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REVIEW ARTICLE

# Measuring and reporting treatment adherence: What can we learn by comparing two respiratory conditions?

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Medication non-adherence, defined as any deviation from the regimen recommended by their healthcare provider, can increase morbidity, mortality and side effects, while reducing effectiveness. Through studying two respiratory conditions, asthma and tuberculosis (TB), we thoroughly review the current understanding of the measurement and reporting of medication adherence. In this paper, we identify major methodological issues in the standard ways that adherence has been conceptualised, defined and studied in asthma and TB. Between and within the two diseases there are substantial variations in adherence reporting, linked to differences in dosing intervals and treatment duration. Critically, the communicable nature of TB has resulted in dose-by-dose monitoring becoming a recommended treatment standard. Through the lens of these similarities and contrasts, we highlight contemporary shortcomings in the generalised conceptualisation of medication adherence. Furthermore, we outline elements in which knowledge could be directly transferred from one condition to the other, such as the application of large-scale cost-effective monitoring methods in TB to resource-poor settings in asthma. To develop a more robust evidence-based approach, we recommend the use of standard taxonomies detailed in the ABC taxonomy when measuring and discussing adherence. Regimen and intervention development and use should be based on sufficient evidence of the commonality and type of adherence behaviours displayed by patients with the relevant condition. A systematic approach to the measurement and reporting of adherence could improve the value and generalisability of research across all health conditions.

**KEYWORDS**
adherence, asthma, compliance, persistence, tuberculosis

## 1 | INTRODUCTION

Medication adherence is defined as the process by which a patient takes their medication, compared to the regimen recommended with their healthcare provider. The World Health Organization (WHO) describes the dimensions affecting adherence in five interacting categories: the health system, the condition, the treatment regimen, the socioeconomic environment and the patient themselves.[1] Many frameworks have detailed the resulting barriers, including forgetting, incapacity (such as being unable to self-administer or financial constraints), incorrectly interpreting instructions, deviating from the regimen due to beliefs about the necessity or safety of a treatment, health system factors and a lack of social support.[1–5] Non-adherence is associated with poor clinical outcomes,[6–11] and contributes towards

the emergence of drug-resistant infections.[12–14] It may lead to unnecessary dose escalation and/or additional treatment to control symptoms, itself resulting in the onset of avoidable side-effects.[15–19] Non-adherence may also result in adverse events related to discontinuation[20–22] or re-initiation.[23,24] Furthermore, increased expenditure is incurred through preventable unscheduled primary and secondary care engagement (including primary care consultations and emergency department presentation), and wasted medication.[18,25–31] The burden of non-adherence in chronic diseases is high (around 50%),[1] and the prevalence is highest in those with polypharmacy and comorbidities.[32,33]

Measuring adherence is vital for estimating associated costs (both financial and quality of life),[28,34,35] identifying people who are at most risk during their treatment regimen, undertaking targeted intervention development,[36–38] and accurately assessing the impact of novel interventions.[39,40] A substantial challenge in adherence measurement is that the field is not standardised and different measures have been introduced, the comparability of which is typically unclear.[41–43] To address this lack of uniformity in definitions, and the inherent complexity of adherence data, in 2012 Vrijens et al. proposed a new taxonomy (called ABC) for describing adherence in three phases: initiation, implementation and persistence.[51] As shown in Figure 1, treatment is *initiated* at the first dose taken of a prescribed medication and *discontinued* at the last dose taken. *Implementation* describes the agreement between the patient's dosing regimen and the prescribed regimen, in the period between initiation and discontinuation. *Persistence*, the continuity of treatment, describes the duration and incidence of unscheduled intermissions (an extended duration of consecutively missed doses, with the minimum duration varying by treatment and condition[44–48]).

There are multiple pharmacokinetic mechanisms which influence a medication's *forgiveness* (the number of doses that can be skipped without decline in therapeutic effect).[49] These include storage elsewhere in the body to the target organ in a releasable manner, that their effect is delayed compared to the concentration in the blood, that the dose strength is sufficiently high that a small decrease would result in only a minor change in effect, or that medication has a long elimination half-life (the time by which approximately half of the medication has left the body).

In this study, we review the methods employed for measuring and reporting adherence in two respiratory diseases, tuberculosis (TB) and asthma. TB and asthma both have high disease burden[50,51] and apparently prevalent non-adherence,[7,52–54] but differ substantially in their drug delivery method and treatment time scale, and their global hotspots. By comparing and contrasting procedures in these two very different conditions, we highlight the similarities and transferable lessons which are masked by differences in adherence conceptualisation when confined to the investigation of either disease. By applying a standard taxonomy, greater awareness into these parallels is facilitated, and research can be conducted with greater efficiency and rigour. The key aims of the study were to gain insights into: (a) the generalised conceptualisation of adherence assessment; and (b) how adherence comparison between and within conditions should be approached.

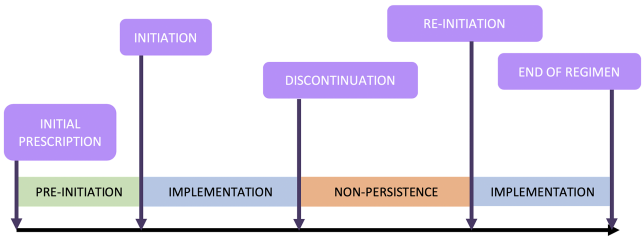


**FIGURE 1** Diagram highlighting the three phases of medication adherence in the ABC taxonomy, relative to patient-level prescription events

## 2 | BACKGROUND: PATHOPHYSIOLOGY, EPIDEMIOLOGY AND TREATMENT

### 2.1 | Asthma

Asthma is a chronic disease that is characterised by hyperresponsiveness to stimuli, leading to inflammation which restricts airflow and thus oxygen supply. When poorly controlled, even mild asthma can lead to an increased risk of an attack (acute exacerbation);[55] a sudden drastic worsening of symptoms, which without treatment result in loss of consciousness and, eventually, death.[56] Asthma has been estimated to affect between 235 and 339 million people worldwide.[50,57] The UK is amongst the countries with the highest prevalence[58] and asthma was listed as the primary cause of 3.8 deaths per day in 2015.[59]

Most medications for controlling asthma are taken twice each day by inhalation. Asthma therapy follows a fairly linear path, *stepping up* dosage of controller medications when necessary or incorporating add-on therapies.[60] Asthma treatment is required for most patients to be taken continuously after diagnosis, for the patient's entire life. Recent evidence indicates that asthma is forgiving to poor therapy adherence, and that it is possible to achieve similar levels of exacerbation reduction in mild asthma with less frequent doses of inhaled steroids than are typically prescribed.[61] Given that drug effects may persist for several days after administration,[62] asthma medications with longer durations of efficacy may be particularly forgiving.[63–65] Importantly, the same medication may also be eliminated at different rates in different people (known as "pharmacokinetic variability"), based on factors such as age, sex, smoking status and body size.[66–68]

### 2.2 | Tuberculosis

TB primarily manifests as a pulmonary condition, although disease also occurs at other bodily sites.[69] Symptoms are generic and include fever, tiredness and weight loss. Individuals with pulmonary disease may have a persistent and productive cough (including haemoptysis). TB remains one of the top 10 causes of death globally;[70] in 2018, 1.5 million people died of the disease.[51] In the absence of treatment,

approximately 30% of patients die within 18 months of diagnosis, 30% spontaneously self-cure, and 40% remain sputum smear positive.[71] The incidence of TB is unevenly distributed, with eight countries bearing two-thirds of the burden (Bangladesh, China, India, Indonesia, Nigeria, Pakistan, the Philippines, South Africa) and India alone accounting for 27% (2018). Most of the highest ranking countries by incidence rates are in southern and central Africa.[72]

Treatment for TB is time-limited and depends upon the presence and extent of drug resistance in the underlying infecting strain(s). Drug-sensitive disease is treated for six months,[73] while multi-drug resistant (MDR) disease treatment is extended to between 9 and 20 months.[74] The WHO recommends that treatment for drug-sensitive TB is administered once daily,[75] although in some settings less-forgiving thrice weekly regimens are utilised to allow for the direct observation of treatment. Dosing of regimens for drug-resistant disease can be complex (multiple doses per day or non-daily dosing) and depend upon the individual resistance pattern.[74]

## 3 | APPLICATIONS OF THE ABC TAXONOMY

### 3.1 | Asthma

The first phase of the ABC taxonomy, initiation, is simply defined in asthma as the first administered dose (including inhaler actuation, nebulising solution inhalation, monoclonal antibody injection, and more). Treatment initiation is a great opportunity for healthcare providers to promote good adherence, and to train patients how inhalers should be used.

