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The impact of medication adherence on lung health outcomes in cystic fibrosis

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Abstract

Purpose of review—As new medications continue to come to market to improve health in individuals with cystic fibrosis (CF), patient adherence is increasingly more important to address. Currently, adherence for pulmonary medications is approximately 50% for people with CF. There has been recent research that has demonstrated that poor adherence is linked to worse health outcomes. This review summarizes recent research on the impact of adherence on lung health and highlights future areas of research and clinical practice to address this growing need.

Recent findings—Recent research has indicated that nonadherence is associated with increased hospitalizations and pulmonary exacerbations, lower baseline lung function, and longer length of stays. However, most of the research has been done using pharmacy refill records as an objective measure of adherence. Electronic monitoring of medications provides more detailed information about patterns of use, which can directly inform clinical care. Furthermore, there have been few published clinical trials evaluating behavioral interventions to promote adherence.

Summary—Given the recent research linking adherence to lung health outcomes, there is a growing need to measure and evaluate adherence in clinical care. As new medications are approved for CF, methods to monitor adherence also need to be developed and approved. Clinicians need to continue to assess barriers to adherence to be able to individually tailor interventions to a patient's needs.

Keywords

cystic fibrosis; lung health; medication adherence

INTRODUCTION

In the past few years, our knowledge of the impact of medication adherence on lung health outcomes has progressed dramatically. There is greater understanding about the importance of adherence, how to measure it, and which interventions might be effective. We have realized that an expectation for perfect adherence is unrealistic given the complexity and

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time burden of the typical cystic fibrosis (CF) regimen [1]. In fact, objective measures of adherence have indicated that adherence to chronic pulmonary medication ranges between 35 and 75% depending on the drug and person's age [2,3]. This review will focus on current studies examining the impact of adherence on health outcomes in CF as well as methods to help improve medication adherence to improve patients' health.

MEASURES OF MEDICATION NONADHERENCE

In order to best understand the impact of adherence on patients' health and functioning, it is imperative to develop appropriate measures. It is known that patient-reported adherence is consistently higher compared with objectively measured adherence [4,5], suggesting a positive self-report bias. Furthermore, physician assessment of patient adherence is inaccurate and often no better than chance [3]. These limitations of self-report or clinician estimate highlight the importance of objective measures of adherence in order to evaluate treatment efficacy and provide appropriate adherence supports.

There are two primary methods to objectively measure adherence: pharmacy refill records using measures of drug availability [e.g., medication possession ratios (MPR) or continuous medication availability [6,7] or gaps in drug coverage (e.g., gap days [6])] and electronic monitors such as the I-Neb Adaptive Aerosol Device [8]. Given the advent of electronic medical and prescription records, pharmacy refill records are becoming increasingly more available and convenient in assessing adherence. However, these data only measure if the medication was picked up at the pharmacy and does not assess actual drug consumption. Furthermore, the length of time for assessing adherence using refill records may be problematic as many patients obtain 90-day supplies of medications, which requires at least 12 months of data to obtain an appropriate length of time for calculation. This also limits the ability to detect change in adherence using pharmacy refill records because the length of time until a fill is picked up is too long [7].

Electronic monitors have a data logging capability that provides a date/time stamp when medication was administered. This allows patients and clinicians to not only measure overall adherence but also track patterns of medication use. A recent study of 24 adolescents in the UK illustrated that overall medication adherence to nebulized medications was 65±28% [9■■]. However, large variations were identified, with patients having higher adherence during the weekday and school sessions compared with weekends or summer/holiday breaks. This pattern of lower adherence during the summer has also been shown using pharmacy records [10■]. Major limitations in the use of electronic medication monitors are increased cost, many require additional staffing to manage, and many monitors are not yet widely approved for use as or with a drug delivery device. Regardless, electronic devices should continue to be developed and tested, as they provide the most comprehensive adherence information possible.

PREVALENCE OF NONADHERENCE

Medication adherence in CF is approximately 50% but can range from approximately 35–75% depending on the type of measure, medication, and population characteristics. Overall,

research has shown that adherence begins to decline in adolescence [11], with young adults having the lowest adherence [2,10■]. Adolescence is the developmental period when parents begin to shift responsibility of adherence to the adolescent [12], with a complete transfer occurring during young adulthood. Thus, the transfer of responsibility during adolescence is a potential target for intervention during this risk period; however, future research is needed to evaluate the efficacy of such interventions.

IMPACT OF MEDICATION ADHERENCE ON LUNG HEALTH OUTCOMES

The impact of medication adherence on lung health outcomes in patients with CF has only recently been evaluated. Recent studies have indicated that poor adherence to CF medication therapy is associated with longer hospital stays [10■], higher respiratory exacerbation cost [10■], increased hospitalizations [13], increased number of pulmonary exacerbations requiring intravenous (i.v.) antibiotics [2], and lower baseline lung function [2].

A recent study of 95 patients at one CF center evaluated the association of adherence to pulmonary medications and lung health outcomes (lung function and pulmonary exacerbations) [2]. This study utilized pharmacy refill records in the previous 12 months for the following medications: dornase alpha, tobramycin, hypertonic saline, and azithromycin. Using the refill records, an MPR was calculated such that the numerator was the number of days supply medication was dispensed and denominator was the number of days in the study period (365 days – days hospitalized) [6]. MPRs were calculated for each medication, and then averaged together to create a composite MPR score for overall adherence.

