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

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Abstract (234/250 Words)

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.

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 themselves¹. 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 systems' factors and a lack of social support¹⁻⁵. Non-adherence is associated with poor clinical outcomes⁶⁻¹¹, and contributes towards the emergence of drug-resistant infections¹²⁻¹⁴. It may lead to unnecessary dose escalation and/or additional treatment to control symptoms, itself resulting in the onset of avoidable side-effects¹⁵⁻¹⁹. Non-adherence may also result in adverse events related to discontinuation²⁰⁻²² 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 most at-risk during their treatment regimen, undertaking targeted intervention development³⁶⁻³⁸, and accurately assessing the impact of novel interventions^{39,40}. A substantial challenge in adherence measurement is that the field is not standardized and different measures have been introduced, the comparability of which is typically unclear⁴¹⁻⁴³. 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 persistence⁵¹. 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 condition⁴⁴⁻⁴⁸).

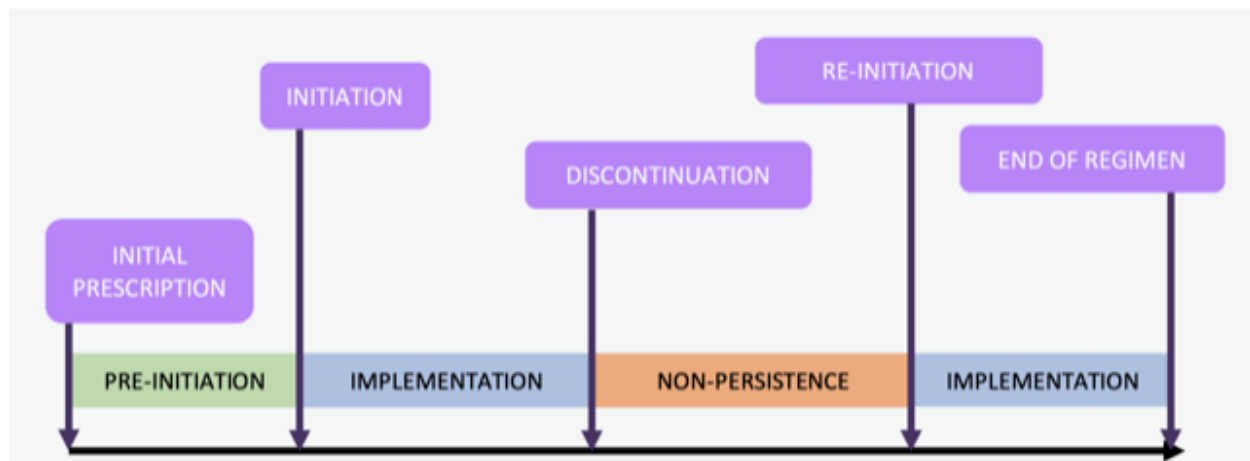


Figure 1: Diagram highlighting the three phases of medication adherence in the ABC taxonomy, relative to patient-level prescription events.

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.

Background: Pathophysiology, Epidemiology, and Treatment

Asthma

Asthma is a chronic disease that is characterised by hyper-responsiveness 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 level 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.

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 in 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 nine and 20 months ⁷⁴. 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.

Applications of the ABC Taxonomy

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 inhaler³⁸, 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 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^{78–80}. Relievers are taken only *as needed* to relieve heightened symptoms, or as a short-term preventative measure (such as before exercise^{81,82}). 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^{61,83,84}. For those patients where the 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 asthma⁸⁵ and occupational asthma⁸⁶). Unsanctioned discontinuation is also common⁸⁷. Periods of non-persistence can be analysed to understand what triggers their occurrence, as well as what triggers subsequent re-initiation⁴².

Tuberculosis

Delayed initiation of treatment in TB is problematic in 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 TB⁵¹, 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 WHO to reduce pill burden⁷⁴. 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 WHO has resulted in a set of standardised definitions that capture part of medication discontinuation, in the form of Loss to Follow-Up (LFU)⁸⁸. LFU (previously called default) is defined as a break in treatment of two 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^{89,90}.

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.

Adherence Measurement

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

regimen⁸⁴. 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, standardized questionnaires, and psychometric scales⁸⁴. 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)⁹¹, Medication Adherence Report Scale for Asthma (MARS-A)^{92,93}, and the Brooks *et al.* scales for inhaled and oral asthma medications⁹⁴, 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)⁹¹, however it does not explicitly cover non-initiation. Estimates of implementation can also be made using inhaler technique assessment checklists³⁸, as poor inhaler technique is known to result in suboptimal drug delivery⁹⁵.

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 taken⁹⁶. 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^{97,98}. 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^{99,100}. 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 adherence¹⁰¹. 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 duration¹⁰², particularly when they occur soon before clinic or trial assessments¹⁰³. 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 canister, and holding breath after actuation)^{84,104}.

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)^{105–109}, and device monitoring such as canister weighing¹¹⁰. A lack of detectable medication in biological samples would imply either non-initiation or discontinuation, depending on the time-scale, and the expected to 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 ¹¹¹. 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 ¹¹².

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 ¹¹³; TBMAS), and directly e.g. through urine or blood testing ¹¹⁴. 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 ¹¹⁵. 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.* ¹¹⁶. 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 ¹¹⁷).

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

Adherence Reporting

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^{7,110,118,119}. Indeed, Normansell *et al.*'s recent Cochrane review of asthma adherence interventions³⁸ 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 measure⁷. 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 (ICS, LABA or ICS+LABA combination inhalers), and found that estimated varied widely - ranging between 15-54% in adults⁷. Similarly,

Morton *et al.*'s review of asthma EMD studies in children found the mean ranged between 34 and 73% ¹²⁰. 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 ^{121,122}. 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 ¹²³. They found that 42.7% of the patients (all on ICS+LABA therapy, N=19126) were compliant, and only 29.3% were persistent. Persistence was strongly associated with all outcomes in adjusted analyses, but severe outcomes such as ICU admission 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% ^{9,52,111,124}. Both Gamble *et al.* ¹²¹ and Makhinova *et al.* ¹²⁵ 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.* ¹²⁶:

“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 ^{126,127}.

Regarding inhaler technique, adherence is typically reported as binary indicators of whether specific errors (such as patients forgetting to tilt their head) were made ^{128–130}, 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) ¹²⁸. 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 ^{129,130}.

Tuberculosis

Classical approaches to assessing adherence to anti-TB treatment have focussed on determining the proportion of patients taking greater than or equal to 80% or 90% of their daily doses^{131–134}. Exceptions to the use of simple percentage thresholds are included in the work of Podewils *et al.* and Bastard *et al.*^{135,136}, 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 (for example, see the studies of Imperial *et al.* and Kayigamba *et al.*)^{137,138}, the deployment of DATs on a large scale provides substantial opportunities to provide greater insights into the relationship between adherence patterns and treatment outcomes¹³⁹.

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 six 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 China⁵³. 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.

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, nebulisers, 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 adherence¹⁴⁰, particularly in elderly and cognitively impaired patients¹⁴¹. In TB, an area of polypharmacy is the intersection with HIV and therefore antiretrovirals; approximately 8.6% of TB patients are in people living with this coinfection⁵¹.

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 be easily 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 thank 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 therapies¹⁴² 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 ¹⁴³. 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 aggregation and categorisation, which mask substantial variations in medication taking behaviour ¹²⁶, 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 ^{52,111,124}. 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.

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, Stuafter *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 ¹⁴⁴, 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) ¹⁴⁵ 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 ¹¹⁶. 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 ¹⁴⁶. 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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