Implementation, the second phase, is more multi-faceted. There are a number of steps to the correct usage of an inhaler,[38] such as allowing the chamber to refill between consecutive doses. Incorrect technique contributes towards a lower than desired volume of medication ingested and can be considered a component of adherence. Furthermore, inhaled corticosteroids are usually required to be taken once or twice a day and for twice-daily regimens, the two doses should be roughly 12 hours apart in the morning and evening.

Dose interval length for other maintenance treatments, including long-acting beta-agonists (LABAs) and add-on therapies such as allergy treatments and biologicals, vary greatly. For example, some monoclonal antibody treatments such as omalizumab are only administered at four-weekly intervals.[76–78] Relievers are taken only *as needed* to relieve heightened symptoms, or as a short-term preventative measure (such as before exercise[79,80]). Although, as previously discussed, inhaled asthma medications are usually taken every day, it is becoming more common to recommend patients self-manage their treatment to some extent, and use their inhaler only as needed.[61,81,82] For those patients where inhaler use is not following a systematic prescribed pattern, it is not meaningful to measure their adherence to their regimen. Medication usage patterns, however, can still be measured and reported in the same way, as they can provide data to inform studies predicting the risks of clinical outcomes.

Due to the unbounded duration of treatment for asthma, there are many opportunities for discontinuation and re-initiation. Treatment may be discontinued by a healthcare provider following a revised diagnosis, a change in regimen, or resolution of the condition (such as in childhood asthma[83] and occupational asthma[84]). Unsanctioned discontinuation is also common.[85] Periods of non-persistence can be analysed to understand what triggers their occurrence, as well as what triggers subsequent re-initiation.[42]

### 3.2 | Tuberculosis

Delayed initiation of treatment in TB is problematic on two fronts. First, bacteria have an extended time to replicate, thus increasing a patient's bacterial load and potentially the severity of disease. Secondly, this allows a greater window of time in which transmission of infection can occur. Given the global prevalence of drug-resistant TB,[51] it is important to test for drug resistance before treatment initiation, in order to ensure an appropriate number of effective drugs is present in the regimen. Without this, a regimen may not only fail to cure the patient, but the bacteria may additionally gain further drug resistance.

Unlike in asthma, the standard regimen for drug-sensitive TB consists of oral pills and thus technique in taking medications is of lesser concern. Fixed dose combination (FDCs) pills (of up to all four drugs in the initiation phase and both drugs in the continuation phase) are recommended by the WHO to reduce pill burden.[74] Patients using FDCs are therefore non-adherent to all drugs when they miss a dose of treatment. Due to drug absorption characteristics, patients are generally advised to take their medication on an empty stomach. The number and type of drugs for drug-resistant disease means that dosing becomes more complex; administration technique can then become more important, e.g. for injectable medications. In complete contrast to asthma, antibiotics are never taken 'as needed'.

Surveillance reporting of treatment outcome data to the WHO has resulted in a set of standardised definitions that capture part of medication discontinuation, in the form of loss to follow-up (LFU).[86] LFU (previously called default) is defined as a break in treatment of 2 months or more, often measured by patients failing to appear for medical appointments, or to collect their drugs. This can include non-initiation. The risk of developing drug resistance means that (unsanctioned) drug holidays are not permitted in TB, although short intermissions (e.g. due to side effects) can be provider-sanctioned. Although it is possible for patients to have discontinued treatment and still be attending appointments (and vice versa, to have disappeared from their original clinical care provider, but still be taking medication obtained from another source or a reserve of drugs), LFU remains an important source of non-adherence to TB treatment. Work in both drug-sensitive and MDR TB has documented the prevalence and temporality of LFU.[87,88]

The time-bounded nature of TB treatment means that, unlike for asthma, discontinuation without subsequent re-initiation is possible, i.e. a patient may discontinue treatment close enough to the end of

their regimen, and display sufficient recovery, for treatment not to need to be re-started.

## 4 | ADHERENCE MEASUREMENT

### 4.1 | Asthma

Asthma medication adherence can be measured using pharmacy refill records, either aggregated to a single summary statistic over an extended duration (such as a clinical trial, or a single year) such as the *medication possession ratio*, or as a time-series such as the *continuous measure of medication gaps*.[41–43] Prescription recording systems cannot record whether a medication is actually taken. As such, they can be considered a good estimator of treatment initiation and persistence (or discontinuation), but not an accurate reflection of the implementation of the regimen.[82] They can, however, flag cases of over-use of reliever medication, which may be indicative of poor asthma control and/or poor controller adherence.

Adherence can also be measured by patient self-report, such as asthma diaries, standardised questionnaires and psychometric scales.[82] While many scales are intended for use across multiple medical conditions, there are asthma-specific scales such as the *Medication Intake Survey – Asthma* (MIS-A),[89] Medication Adherence Report Scale for Asthma (MARS-A),[90,91] and the Brooks et al. scales for inhaled and oral asthma medications,[92] respectively. Depending on their structure, however, they may be able to capture all three phases of the ABC taxonomy. For example, the MIS-A looks at the proportion of time with both correct dosing (implementation) and the proportion of weeks with at least some medication use (persistence);[89] however, it does not explicitly cover non-initiation. Estimates of implementation can also be made using inhaler technique assessment checklists,[38] as poor inhaler technique is known to result in suboptimal drug delivery.[93]

Digital adherence technologies (DATs) are digital systems to aid in the measurement and management of medication adherence. Electronic monitoring devices (EMDs) are DATs which directly and automatically measure the time and date of a dose being taken.[94] Smart inhalers, for example, are devices (or additions to existing devices) which collect data on inhaler usage and can transmit data (e.g. using Bluetooth) to a linked application on the user's mobile device.[95,96] EMDs are highly accurate, as they directly measure the dispensation of medication, do not aggregate across medication refill periods (i.e. dose-by-dose data are available), and are far less subject to sources of measurement error.[97,98] When inhaled medication monitoring is conducted overtly, however, there is the potential for 'dose dumping'; deliberately actuating multiple consecutive times in order to conceal poor adherence.[99] Many EMDs have functionality which allows these episodes to be detected; such as flagging occurrences of over a certain number of actuations in a short time duration,[100] particularly when they occur soon before clinic or trial assessments.[101] Furthermore, some inhalers are able to provide feedback on inhaler technique, using sensors or audio segmentation to identify individual actions that comprise the correct usage instructions (such as shaking the cannister, and holding breath after actuation).[82,102]

Adherence to asthma medication regimens can also be measured directly for some medications using biochemical measurements reflecting the amount of medication ingested (including hair, urine and blood samples),[103–107] and device monitoring such as canister weighing.[108] A lack of detectable medication in biological samples would imply either non-initiation or discontinuation, depending on the time-scale, and the expected observed medication quantities could be used to estimate roughly implementation.

Directly observed therapy (DOT), which entails a trained third party (including doctors, nurses and community health workers) observing medication consumption, has also been trialled in asthma treatment; usually in children. DOT enables treatment persistence to be measured, as well as implementation components such as timing, technique and dosage. Schools have been identified as viable settings for supervised asthma therapy administration, as multiple children could be monitored consecutively or concurrently.[109] In adults, DOT is fairly impractical for daily medications, such as most inhaled asthma medications. However, DOT has been suggested as an intervention to improve adherence in new biological asthma therapies, which may be delivered at monthly (or greater) intervals.[110]

### 4.2 | Tuberculosis

Where such data are available (i.e. the formal healthcare sector), adherence to anti-TB regimens can also be measured indirectly through pharmacy refill records (typically on a monthly basis) or patient-reported outcome measures (such as the TB Medication Adherence Scale;[111] TBMAS), and directly, e.g. through urine or blood testing.[112] The use of the WHO recommended strategy of DOT to ensure adherence to treatment means, however, that this is the most widely available source of information.[113] Direct observation means that information on the consumption of each dose of treatment is recorded (particularly during the intensive phase), providing an exceptionally granular data source of all domains of adherence.