Eakin *et al.* [2] found that the composite MPR score significantly predicted courses of i.v. antibiotics in the concurrent 12-month period, such that the group with the lowest adherence (<50%) had the highest probability of having an exacerbation (incidence rate ratio = 2.34, $P = 0.05$), after controlling for disease severity and regimen complexity. Furthermore, medication adherence was associated with baseline lung function (estimate = 29.81, $P = .007$), although it did not predict lung function decline over the 12-month period. Although this study is based on a small sample and retrospective data, this is one of the first studies to demonstrate a link between medication adherence and lung health outcomes in CF. The results of this study need to be further evaluated in a larger prospective national sample with a longer evaluation period to validate these preliminary findings and determine whether adherence impacts lung function decline and other important health outcomes over time.

There have been a few recent studies that utilized the MarketScan database [14] or HealthCore Integrated Research Database (HIRD) to evaluate the impact of refills of particular medications (dornase alpha [10■] and tobramycin [13,15]) on exacerbations, frequency of hospitalizations, and length of stay and costs (Table 1). One study found that the lower adherence to dornase alpha was associated with the longer length of stays in the hospital and higher costs for respiratory exacerbations. However, there was no association between adherence and frequency of exacerbations and, in fact, higher adherence was associated with higher medical costs overall because of the high cost of dornase alpha [10■]. Exacerbations were defined as a medical code for pneumothorax, acute asthma, acute respiratory infection, pneumonia, influenza, acute respiratory failure, or bronchospasm; or

the presence of a pharmacy claim for oral or i.v. antibiotics. Briesacher *et al.* [13] found that higher numbers of tobramycin refills were associated with a decreased risk of hospitalization (adjusted odds ratio 0.40; 95% confidence interval 0.19–0.84), decreased outpatient costs and increased outpatient prescription drug costs. Wertz *et al.* [15] also found that the adherence to tobramycin was associated with lower total costs; in fact CF-related inpatient costs decreased by $1171 (49%; $P = 0.01$) for the group with the highest adherence compared with the group with lowest adherence.

These studies utilized large deidentified databases and focused solely on one medication. This design has several limitations because they are not able to adequately control for disease severity (e.g., lung function, BMI, or other disease characteristics) and cannot examine the impact of overall medication adherence on important clinical outcomes such as lung function. Furthermore, the definition for exacerbations or other clinical events is based on a limited number of billing data elements and may not accurately reflect the full clinical care. Conversely, the benefits of these types of MarketScan databases allow us to examine the association between prescription refills and outcomes on very large representative samples in a more real world setting.

INTERVENTIONS TO IMPROVE MEDICATION ADHERENCE

Given the potential impact nonadherence may have on an individual's overall health and well-being, it is important to begin to identify and implement efficacious interventions to improve adherence. A Cochrane review has illustrated that behavioral interventions are effective in improving medication adherence [16,17]. However, there are few published interventions that have been specifically implemented with patients with CF.

The first step in designing an intervention is to understand that patient's unique barriers to adherence. Recent research has focused on identifying potential barriers and facilitators to adherence in adolescents and young adults with CF [18,19]. There are a variety of barriers to adherence that may include the following: healthcare system factors such as co-pays, delays in prior authorizations, or low access to care; individual factors such as depression, health beliefs about medications, knowledge, time management, and planning; and/or provider factors such as poor patient–provider communication, and unclear treatment planning. In order to provide the most effective interventions, it is important that we appropriately assess each individual's barriers to adherence and tailor interventions for that individual. Recent research from asthma has indicated that the use of tailored self-management interventions resulted in improved health outcomes [20,21]. More research is needed to evaluate the use of individually tailored behavioral interventions to improve medication adherence by systematically addressing barriers in CF.

EMERGING ISSUES IN MEDICATION ADHERENCE

A major barrier to adherence that is often discussed is the treatment burden and time to take these medications [22]. Over time, the time spent each day taking medications has increased for individuals with CF, especially for adults [22]. However, most CF patients also mention that there is an added time burden in working with their insurance payers and pharmacies to

obtain the appropriate prior authorizations and approvals for these specialized medications. Cost containment efforts by payers not including these medications on their formulary lists presents additional burden for patients and providers. Policy efforts are needed to streamline this process to help individuals in efficiently obtaining their medications on a routine basis.

In order for efficacious interventions to improve adherence to have an impact on the overall public health of people with CF, these interventions will need to be able to be readily available to them to address adherence to all aspects of the prescribed regimen. Often behavioral interventions are not designed or evaluated in a setting that is accessible or convenient for many individuals [23]. There is an urgent need for interventions to be designed and evaluated in settings that can be scaled up for implementation at a care center or remotely using technology [24].

CONCLUSION

Medication adherence is suboptimal for people with CF. Recent research has illustrated that low adherence is associated with greater probability of a pulmonary exacerbation, lower baseline lung function, more frequent hospitalizations, and longer hospital stays. However, more research is needed to further delineate the link between adherence and lung health outcomes in larger representative samples with a longer observation period. Previous research has indicated the importance of objective measures of adherence to reduce bias. Currently, most research is relying on the use of pharmacy records as a measure of adherence, but this has methodological limitations. Electronic medication monitors can provide a more real-time sensitive measure of adherence but they are of limited availability for patients and cannot be used for all medications. There is a great need for the development and validation of electronic education monitors for adherence measurement for both research and clinical practice. Behavioral interventions have been shown to be effective in improving adherence; however, very few have been evaluated with people with CF. As we begin to identify the negative impact that nonadherence has on lung health, there will be a need for more concerted effort to develop and evaluate interventions to improve adherence that can be implemented with large patient populations to have the largest public health impact.

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

■■ of outstanding interest

1. Sawicki GS, Sellers DE, