-tailoring of asthma

Between visits lack of information is usually seen as the unmet need for assessing correctly the every day's life of asthma patients. Internet offers a broader approach than all other tools but only in patients adherent to the concept.

Different experiences of internet-based home-monitoring of asthma (encompassing adherence reinforcement, repeated assessments of control, PEF measurements, education and information supports, etc.) have now been reported [34–38]. Even though the absolute result in terms of asthma exacerbations and control are not evenly reported, it seems that at least large indicators

Table 5. Education in asthma meta-analysis published since 2000

Author	N	Objectives	Main result
Haby ⁵¹	8 studies Children	Education Impact in the ER and after ER visits	No modification of hospitalization and ER visits rate
Gibson ⁵²	11 studies Adults > 16 years	Impact of asthma knowledge on medical outcomes	No improvement
Gibson (2002)	36 studies Adults > 16 years Mild to moderate asthma	Impact of autogestion (written action plan, autocontrol and regular visits)	Decrease in unscheduled visits Decrease in symptoms levels and improved lung function
Guevara ⁵³	32 studies Children/teenagers	Peak flow based action plan	Decrease in ER visits. Improved lung function Better autocontrol perception Decrease in health care consumption and absenteeism
Toelle ⁵⁴	7 studies Children/adults	Impact of individual action plan	No improvement of health outcomes
Smith ⁵⁵	57 studies (21 adults, 35 children) Difficult asthma	Psycho educative interventions	Low reduction in hospitalization for adults and children. Symptom improvement in children
Bhagal ⁵⁶	4 studies Children/teenagers	Impact of individualized action plan (symptoms vs. peak-flow)	Symptoms based Action plan was more efficient than peak flow in ER visits decrease
Tapp ⁵⁷	12 studies Adults	Education Impact in the ER and after ER visits	Decrease in readmission rate. Improved inhalers handling Lower rate of missed visits. Cost effective
Bailey ⁵⁸	4 studies Children/adults	Cultural vs. standard educative approach	Improved knowledge Improvement of QOL
Coffman ⁵⁹	37 studies Children aged 2–17 years	Health care use in Emergency situations	Decreased rates of hospitalization and ER visits. No modification of unscheduled visits
Sarver ⁶⁰	Children	Comparing educative strategies directed towards patients vs. disease	Strategies directed towards patients improved asthma control

of health care status such as quality of life can be improved using such tools. Specifically, Van der Meer reported in a controlled study of 200 adults with asthma a sustained improvement in quality of life at 3 and 12 months (AQLQ); moreover, FEV1s values improved in the intervention group of 200 mL at 1 year (p 0.038). This technique tended to improve ACQ of one step (uncontrolled to partly controlled, partly controlled to totally controlled) and is cost-effective [35–37].

These results are more contrasted in adolescents and children. To the most, home monitoring of asthma using FeNO sounded like a promising future of asthma management especially in populations where questioning and reliability are supposed to be low or variable. Interestingly, the first large-scale study addressing the question of FeNO home-tailoring reported negative results [67]. The percentage of days free of symptoms improved in both intervention and control groups in a similar range, potentially due to the high frequency of phone calls (once a week) and visits (every 9 weeks) in this 30-week study. All of us can now understand how anybody will feel or not, the interest and benefits of this kind of help. Some specific populations are potentially to be selected and identified, as those intuitively studied first (children and adolescent) did not respond.

Assessing the true environment for a given patient

In a larger view, environmental advisers who can provide in-home visits and adequate environmental measurements in the setting of a partnership with the patient (evident or hidden allergens, smoking, pollutions, indoor organic volatile compounds, CO concentration, etc.) will potentially address the question of a broader approach of what is adherence when the physician claims for a perfect environment control. Time for education and developed advices in a more appropriate site (where the patient lives, outside the hospital which is clearly not the best site for therapeutic education) are the immediate consequences of this integrated approach mixing measurement and intervention. Of course, patient's agreement is a pre-requirement and potentially this approach will forget the best candidates as asthma schools did in the past.

Conclusion

Adherence is a vast domain of competency where a pluridisciplinary approach is required. Specific tools are urgent unmet needs while their place in patients' management is a source of debate especially in patients

considered as severe. Accordingly, highest steps of severity should be restricted to patients extensively investigated with a special focus on persistent adherence. Medical consequences are important enough to justify increasing efforts of understanding and prevention interventions are personalized using an educational diagnosis. Growing psychological assessment and understanding of adherence in the field of severe

asthma is a promising way of improvement in therapeutic decision-making.

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References

- Chanez P, Wenzel SE, Anderson GP *et al.* Severe asthma in adults: what are the important questions? *J Allergy Clin Immunol* 2007; 119: 1337–48.
- WHO/NHLBI workshop report. *Global Strategy for Asthma Management and Prevention*. National Institutes of Health, National Heart, Lung and Blood Institute Publication Number 92-2737 1991. Bethesda: NHLBI Health Information Center.
- British thoracic society winter meeting. London, 11–13 December 1995. Abstracts. *Thorax* 1995; 50(Suppl. 2):A1–88.
- WHO/NHLBI workshop report. *Global strategy for asthma management and prevention*. National Institutes of Health, National Heart, Lung and Blood Institute Publication Number 02-3659 2002.
- National asthma education and prevention program. Expert panel report: guidelines for the diagnosis and management of asthma update on selected topics–2002. *J Allergy Clin Immunol* 2002; 110:S141–219.
- Cochrane GM, Horne R, Chanez P. Compliance in asthma. *Respir Med* 1999; 93:763–9.
- Chung KF, Godard P, Adelroth E *et al.* Difficult/therapy-resistant asthma: The need for an integrated approach to define clinical phenotypes, evaluate risk factors, understand pathophysiology and find novel therapies. *Ers task force on difficult/therapy-resistant asthma*. European respiratory society. *Eur Respir J* 1999; 13:1198–208.
- Robinson DS, Campbell DA, Durham SR, Pfeffer J, Barnes PJ, Chung KF. Systematic assessment of difficult-to-treat asthma. *Eur Respir J* 2003; 22:478–83.
- Williams LK, Pladevall M, Xi H *et al.* Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma. *J Allergy Clin Immunol* 2004; 114:1288–93.
- Wareham NJ, Harrison BD, Jenkins PF, Nicholls J, Stableforth DE. A district confidential enquiry into deaths due to asthma. *Thorax* 1993; 48:1117–20.
- Haynes RB, Taylor DW, Sackett DL. *Compliance in health care*. Baltimore: John Hopkins University Press, 1979.
- Uldry C, Leuenberger P. De l'observance à l'adhésion thérapeutique dans l'asthme. *Med et Hyg* 1997; 55:2316–9.
- Tourette-Turgis C, Rébillon M, Pereira-Paulo L. De l'adhésion à l'observance thérapeutique: Réunir les conditions d'une primo-observance et développer une multiplicité d'interventions dans la durée. *Counselling, Santé et Développement* 2005; 1:1–8.
- Trostle JA. Medical compliance as an ideology. *Soc Sci Med* 1988; 27:1299–308.
- Leake H, Horne R. Optimising adherence to combination therapy. *J HIV Ther* 1998; 3:67–71.
- Horne R. Compliance, adherence, and concordance: implications for asthma treatment. *Chest* 2006; 130:65S–72S.
- Gamble J, Stevenson M, McClean E, Heaney LG. The prevalence of nonadherence in difficult asthma. *Am J Respir Crit Care Med* 2009; 180:817–22.
- Williams LK, Joseph CL, Peterson EL *et al.* Patients with asthma who do not fill their inhaled corticosteroids: a study of primary nonadherence. *J Allergy Clin Immunol* 2007; 120:1153–9.
- Watts RW, McLennan G, Bassham I, el-Saadi O. Do patients with asthma fill their prescriptions? A primary compliance study. *Aust Fam Physician* 1997; 26(Suppl. 1):S4–6.
- Kandane-Rathnayake RK, Matheson MC, Simpson JA *et al.* Adherence to asthma management guidelines by middle-aged adults with current asthma. *Thorax* 2009; 64:1025–31.
- Bender BG, Pedan A, Varasteh LT. Adherence and persistence with fluticasone propionate/salmeterol combination therapy. *J Allergy Clin Immunol* 2006; 118:899–904.
- Halimi L, Pry R, Pithon G, Godard P, Varrin M, Chanez P. Severe asthma and adherence to peak flow monitoring: longitudinal assessment of psychological aspects. *J Psychosom Res* 2010; 69:331–40.
- Salmeron S, Liard R, Elkharrat D, Muir J, Neukirch F, Ellrodt A. Asthma severity and adequacy of management in accident and emergency departments in France: a prospective study. *Lancet* 2001; 358:629–35.
- Reddel HK, Toelle BG, Marks GB, Ware SI, Jenkins CR, Woolcock AJ. Analysis of adherence to peak flow monitoring when recording of data is electronic. *BMJ* 2002; 324:146–7.
- Bender B, Milgrom H, Apter A. Adherence intervention research: what have we learned and what do we do next? *J Allergy Clin Immunol* 2003; 112:489–94.
- Hyland ME. Types of noncompliance. *Eur Respir Rev* 1998; 56:225–9.
- Rand CS. Non-adherence with asthma therapy: more than just forgetting. *J Pediatr* 2005; 146:157–9.
- Bailey WC, Richards JM Jr, Brooks CM, Soong SJ, Windsor RA, Manzella BA. A randomized trial to improve self-management practices of adults with asthma. *Arch Intern Med* 1990; 150:1664–8.
- Bosley CM, Couchner J, Cochrane GM. Non-compliance or rational decision. *Lancet* 1993; 342:1427.
- Brooks-Gunn J, Graber JA. Puberty as a biological and social event: implications for research on pharmacology. *J Adolesc Health* 1994; 15:663–71.
- Horne R. *Concordance and medicines management in the respiratory arena*. London: Hayward Medical Publications, 2003.
- Careless AL, Beaver K, Luker K, Campbell M, Woodcock A. Involvement in

- treatment decisions: what do adults with asthma want and what do they get? Results of a cross sectional survey. *Thorax* 2005; **60**:199–205.
- 33 Fischer GN, Tarquinio NG. Les aspects psychosociaux dans les méthodologies en psychologie de la santé. *Pratiques Psychologiques* 1999; **4**:31–43.
 - 34 Deschildre A, Beghin L, Salleron J et al. Home telemonitoring (forced expiratory volume in 1 s) in children with severe asthma does not reduce exacerbations. *Eur Respir J* 2012; **39**:290–6.
 - 35 van der Meer V, Bakker MJ, van den Hout WB et al. Internet-based self-management plus education compared with usual care in asthma: a randomized trial. *Ann Intern Med* 2009; **151**:110–20.
 - 36 van der Meer V, van den Hout WB, Bakker MJ et al. Cost-effectiveness of internet-based self-management compared with usual care in asthma. *PLoS ONE* 2011; **6**:e27108.
 - 37 van der Meer V, van Stel HF, Bakker MJ et al. Weekly self-monitoring and treatment adjustment benefit patients with partly controlled and uncontrolled asthma: an analysis of the smashing study. *Respir Res* 2010; **11**:74.
 - 38 van der Meer V, van Stel HF, Detmar SB, Otten W, Sterk PJ, Sont JK. Internet-based self-management offers an opportunity to achieve better asthma control in adolescents. *Chest* 2007; **132**:112–9.
 - 39 Barr RG, Somers SC, Speizer FE, Camargo CA Jr. Patient factors and medication guideline adherence among older women with asthma. *Arch Intern Med* 2002; **162**:1761–8.
 - 40 Kolbe J, Fergusson W, Vamos M, Garrett J. Case-control study of severe life threatening asthma (slta) in adults: psychological factors. *Thorax* 2002; **57**:317–22.
 - 41 Kolbe J, Fergusson W, Garrett J. Rapid onset asthma: a severe but uncommon manifestation. *Thorax* 1998; **53**:241–7.
 - 42 Reach G. *Pourquoi se soigne-t-on ? Une esquisse philosophique de l'observance*. Latresne: Le bord de l'eau, 2005.
 - 43 Meichelbaum D, Turk D. *Factors affecting adherence. Facilitating treatment adherence*. New York & London: Plenum Press; 1987: 41–68.
 - 44 Bender B, Milgrom H, Rand C. Nonadherence in asthmatic patients: is there a solution to the problem? *Ann Allergy Asthma Immunol* 1997; **79**:177–85; quiz 185–176.
 - 45 Ho J, Bender BG, Gavin LA, O'Connor SL, Wamboldt MZ, Wamboldt FS. Relations among asthma knowledge, treatment adherence, and outcome. *J Allergy Clin Immunol* 2003; **111**:498–502.
 - 46 Kamal KM, Miller LA. Psychosocial factors and asthma. *Am J Respir Crit Care Med* 2004; **169**:1253; author reply 1253–4.
 - 47 ten Brinke A, Ouwerkerk ME, Zwinderman AH, Spinhoven P, Bel EH. Psychopathology in patients with severe asthma is associated with increased health care utilization. *Am J Respir Crit Care Med* 2001; **163**:1093–6.
 - 48 Carr RE. Panic disorder and asthma: causes, effects and research implications. *J Psychosom Res* 1998; **44**: 43–52.
 - 49 Centanni S, Di Marco F, Castagna F, Boveri B, Casanova F, Piazzini A. Psychological issues in the treatment of asthmatic patients. *Respir Med* 2000; **94**:742–9.
 - 50 Halimi L, Vachier I, Godard P, Pithon G, Chanez P. Interference of psychological factors in difficult-to-control asthma. *Respir Med* 2007; **101**:154–61.
 - 51 Halimi L, Vachier I, Mezziane H, Godard P, Chanez P. *Psychological factors affect compliance in severe asthma*. San Francisco, Etats-Unis: American Thoracic Society Congress, 2001, May.
 - 52 Bertolotti G, Carone M, Viaggi S et al. Reliability of a questionnaire for evaluating the understanding of asthma. *Monaldi Arch Chest Dis* 2001; **56**: 11–6.
 - 53 Apter A, Boston R, Joffe M et al. *Can self-report of past adherence in asthma reflect subsequent adherence?* Atlanta, Etats-Unis: American Thoracic Society, 2002.
 - 54 Apter AJ, Reisine ST, Affleck G, Barrows E, ZuWallack RL. Adherence with twice-daily dosing of inhaled steroids. Socioeconomic and health-belief differences. *Am J Respir Crit Care Med* 1998; **157**:1810–7.
 - 55 Halimi L, Chanez P. Patient-centred asthma education in the emergency department: the case against. *Eur Respir J* 2008; **31**:922–3.
 - 56 Charles T, Quinn D, Weatherall M, Aldington S, Beasley R, Holt S. An audio-visual reminder function improves adherence with inhaled corticosteroid therapy in asthma. *J Allergy Clin Immunol* 2007; **119**:811–6.
 - 57 Bender BG, Apter A, Bogen DK et al. Test of an interactive voice response intervention to improve adherence to controller medications in adults with asthma. *J Am Board Fam Med* 2010; **23**:159–65.
 - 58 Weinstein AG. Clinical management strategies to maintain drug compliance in asthmatic children. *Ann Allergy Asthma Immunol* 1995; **74**:304–10.
 - 59 Burgess SW, Sly PD, Devadason SG. Providing feedback on adherence increases use of preventive medication by asthmatic children. *J Asthma* 2010; **47**:198–201.
 - 60 Nides MA, Tashkin DP, Simmons MS, Wise RA, Li VC, Rand CS. Improving inhaler adherence in a clinical trial through the use of the nebulizer chronolog. *Chest* 1993; **104**:501–7.
 - 61 Bateman ED, Boushey HA, Bousquet J et al. Can guideline-defined asthma control be achieved? The gaining optimal asthma control study. *Am J Respir Crit Care Med* 2004; **170**:836–44.
 - 62 Bateman ED, Bousquet J, Busse WW et al. Stability of asthma control with regular treatment: an analysis of the gaining optimal asthma control (goal) study.. *Allergy* 2008; **63**:932–8.
 - 63 Rabe KF, Vermeire PA, Soriano JB, Maier WC. Clinical management of asthma in 1999: the asthma insights and reality in europe (aire) study. *Eur Respir J* 2000; **16**:802–7.
 - 64 Godard P, Huas D, Sohler B, Pribil C, Boucot I. Asthma control in general practice: a cross-sectional survey of 16,580 patients. *Presse Med* 2005; **34**:1351–7.
 - 65 Chanez P, Vachier I, Mezziane H, Michel FB, Godard P. Asthme difficile. *Rev Mal Respir* 2000; **17**:827–37.
 - 66 Halimi L, Bourdin A, Mahjoub BA, Godard P. Treatment education for patients with asthma. *Presse Med* 2009; **38**:1788–96.
 - 67 de Jongste JC, Carraro S, Hop WC, Baraldi E. Daily telemonitoring of exhaled nitric oxide and symptoms in the treatment of childhood asthma. *Am J Respir Crit Care Med* 2009; **179**:93–7.