Recent technological advances have resulted in a variety of DATs to measure adherence to anti-TB treatment, as reviewed by Subbaraman et al.[114] These fall into five major categories, all of which document treatment-taking individually for each dose: (1) digital pillboxes, a type of EMD, which monitor and record each time that they are opened, and can also use sound or light effects as reminders, (2) 99Dots, where dispensing a dose of TB medication from the blister pack reveals an unpredictable toll-free number, to which the patient places a call, (3) short message service (SMS) systems, where patients confirm that they have taken their medication by sending a message to their healthcare provider, (4) video DOT, which allows individuals to take their treatment without the proximal presence of an observer and can be synchronous or asynchronous, and (5) ingestible sensors, which are placed within pills and send a signal to a monitor worn by the patient, which is, in turn, relayed by their mobile phone (such as Proteus[115]).

## 5 | ADHERENCE REPORTING

### 5.1 | Asthma

Many epidemiological and intervention studies still describe medication adherence using only a single measure (typically implementation related), often aggregated over an extended duration, such as percentage of days on which the prescribed doses of inhaled corticosteroids were taken.[7,108,116,117] Indeed, the recent Cochrane review by Normansell et al. of asthma adherence interventions[118] reported: "Almost all included studies reported some measure of adherence, usually as a percentage, with 100% showing complete adherence, but the way in which this was captured and calculated varied between studies."

In a 2015 review of 23 studies looking at the association between adherence and risk of asthma attacks, Engelkes et al. found that only 3 (13%) used more than one measure.[7] As asserted by Boissel et al.[49]: "One challenge in studying varying compliance […] is that no single feature can express it." Of the studies in the Engelkes et al. review, five used the medication possession ratio (MPR), defined as the total number of day's supply for all refills in a particular time period, divided by the duration of the period, for controller medications (inhaled corticosteroids [ICS], LABA or ICS + LABA combination inhalers), and found that estimates varied widely, ranging between 15 and 54% in adults.[7] Similarly, the review of asthma EMD studies in children by Morton et al. found the mean ranged between 34 and 73%.[119] Asthma subtypes may also contribute towards this variation in results, even within adherence measurement methods; however, poor adherence has been reported even in those with *severe* asthma.[120,121] Ismaila et al. assessed two dimensions of adherence within their pharmacy claims data analysis: implementation according to the medication possession ratio (dichotomised at 80%), and persistence defined as continuously renewing prescriptions without a gap of more than 30 days.[122] They found that 42.7% of the patients (all on ICS + LABA therapy, $n$ = 19,126) were compliant, and only 29.3% were persistent. Persistence was strongly associated with all outcomes in adjusted analyses, but severe outcomes such as admission to intensive care and intubation were not associated with implementation.

Many studies have aggregated their data even further; using binary thresholds of adherence to benchmark individuals and to dichotomise a sample into good and poor adherers, commonly 80%.[9,52,109,123] Both Gamble et al.[120] and Makhinova et al.[124] used a cut-off of 50%, with the latter noting that using an 80% threshold instead would have reduced the number of adherent individuals from 14.9% (of their population of over 30,000) to only 4.1%.

While researchers are often still able to show clinical effect with single, aggregated measures, identifying and understanding the nuances of medication-taking is important, potentially aiding the effective intervention design to target the most harmful non-adherence patterns. Furthermore, due to the long-term nature of treatment for chronic conditions such as asthma, and particularly the variability in airway responsiveness over a short period, measuring adherence aggregated over an extended duration of treatment is insufficient. As noted by Alleman et al.[125]: "Some temporal sequences of deviations from the prescribed regimen may be more detrimental to treatment effectiveness and safety compared to others."

It is vital to consider the time-varying, multi-dimensional, elements of adherence. This may be simply measured as the variation in measures between intervals (such as prescription refills, or years of age), or as a moving average measure.[125,126]

Regarding inhaler technique, adherence is typically reported as binary indicators of whether specific errors (such as patients forgetting to tilt their head) were made,[127–129] reported either individually or as a proportion or sum. A recent study by Price et al. examined the effect that each error in isolation had on asthma control (stratified by inhaler device).[127] They found that failing to breath out before inhalation was a common error in metered dose inhalers (25.4% prevalence) and resulted in 1.9 times higher odds of uncontrolled asthma than when that error was averted. The most compromising error was failing to remove the cap of the inhaler, but fortunately that was a rare occurrence (prevalence 0.4%). Finally, some studies simply rate technique categorically, such as "good", "adequate" and "inadequate", according to clinician review.[128,129]

### 5.2 | Tuberculosis

Classical approaches to assessing adherence to anti-TB treatment have focused on determining the proportion of patients taking greater than or equal to 80% or 90% of their daily doses.[130–133] Exceptions to the use of simple percentage thresholds are included in the work of Bastard et al. and Podewils et al.,[134,135] both of whom looked at the implications of different intermission lengths on treatment outcomes. Although the weight of evidence is in favour of patients below these thresholds having a greater likelihood of a negative treatment outcome (e.g., see the studies of Kayigamba et al. and Imperial et al.),[136,137] the deployment of DATs on a large scale provides substantial opportunities to provide greater insights into the relationship between adherence patterns and treatment outcomes.[138]

Estimates of the prevalence of adherence to anti-TB medication vary substantially globally. For example, in a study in south-eastern Malawi between 2007 and 2008, 35.1% of smear positive pulmonary TB patients aged 18 years or over and treated for 6 months were assessed to not have been fully adherent, based on treatment card data (documentation of directly observed dosing; during the continuation phase of treatment, cards were held by the patients).[52] By comparison, in Kosovo in 2012, among all TB patients, 14.5% were estimated to have not taken their TB drugs for more than three days (self-reported data).[54]

Similarly to asthma, the time-varying nature of dose-by-dose adherence has not been sufficiently explored. In a recent study, Stagg et al. mapped adherence patterns across the entire treatment duration for a population of pulmonary disease patients in China.[53] Within the cohort, 95.9% of patients were found to have missed at least one dose of treatment in a thrice weekly regimen; 14.4% had discontinued by four months. Critical for intervention design, early-stage

suboptimal implementation was associated with increased discontinuation rates.

## 6 | CROSS-COMPARISON OF MEASUREMENT AND REPORTING METHODS BETWEEN TB AND ASTHMA

There are a number of similarities in adherence measurement and reporting in TB and asthma. Firstly, methodological assessment is similar in terms of measurement, such as pharmacy refill measurements, EMDs and patient self-report (see Table 1). Secondly, it is common in both conditions for adherence to be aggregated over an extended duration, and even categorised or dichotomised in reports. There are, however, several key differences to consider when comparing adherence in asthma and TB. Firstly, asthma medications are prominently delivered using an inhaler which can be mis-used, resulting in poorer adherence than a patient may intend, or even realise.

Secondly, dose-by-dose monitoring methods, such as DOT, are more common in TB than in asthma due to the shorter treatment timescale in TB (better feasibility). In asthma, the financial burden of DOT monitoring methods would be substantial, and with the incidence of attacks low, the return on investment would be very low to implement at a population level. There is also a higher cost incentive for such a high resource measurement method in TB, as poor adherence leads to an increased risk of subsequent transmission, including strains with secondary, adherence-induced, drug resistance.

Finally, adherence is more complicated to conceptualise and define when treatment includes multiple medications (known as "polypharmacy"). Polypharmacy is more common in asthma than TB, and often includes medications of different formulations (such as inhalers, nebules and tablets) which are taken at different times of the day. While adherence in asthma is commonly considered to be solely related to controller medication (typically either ICS or ICS + LABA medications, or sometimes with the addition of stand-alone LABA medications), the variation between adherence to these medications and add-on therapies such as LAMAs is less examined. In asthma, it has been found that higher numbers of prescribed medications can result in lower overall adherence,[139] particularly in elderly and cognitively impaired patients.[140] In TB, an area of polypharmacy is the intersection with HIV and therefore antiretrovirals; approximately 8.6% of TB patients are are living with this coinfection.[51]

## 7 | DISCUSSION

In this paper, we have compared the measurement and reporting of medication adherence in depth across two exemplar respiratory diseases, asthma and TB. Commonalities in the conceptualisation of adherence between the two conditions, which are commonly overlooked due to their more elementary differences, become harder to compare due to differences in measuring and reporting procedures. In examining these commonalities more closely, we can demonstrate the benefits of standardised terminologies and practices.

We assert that, despite the established differences, it is possible to cross-reference protocols for assessments, treatments, and inform best practices between the asthma and TB communities. For example, DOT could easily be applied to the rapidly expanding field of asthma biologics adherence. Such treatments require less frequent administration, and are starting to transition from the hospital setting to the home environment thanks to new auto-injectors. Guidelines to overcoming barriers to DOT could be translated from TB to asthma to develop systems-level approaches to improve adherence in those with the highest likelihood of non-adherence to such treatments. Similarly, if continued efforts to develop inhalation TB therapies[141] are fruitful, delivery vehicles could be designed using the knowledge of common asthma inhaler technique errors.

We can also transfer learnings from other, non-respiratory, diseases in the same way. One disease with particular success in evidence-based adherence research is HIV, where there has been substantial discussion on the adherence levels required for sufficient viral suppression and how this varies from regimen to regimen.[142] Similar levels of evidence should be the norm for other conditions, to aid both clinical approaches to adherence (when to intervene) and to determine how much should be invested in monitoring of drug-taking worldwide.

We also see common examples of poor research practice reoccurring across different conditions, including excessive

**TABLE 1** Direct and indirect adherence measurement in asthma and tuberculosis

| | Asthma | Tuberculosis (TB) |
|---|---|---|
| Pharmacy refills | Aggregate measures of when medications are collected from the pharmacy | |
| DOT | Uncommon | World Health Organization recommends DOT; digital version video DOT |
| Biochemical measurements | Presence of medication in urine, blood, or hair | |
| Electronic monitoring devices | Predominantly smart inhalers (inhaled asthma medications) | Predominantly electronic pillboxes and ingestible sensors |
| Patient self-report | Asthma medication diaries, psychometric scales and questionnaires such as MIS-A and MARS-A | Questionnaires such as the TBMAS, and (real-time) SMS-based reporting systems |

DOT, directly observed therapy; SMS, short messaging system; TB, tuberculosis; MIS-A, Medication Intake Survey – Asthma; MARS-A, Medication Adherence Report Scale for Asthma; TBMAS, TB Medication Adherence Scale

aggregation and categorisation, which mask substantial variations in medication-taking behaviour,[125] such as temporal changes in adherence across seasons, during school holidays, at weekends, after events such as treatment reviews, or with worsening symptoms. Many studies have used a binary threshold of 80% adherence to benchmark individuals and to dichotomise a sample into good and poor adherers.[52,109,123] Indeed, Andrade et al. reported that in 136 studies of adherence using routine medical data, 38 used some dichotomisation, and 75% of these used the 80% threshold.[42] These studies covered therapeutic areas including migraines, cancer, diabetes, and incontinence.

The rationale for this threshold was often lacking an evidence base, such as that by Murphy et al.[9]: "We feel that 80% is a sensible cutoff because it allows for realistic expectations of patient behaviour while ensuring clinical efficacy of the drug."

Some people hypothesise the existence of an adherence threshold, above which the therapeutic effect of a drug is maintained; however, Stauffer et al. demonstrate that the adherence threshold varied greatly even between drugs of the same class (40–80%).[65] Furthermore, Morrison et al. have shown that the conceptual adherence threshold only holds assuming that doses are not missed consecutively for a longer duration than some drug-specific threshold,[143] known as the "forgiveness" of the drug.[49]

Critically, the ABC taxonomy, which has not been applied extensively in either TB or asthma, allows stakeholders across disciplines to use a unified and standardised language to aid in the reporting of medication adherence. There has been no impact study reporting its use; however, its uptake has been particularly prompted by its promotion within the International Society for Medication Adherence (ESPACOMP; formerly known as the European Society for Patient Adherence, Compliance, and Persistence) Medication Adherence Reporting Guidelines (EMERGE)[144] in 2018. For both conditions, the use of a standardised framework coupled with the granular data that is becoming increasingly available through DATs/EMDs could prove a game-changer in how we assess adherence globally.

Due to the breadth of the scope of the review's investigation, it was not feasible to conduct a systematic review of every paper relating to, or discussing, adherence in TB and asthma. Where possible, we have cited systematic reviews in specific sub-areas of the paper, such as the Engelkes et al. review of studies measuring the association between adherence and risk of asthma attacks,[7] and the Subbaraman et al. review of DATs used to measure adherence to anti-TB treatment.[114] We have also carefully reviewed recent papers which have cited the ABC taxonomy paper, in order to identify any crucial developments in the field. Despite this, there may be additional trends in adherence research that we have not described.

There is still considerable work to be done in improving adherence measurement and reporting. The lessons we can learn from other conditions can be synthesised to define the knowledge gaps and aspirations of the adherence field, for all stakeholders. For clinicians, a detailed understanding of individual patient adherence and the associated risks will promote better advised treatment plans. For patients, research into acceptability and effect of adherence measurement is crucial. In clinical trials, knowledge about how adherence should be measured to best understand the relationship to clinical outcomes will allow better adjustment for patient adherence and better projections about expected prevalence of adverse events.[145] Finally, researchers must learn to most efficiently use systematic and consistent data sources such as medical records and DATs.

By contrasting and comparing the measurement and reporting of medication adherence in two long-term respiratory diseases, one infectious (asthma) and the other non-infectious (TB), we provide further evidence for the benefits of the standardised terminologies and practices detailed in the ABC taxonomy and EMERGE guidelines when addressing this global issue for medication effectiveness. Health researchers can improve the value and generalisability of research across all health conditions by applying the proposed systematic approach to the measurement and reporting of adherence. Consistent use of the taxonomy also promotes the conceptualisation of non-adherence as a dynamic process, encouraging health professionals to explore the issue with patients during treatment, improving the consistency of dialogue between the health care providers a patient encounters, and providing guidance in the deployment of interventions: both clinical trials and interventions for adherence itself.

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## COMPETING INTERESTS

There are no competing interests to declare.

## CONTRIBUTORS

H.T. and H.R.S. conceived of the presented idea, wrote the manuscript with support from M.F., A.S., A.T., R.H., B.V. and S.d.G. All authors provided critical feedback and approved the final manuscript.

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## REFERENCES

1. World Health Organization. *Adherence to Long-Term Therapies: Evidence for Action*. 2003, Geneva: World Health Organization. http://apps.who.int/medicinedocs/pdf/s4883e/s4883e.pdf. Accessed March 9, 2018.
2. DiMatteo MR, Haskard-Zolnierek KB, Martin LR. Improving patient adherence: a three-factor model to guide practice. *Health Psychol Rev*. 2012;6(1):74-91. https://doi.org/10.1080/17437199.2010.537592

3. Horne R, Hankins M, Jenkins R. The Satisfaction with Information about Medicines Scale (SIMS): a new measurement tool for audit and research. *Qual Heal Care*. 2001;10:135-140. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1743429/pdf/v010p00135.pdf
4. King C, Nightingale R, Phiri T, et al. Non-adherence to oral antibiotics for community paediatric pneumonia treatment in Malawi—a qualitative investigation. *PLoS One* 2018;13(10):e0206404. https://doi.org/10.1371/journal.pone.0206404
5. Horne R, Chapman SCE, Parham R, Freemantle N, Forbes A, Cooper V. Understanding patients' adherence-related beliefs about medicines prescribed for long-term conditions: a meta-analytic review of the necessity-concerns framework. *PLoS One*. 2013;8(12):e80633. https://doi.org/10.1371/journal.pone.0080633
6. Papi A, Ryan D, Soriano JB, et al. Relationship of inhaled corticosteroid adherence to asthma exacerbations in patients with moderate-to-severe asthma. *J Allergy Clin Immunol Pract*. 2018;6(6):1989-1998.e3. https://doi.org/10.1016/j.jaip.2018.03.008
7. Engelkes M, Janssens HM, De Jongste JC, Sturkenboom MCJM, Verhamme KMC. Medication adherence and the risk of severe asthma exacerbations: a systematic review. *Eur Respir J*. 2015;45(2):396-407. https://doi.org/10.1183/09031936.00075614
8. Fernandes AGO, Souza-Machado C, Coelho RCP, et al. Risk factors for death in patients with severe asthma. *J Bras Pneumol*. 2014;40(4):364-372. https://doi.org/10.1590/S1806-37132014000400003
9. Murphy AC, Proeschal A, Brightling CE, et al. The relationship between clinical outcomes and medication adherence in difficult-to-control asthma. *Thorax*. 2012;67(8):751-753. https://doi.org/10.1136/thoraxjnl-2011-201096
10. Friedman C, Rubin J, Brown J, et al. Toward a science of learning systems: a research agenda for the high-functioning learning health system. *J Am Med Informatics Assoc*. 2014;22(1):43-50. https://doi.org/10.1136/amiajnl-2014-002977
11. Granger BB, Swedberg K, Ekman I, et al. Adherence to candesartan and placebo and outcomes in chronic heart failure in the CHARM programme: double-blind, randomised, controlled clinical trial. *Lancet* 2005;366(9502):2005–2011. https://doi.org/10.1016/S0140-6736(05)67760-4
12. Sethi AK, Celentano DD, Gange SJ, Moore RD, Gallant JE. Association between adherence to antiretroviral therapy and human immunodeficiency virus drug resistance. *Clin Infect Dis*. 2003;37(8):1112-1118. https://doi.org/10.1086/378301
13. Kardas P. Patient compliance with antibiotic treatment for respiratory tract infections. *J Antimicrob Chemother*. 2002;49(6):897-903. https://doi.org/10.1093/jac/dkf046
14. Sumartojo E. When tuberculosis treatment fails: a social behavioral account of patient adherence. *Am Rev Respir Dis*. 1993;147(5):1311-1320. https://doi.org/10.1164/ajrccm/147.5.1311
15. Price DB, Trudo F, Voorham J, Xu X, Kerkhof M, Tran TN. Adverse outcomes from initiation of systemic corticosteroids for asthma: long-term observational study. *J Asthma Allergy*. 2018;11:193-204. https://doi.org/10.2147/jaa.s176026
16. Suissa S, Kezouh A, Ernst P. Inhaled corticosteroids and the risks of diabetes onset and progression. *AJM*. 2010;123(11):1001-1006. https://doi.org/10.1016/j.amjmed.2010.06.019
17. Bloechliger M, Reinau D, Spoendlin J, et al. Adverse events profile of oral corticosteroids among asthma patients in the UK: cohort study with a nested case-control analysis. *Respir Res*. 2018;19:75. https://doi.org/10.1186/s12931-018-0742-y
18. Osterberg L, Blaschke T. Drug therapy: adherence to medication. *N Engl J Med*. 2005;353(5):487-497. https://doi.org/10.1056/NEJMra050100
19. Muzina DJ, Malone DA, Bhandari I, Lulic R, Baudisch R, Keene M. Rate of non-adherence prior to upward dose titration in previously stable antidepressant users. *J Affect Disord*. 2011;130(1–2):46-52. https://doi.org/10.1016/J.JAD.2010.09.018
20. Dominguez RA, Goodnick PJ. Adverse events after the abrupt discontinuation of paroxetine. *Pharmacothery*. 1995;15(6):778-780. https://doi.org/10.1002/j.1875-9114.1995.tb02896.x
21. Hamlyn A, Foo K, Bhatia A, Bobrin B. Manifestations of pregabalin withdrawal. *J Psychiatry*. 2017;20(5):418. https://doi.org/10.4172/2378-5756.1000418
22. Demyttenaere K, Haddad P. Compliance with antidepressant therapy and antidepressant discontinuation symptoms. *Acta Psychiatr Scand*. 2000;101(s403):50-56. https://doi.org/10.1111/j.1600-0447.2000.tb10948.x
23. McCormack JP, Allan GM, Virani AS. Is bigger better? An argument for very low starting doses. *Can Med Assoc J*. 2011;183(1):65-69. https://doi.org/10.1503/cmaj.091481
24. Ferrendelli JA. Concerns with antiepileptic drug initiation: safety, tolerability, and efficacy. *Epilepsia*. 2001;42(Suppl. 4):28-30.
25. Van Boven JFM, Chavannes NH, Van Der Molen T, Rutten-Van Mölken MPMH, Postma MJ, Vegter S. Clinical and economic impact of non-adherence in COPD: a systematic review. *Respir Med*. 2014;108(1):103-113. https://doi.org/10.1016/j.rmed.2013.08.044
26. Hommel KA, Mcgrady ME, Peugh J, et al. Longitudinal patterns of medication nonadherence and associated health care costs. *Inflamm Bowel Dis*. 2017;23(9):1577-1583. https://doi.org/10.1097/MIB.0000000000001165
27. Iuga AO, Mcguire MJ. Adherence and health care costs. *Risk Manag Healthc Policy*. 2014;7:35-44. https://doi.org/10.2147/RMHP.S19801
28. Cutler RL, Fernandez-Llimos F, Frommer M, Benrimoj C, Garcia-Cardenas V. Economic impact of medication non-adherence by disease groups: a systematic review. *BMJ Open*. 2018;8(1):e016982. https://doi.org/10.1136/bmjopen-2017-016982
29. Ho SC, Chong HY, Chaiyakunapruk N, Tangiisuran B, Jacob SA. Clinical and economic impact of non-adherence to antidepressants in major depressive disorder: a systematic review. *J Affect Disord J*. 2016;193:1-10. https://doi.org/10.1016/j.jad.2015.12.029
30. Dragomir A, Côté R, Roy L, et al. Impact of adherence to antihypertensive agents on clinical outcomes and hospitalization costs. *Med Care*. 2010;48(5):418-425. https://doi.org/10.1097/MLR.0b013e3181d567bd
31. Toy EL, Beaulieu NU, McHale JM, et al. Treatment of COPD: relationships between daily dosing frequency, adherence, resource use, and costs. *Respir Med*. 2011;105(3):435-441. https://doi.org/10.1016/j.rmed.2010.09.006
32. Marcum ZA, Zheng Y, Perera S, et al. Prevalence and correlates of self-reported medication non-adherence among older adults with coronary heart disease, diabetes mellitus, and/or hypertension. *Res Soc Adm Pharm*. 2013;9(6):817-827. https://doi.org/10.1016/J.SAPHARM.2012.12.002
33. Timmerman L, Stronks DL, Groeneweg JG, Huygen FJ. Prevalence and determinants of medication non-adherence in chronic pain patients: a systematic review. *Acta Anaesthesiol Scand*. 2016;60(4):416-431. https://doi.org/10.1111/aas.12697
34. Patel AR, Campbell JR, Sadatsafavi M, et al. Burden of non-adherence to latent tuberculosis infection drug therapy and the potential cost-effectiveness of adherence interventions in Canada: a simulation study. *BMJ Open*. 2017;7(9):e015108. https://doi.org/10.1136/bmjopen-2016-015108
35. Mckenzie SJ, Mclaughlin D, Clark J, Doi SA. The burden of non-adherence to cardiovascular medications among the aging population in Australia: a meta-analysis. *Drugs Aging*. 2015;32(3):217-225. https://doi.org/10.1007/s40266-015-0245-1

36. Cutrona SL, Choudhry NK, Fischer MA, et al. Targeting cardiovascular medication adherence interventions. *J Am Pharm Assoc*. 2012;52(3):381-397. https://doi.org/10.1331/JAPhA.2012.10211
37. Haberer JE, Sabin L, Amico KR, et al. Improving antiretroviral therapy adherence in resource-limited settings at scale: a discussion of interventions and recommendations. *J Int AIDS Soc*. 2017;20(1):21371. https://doi.org/10.7448/IAS.20.1.21371
38. Normansell R, Kew KM, Mathioudakis AG. Interventions to improve inhaler technique for people with asthma. *Cochrane Database Syst Rev*. 2017;3(3). https://doi.org/10.1002/14651858.CD012286.pub2
39. Valgimigli M, Garcia-Garcia HM, Vrijens B, et al. Standardized classification and framework for reporting, interpreting, and analysing medication non-adherence in cardiovascular clinical trials: a consensus report from the Non-adherence Academic Research Consortium (NARC). *Eur Heart J*. 2019;40(25):2070-2085. https://doi.org/10.1093/eurheartj/ehy377
40. DeWorsop D, Creatura G, Bluez G, et al. Feasibility and success of cell-phone assisted remote observation of medication adherence (CAROMA) in clinical trials. *Drug Alcohol Depend*. 2016;163:24-30. https://doi.org/10.1016/j.drugalcdep.2016.02.045
41. Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. *J Clin Epidemiol*. 1997;50(1):105-116. https://doi.org/10.1016/S0895-4356(96)00268-5
42. Andrade SE, Kahler KH, Frech F, Chan KA. Methods for evaluation of medication adherence and persistence using automated databases. *Pharmacoepidemiol Drug Saf*. 2006;15(8):565-574. https://doi.org/10.1002/pds.1230
43. Hess LM, Raebel MA, Conner DA, Malone DC. Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. *Ann Pharmacother*. 2006;40(7-8):1280-1288. https://doi.org/10.1345/aph.1H018
44. Ciechanowski PS, Katon WJ, Russo JE. Depression and diabetes: impact of depressive symptoms on adherence, function, and costs. *Arch Intern Med*. 2000;160(21):3278. https://doi.org/10.1001/archinte.160.21.3278
45. Carroll CL, Feldman SR, Camacho FT, Manuel JC, Balkrishnan R. Adherence to topical therapy decreases during the course of an 8-week psoriasis clinical trial: commonly used methods of measuring adherence to topical therapy overestimate actual use. *J Am Acad Dermatol*. 2004;51(2):212-216. https://doi.org/10.1016/j.jaad.2004.01.052
46. Yeaw J, Benner JS, Walt JG, Sian S, Smith DB. Comparing adherence and persistence across 6 chronic medication classes. *J Manag Care Pharm*. 2009;15(9):728-740. https://doi.org/10.18553/jmcp.2009.15.9.728
47. Huiart L, Bouhnik AD, Rey D, et al. Early discontinuation of tamoxifen intake in younger women with breast cancer: is it time to rethink the way it is prescribed? *Eur J Cancer*. 2012;48(13):1939-1946. https://doi.org/10.1016/j.ejca.2012.03.004
48. Rinfret S, Rodés-Cabau J, Bagur R, et al. Telephone contact to improve adherence to dual antiplatelet therapy after drug-eluting stent implantation. *Heart*. 2013;99(8):562-569. https://doi.org/10.1136/heartjnl-2012-303004
49. Boissel JP, Nony P. Using pharmacokinetic-pharmacodynamic relationships to predict the effect of poor compliance. *Clin Pharmacokinet*. 2002;41(1):1-6. https://doi.org/10.2165/00003088-200241010-00001
50. *Global Asthma Network*. 2018 Auckland, New Zealand: The Global Asthma Report 2018, Global Asthma Network.
51. World Health Organization. *WHO Global Tuberculosis Report 2019*. Geneva: World Health Organization; 2019.
52. Chirwa T, Nyasulu P, Chirwa E, et al. Levels of tuberculosis treatment adherence among sputum smear positive pulmonary tuberculosis patients attending care at Zomba Central Hospital, Southern Malawi, 2007–2008. *PLoS One*. 2013;8(5):e63050. https://doi.org/10.1371/journal.pone.0063050
53. Stagg HR, Lewis JJ, Liu X, et al. Temporal factors and missed doses of tuberculosis treatment: a causal associations approach to analyses of digital adherence data. *Ann Am Thorac Soc*. 17(4), 438-449. https://doi.org/10.1513/AnnalsATS.201905-394OC
54. Krasniqi S, Jakupi A, Daci A, et al. Tuberculosis treatment adherence of patients in Kosovo. *Tuberc Res Treat*. 2017;2017:1-8. https://doi.org/10.1155/2017/4850324
55. Vollmer WM. Assessment of asthma control and severity. *Ann Allergy Asthma Immunol*. 2004;93(5):409-414. https://doi.org/10.1016/S1081-1206(10)61406-8
56. Bush A, Griffiths C. Improving treatment of asthma attacks in children. *BMJ*. 2017;359:j5763. https://doi.org/10.1136/bmj.j5763
57. To T, Stanojevic S, Moores G, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC Public Health*. 2012;12:204. https://doi.org/10.1186/1471-2458-12-204
58. Mukherjee M, Stoddart A, Gupta RP, et al. The epidemiology, healthcare and societal burden and costs of asthma in the UK and its member nations: analyses of standalone and linked national databases. *BMC Med*. 2016;14:113. https://doi.org/10.1186/s12916-016-0657-8
59. Asthma UK. Asthma UK Data Portal—Deaths; 2018.
60. British Thoracic Society, Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. *SIGN Guidel*. 2014;63(Supplement 4):iv1-iv121. https://doi.org/10.1136/thx.2008.097741
61. Bateman ED, Reddel HK, O'Byrne PM, et al. As-needed budesonide–formoterol versus maintenance budesonide in mild asthma. *N Engl J Med*. 2018;378(20):1877-1887. https://doi.org/10.1056/NEJMoa1715275
62. Bardsley G, Daley-Yates P, Baines A, et al. Anti-inflammatory duration of action of fluticasone furoate/vilanterol trifenatate in asthma: a cross-over randomised controlled trial. *Respir Res*. 19(1):133. https://doi.org/10.1186/s12931-018-0836-6
63. Derendorf H, Nave R, Drollmann A, Cerasoli F, Wurst W. Relevance of pharmacokinetics and pharmacodynamics of inhaled corticosteroids to asthma. *Eur Respir J*. 2006;28(5):1042-1050. https://doi.org/10.1183/09031936.00074905
64. Leather DA, Yates L, Svedsater H, et al. Can medicines development improve outcomes in asthma and chronic obstructive pulmonary disease management by driving effectiveness? *Respir Res*. 2019;20:173. https://doi.org/10.1186/s12931-019-1127-6
65. Stauffer ME, Hutson P, Kaufman AS, Morrison A. The adherence rate threshold is drug specific. *Drugs R D*. 2017;17(4):645-653. https://doi.org/10.1007/s40268-017-0216-6
66. Mahmood I. Prediction of drug clearance in children from adults: a comparison of several allometric methods. *Br J Clin Pharmacol*. 2006;61(5):545-557. https://doi.org/10.1111/j.1365-2125.2006.02622.x
67. Soldin OP, Mattison DR. Sex differences in pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet*. 2009;48(3):143-157. https://doi.org/10.2165/00003088-200948030-00001
68. Brill MJE, Diepstraten J, Van Rongen A, Van Kralingen S, Van Den Anker JN, Knibbe CAJ. Impact of obesity on drug metabolism and elimination in adults and children. *Clin Pharmacokinet*. 2012;51(5):277-304. https://doi.org/10.2165/11599410-000000000-00000
69. Pai M, Behr MA, Dowdy D, et al. Primer on tuberculosis. *Nat Rev Dis Prim*. 2016;2(1):16076. https://doi.org/10.1038/nrdp.2016.76
70. World Health Organization. The Top 10 Causes of Death. 2018. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death. Accessed November 6, 2019.
71. National Tuberculosis Institute. Tuberculosis in a rural population of South India: a five-year epidemiological study. *Bull World Health*

*Organ*. 1974;51(5):473-488. http://www.ncbi.nlm.nih.gov/pubmed/4549498
72. Glaziou P, Floyd K, Raviglione MC. Global epidemiology of tuberculosis. *Cold Spring Harb Perspect Med*. 2015;5(03):271-285. https://doi.org/10.1055/s-0038-1651492
73. World Health Organization. *WHO Guidelines for Treatment of Tuberculosis*. Geneva: World Health Organization; 2010.
74. World Health Organization. WHO Consolidated Guidelines on Drug-Resistant Tuberculosis Treatment.
75. World Health Organization. *Treatment of Tuberculosis Guidelines for Treatment of Drug-Susceptible Tuberculosis and Patient Care*. Geneva: World Health Organization; 2017.
76. Mitchell P, El-Gammal A, O'Byrne P. Emerging monoclonal antibodies as targeted innovative therapeutic approaches to asthma. *Clin Pharmacol Ther*. 2016;99(1):38-48. https://doi.org/10.1002/cpt.284
77. Catley MC, Coote J, Bari M, Tomlinson KL. Monoclonal antibodies for the treatment of asthma. *Pharmacol Ther*. 2011;132(3):333-351. https://doi.org/10.1016/j.pharmthera.2011.09.005
78. Koski RR, Grzegorczyk KM. Comparison of monoclonal antibodies for treatment of uncontrolled eosinophilic asthma. *J Pharm Pract*. 2019;33(4):513-522. https://doi.org/10.1177/0897190019840597
79. Aggarwal B, Mulgirigama A, Berend N. Exercise-induced bronchoconstriction: prevalence, pathophysiology, patient impact, diagnosis and management. *NPJ Prim Care Respir Med*. 2018;28(1):31. https://doi.org/10.1038/s41533-018-0098-2
80. Covantev S, Corlateanu A, Botnaru V. Exercise-Induced Bronchoconstriction in Athletes. Vol. 3; 2016. www.austinpublishinggroup.com
81. O'Byrne PM, FitzGerald JM, Bateman ED, et al. Inhaled combined budesonide–formoterol as needed in mild asthma. *N Engl J Med*. 2018;378(20):1865-1876. https://doi.org/10.1056/NEJMoa1715274
82. Vrijens B, Dima AL, Van Ganse E, et al. What we mean when we talk about adherence in respiratory medicine. *J Allergy Clin Immunol Pract*. 2016;4(5):802-812. https://doi.org/10.1016/j.jaip.2016.05.019
83. Anderson HR, Bland JM, Patel S, Peckham C. The natural history of asthma in childhood. *J Epidemiol Community Health*. 1986;40(2):121-129. https://doi.org/10.1136/jech.40.2.121
84. Bernstein JA. Occupational asthma. In: Mahmoudi M, ed. *Allergy and Asthma: Practical Diagnosis and Management, 2nd Edition*. Cham, Switzerland: Springer International Publishing; 2016:253–270. https://doi.org/10.1007/978-3-319-30835-7_17,
85. Boslev C, Md B, Suppli C, Dmsc UM. Asthma and adherence to inhaled corticosteroids: current status and future perspectives. *Respir Care*. 2015;60(3):455-468. https://doi.org/10.4187/respcare.03200
86. World Health Organization. *WHO Definitions and Reporting Framework for Tuberculosis: 2013 Revision, Updated December 2014*. Geneva: World Health Organization; 2015.
87. Kruk ME, Schwalbe NR, Aguiar CA. Timing of default from tuberculosis treatment: a systematic review. *Trop Med Int Heal*. 2008;13(5):703-712. https://doi.org/10.1111/j.1365-3156.2008.02042.x
88. Walker IF, Shi O, Hicks JP, et al. Analysis of loss to follow-up in 4099 multidrug-resistant pulmonary tuberculosis patients. *Eur Respir J*. 2019;54(1):1800353. https://doi.org/10.1183/13993003.00353-2018
89. Dima AL, van Ganse E, Laforest L, Texier N, de Bruin M, The ASTRO-LAB Group. Measuring medication adherence in asthma: development of a novel self-report tool. *Psychol Health*. 2017;32(10):1288-1307. https://doi.org/10.1080/08870446.2017.1290248
90. Chapman S, Dale P, Svedsater H, et al. Modelling the effect of beliefs about asthma medication and treatment intrusiveness on adherence and preference for once-daily vs. twice-daily medication. *NPJ Prim Care Respir Med*. 2017;27:61. https://doi.org/10.1038/s41533-017-0061-7
91. Cohen JL, Mann DM, Wisnivesky JP, et al. Assessing the validity of self-reported medication adherence among inner-city asthmatic adults: the Medication Adherence Report Scale for Asthma. *Ann Allergy Asthma Immunol*. 2009;103(4):325-331. https://doi.org/10.1016/S1081-1206(10)60532-7
92. Brooks CM, Richards JM, Kohler CL, et al. Assessing adherence to asthma medication and inhaler regimens: a psychometric analysis of adult self-report scales. *Med Care*. 1994;32(3):298-307.
93. Sulaiman I, Seheult J, Sadasivuni N, et al. The impact of common inhaler errors on drug delivery: investigating critical errors with a dry powder inhaler. *J Aerosol Med Pulm Drug Deliv*. 2017;30(4):247-255. https://doi.org/10.1089/jamp.2016.1334
94. Chan AHY, Reddel HK, Apter A, Eakin M, Riekert K, Foster JM. Adherence monitoring and E-health: how clinicians and researchers can use technology to promote inhaler adherence for asthma. *J Allergy Clin Immunol Pract*. 2013;1(5):446-454. https://doi.org/10.1016/J.JAIP.2013.06.015
95. Asthma UK. Connected Asthma: How Technology Will Transform Care. 2016. https://www.asthma.org.uk/globalassets/get-involved/external-affairs-campaigns/publications/connected-asthma/connected-asthma---aug-2016.pdf
96. Hew M, Reddel HK. Integrated adherence monitoring for inhaler medications. *JAMA*. 2019;321(11):1045-1046.
97. Blaschke TF, Osterberg L, Vrijens B, Urquhart J. Adherence to medications: insights arising from studies on the unreliable link between prescribed and actual drug dosing histories. *Annu Rev Pharmacol Toxicol*. 2012;52(1):275-301. https://doi.org/10.1146/annurev-pharmtox-011711-113247
98. Hansen RA, Kim MM, Song L, Tu W, Wu J, Murray MD. Comparison of methods to assess medication adherence and classify nonadherence. *Ann Pharmacother*. 2009;43(3):413-422.
99. Chan AHY, Harrison J, Black PN, Mitchell EA, Foster JM. Using electronic monitoring devices to measure inhaler adherence: a practical guide for clinicians. *J Allergy Clin Immunol Pract*. 2015;3(3):335-349.e5. https://doi.org/10.1016/j.jaip.2015.01.024
100. Bogen D, Apter AJ. Adherence logger for a dry powder inhaler: a new device for medical adherence research. *J Allergy Clin Immunol*. 2004;114(4):863-868. https://doi.org/10.1016/j.jaci.2004.07.017
101. Lupinek C, Marth K, Niederberger V, Valenta R. Six-month in vitro validation of a metered-dose inhaler electronic monitoring device: implications for asthma clinical trial use. *J Allergy Clin Immunol*. 2012;130(7):1420-1422. https://doi.org/10.1016/j.jaci.2012.06.028
102. Taylor TE, Zigel Y, De Looze C, Sulaiman I, Costello RW, Reilly RB. Advances in audio-based systems to monitor patient adherence and inhaler drug delivery. *Chest*. 2018;153(3):710-722. https://doi.org/10.1016/j.chest.2017.08.1162
103. Liu AY, Yang Q, Huang Y, et al. Strong relationship between oral dose and tenofovir hair levels in a randomized trial: hair as a potential adherence measure for pre-exposure prophylaxis (PrEP). *PLoS One*. 2014;9(1):e83736. https://doi.org/10.1371/journal.pone.0083736
104. Hawkshead J, Krousel-Wood MA. Techniques for measuring medication adherence in hypertensive patients in outpatient settings. *Dis Manag Heal Outcomes*. 2007;15(2):109-118. https://doi.org/10.2165/00115677-200715020-00006
105. Robinson DS, Campbell DA, Durham SR, et al. Systematic assessment of difficult-to-treat asthma. *Eur Respir J*. 2003;22(3):478-483. https://doi.org/10.1183/09031936.03.00017003
106. Hassall D, Brealey N, Wright W, et al. Hair analysis to monitor adherence to prescribed chronic inhaler drug therapy in patients with asthma or COPD. *Pulm Pharmacol Theraupticss*. 2018;51:59-64. https://doi.org/10.1016/j.pupt.2018.07.001

107. Shah NM, Hawwa AF, Millership JS, et al. Adherence to antiepileptic medicines in children: a multiple-methods assessment involving dried blood spot sampling. *Epilepsia*. 2013;54(6):1020-1027. https://doi.org/10.1111/epi.12126
108. 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(2):159-165. https://doi.org/10.3122/jabfm.2010.02.090112
109. Salazar G, Tarwala G, Reznik M. School-based supervised therapy programs to improve asthma outcomes: current perspectives. *J Asthma Allergy*. 2018;11:205-215. https://doi.org/10.2147/JAA.S147524
110. Bardin PG, Price D, Chanez P, Humbert M, Bourdin A. Managing asthma in the era of biological therapies. *Lancet Respir Med*. 2017;5(5):376-378. https://doi.org/10.1016/S2213-2600(17)30124-8
111. Yin X, Tu X, Tong Y, et al. Development and validation of a tuberculosis medication adherence scale. *PLoS One*. 2012;7(12):e50328. https://doi.org/10.1371/journal.pone.0050328
112. Valencia S, León M, Losada I, Sequera VG, Fernández Quevedo M, García-Basteiro AL. How do we measure adherence to antituberculosis treatment? *Expert Rev Anti Infect Ther*. 2016;15(2):157-165. https://doi.org/10.1080/14787210.2017.1264270
113. Bayer R, Wilkinson D, Bayer R. Directly observed therapy for tuberculosis: history of an idea. *Lancet*. 1995;345(8964):1545-1548. https://doi.org/10.1016/S0140-6736(95)91090-5
114. Subbaraman R, De Mondesert L, Musiimenta A, et al. Digital adherence technologies for the management of tuberculosis therapy: mapping the landscape and research priorities. *BMJ Glob Heal*. 2018;3(5):1018. https://doi.org/10.1136/bmjgh-2018-001018
115. Belknap R, Weis S, Brookens A, et al. Feasibility of an ingestible sensor-based system for monitoring adherence to tuberculosis therapy. *PLoS One*. 2013;8(1):e53373. https://doi.org/10.1371/journal.pone.0053373
116. Ducharme FM, Zemek RL, Chalut D, et al. Written action plan in pediatric emergency room improves asthma prescribing, adherence, and control. *Am J Respir Crit Care Med*. 2011;183(2):195-203. https://doi.org/10.1164/rccm.201001-0115OC
117. Foster JM, Usherwood T, Smith L, et al. Inhaler reminders improve adherence with controller treatment in primary care patients with asthma. *J Allergy Clin Immunol*. 2014;134(6):1260-1268.e3. https://doi.org/10.1016/j.jaci.2014.05.041
118. Normansell R, Kew K, Stovold E. Interventions to improve adherence to inhaled steroids for asthma. *Cochrane Database Syst Rev*. 2017;4(4):CD012226. https://doi.org/10.1002/14651858.CD012226.pub2
119. Morton RW, Everard ML, Elphick HE. Adherence in childhood asthma: the elephant in the room. *Arch Dis Child*. 99(10):949-953. https://doi.org/10.1136/archdischild-2014-306243
120. Gamble J, Stevenson M, McClean E, Heaney LG. The prevalence of nonadherence in difficult asthma. *Am J Respir Crit Care Med*. 2009;180(9):817-822. https://doi.org/10.1164/rccm.200902-0166OC
121. Ranganathan SC, Payne DNR, Jaffe A, McKenzie SA. Difficult asthma: defining the problems. *Pediatr Pulmonol*. 2001;31(2):114-120. https://doi.org/10.1002/1099-0496(200102)31:2<114::AID-PPUL1018>3.0.CO;2-O
122. Ismaila A, Corriveau D, Vaillancourt J, et al. Impact of adherence to treatment with fluticasone propionate/salmeterol in asthma patients. *Curr Med Res Opin*. 2014;30(7):1417-1425. https://doi.org/10.1185/03007995.2014.908827
123. George M, Bender B. New insights to improve treatment adherence in asthma and COPD. *Patient Prefer Adherence*. 2019;13:1325-1334. https://doi.org/10.2147/PPA.S209532
124. Makhinova T, Barner JC, Richards KM, Rascati KL. Asthma controller medication adherence, risk of exacerbation, and use of rescue agents among Texas Medicaid patients with persistent asthma. *J Manag Care Spec Pharm*. 2015;21(12):1124-1132. https://doi.org/10.18553/jmcp.2015.21.12.1124
125. Allemann SS, Dediu D, Dima AL. Beyond adherence thresholds: a simulation study of the optimal classification of longitudinal adherence trajectories from medication refill histories. *Front Pharmacol*. 2019;10:1-13. https://doi.org/10.3389/fphar.2019.00383
126. Franklin JM, Krumme AA, Shrank WH, Matlin OS, Brennan TA, Choudhry NK. Predicting adherence trajectory using initial patterns of medication filling. *Am J Manag Care*. 2015;21(9):e537-e544.
127. Price DB, Román-Rodríguez M, Brett McQueen R, et al. Inhaler errors in the CRITIKAL study: type, frequency, and association with asthma outcomes. *J Allergy Clin Immunol Pract*. 2017;5(4):1071-1081.e9. https://doi.org/10.1016/j.jaip.2017.01.004
128. Cochrane MG, Bala MV, Downs KE, Mauskopf J, Ben-Joseph RH. Inhaled corticosteroids for asthma therapy: patient compliance, devices, and inhalation technique. *Chest*. 2000;117(2):542-550. https://doi.org/10.1378/chest.117.2.542
129. Sanchis J, Gich I, Pedersen S. Systematic review of errors in inhaler use: has patient technique improved over time? *Chest*. 2016;150(2):394-406. https://doi.org/10.1016/j.chest.2016.03.041
130. Nackers F, Huerga H, Espié E, et al. Adherence to self-administered tuberculosis treatment in a high HIV-prevalence setting: a cross-sectional survey in Homa Bay, Kenya. *PLoS One*. 2012;7(3):e32140. https://doi.org/10.1371/journal.pone.0032140
131. Liu X, Lewis JJ, Zhang H, et al. Effectiveness of electronic reminders to improve medication adherence in tuberculosis patients: a cluster-randomised trial. *PLoS Med*. 2015;12(9):e1001876. https://doi.org/10.1371/journal.pmed.1001876
132. Van Der Kop ML, Memetovic J, Patel A, et al. The effect of weekly text-message communication on treatment completion among patients with latent tuberculosis infection: study protocol for a randomised controlled trial (WelTel LTBI). *BMJ Open*. 2014;4(4):e004362. https://doi.org/10.1136/bmjopen-2013-004362
133. Menzies D, Long R, Trajman A, et al. Adverse events with 4 months of rifampin therapy or 9 months of isoniazid therapy for latent tuberculosis infection: a randomized trial. *Ann Intern Med*. 2008;149(10):689-697. https://doi.org/10.7326/0003-4819-149-10-200811180-00003
134. Bastard M, Sanchez-Padilla E, Hewison C, et al. Effects of treatment interruption patterns on treatment success among patients with multidrug-resistant tuberculosis in Armenia and Abkhazia. *J Infect Dis*. 2015;211(10):1607-1615. https://doi.org/10.1093/infdis/jiu551
135. Podewils LJ, Gler MTS, Quelapio MI, Chen MP. Patterns of treatment interruption among patients with multidrug-resistant TB (MDR TB) and association with interim and final treatment outcomes. *PLoS One*. 2013;8(7):e70064. https://doi.org/10.1371/journal.pone.0070064
136. Kayigamba FR, Bakker MI, Mugisha V, et al. Adherence to tuberculosis treatment, sputum smear conversion and mortality: a retrospective cohort study in 48 Rwandan clinics. *PLoS One*. 2013;8(9):e73501. https://doi.org/10.1371/journal.pone.0073501
137. Imperial MZ, Nahid P, Phillips PPJ, et al. A patient-level pooled analysis of treatment-shortening regimens for drug-susceptible pulmonary tuberculosis. *Nat Med*. 2018;24(11):1708-1715. https://doi.org/10.1038/s41591-018-0224-2
138. Van den Boogaard J, Boeree MJ, Kibiki GS, Aarnoutse RE. The complexity of the adherence-response relationship in tuberculosis treatment: why are we still in the dark and how can we get out? *Trop Med Int Heal*. 2011;16(6):693-698. https://doi.org/10.1111/j.1365-3156.2011.02755.x
139. McDonald VM, Hiles SA, Godbout K, et al. Treatable traits can be identified in a severe asthma registry and predict future exacerbations. *Respirology*. 2019;24(1):37-47. https://doi.org/10.1111/resp.13389

140. Ban GY, Trinh THK, Ye YM, Park HS. Predictors of asthma control in elderly patients. *Curr Opin Allergy Clin Immunol*. 2016;16(3):237-243. https://doi.org/10.1097/ACI.0000000000000273
141. Traini D, Young PM. Drug delivery for tuberculosis: is inhaled therapy the key to success? *Ther Deliv*. 2017;8(10):819-821. https://doi.org/10.4155/tde-2017-0050
142. Shuter J. Forgiveness of non-adherence to HIV-1 antiretroviral therapy. *J Antimicrob Chemother*. 2008;61(4):769-773. https://doi.org/10.1093/jac/dkn020
143. Morrison A, Stauffer ME, Kaufman AS. Relationship between adherence rate threshold and drug forgiveness. *Clin Pharmacokinet*. 56 (12):1435-1440. https://doi.org/10.1007/s40262-017-0552-2
144. De Geest S, Zullig LL, Dunbar-Jacob J, et al. ESPACOMP medication adherence reporting guideline (EMERGE). *Ann Intern Med*. 2018;169 (1):30-35. https://doi.org/10.7326/M18-0543
145. Eliasson L, Clifford S, Mulick A, Jackson C, Vrijens B. How the EMERGE guideline on medication adherence can improve the quality of clinical trials. *Br J Clin Pharmacol*. 2020;86(4):687-697. https://doi.org/10.1111/bcp.14240

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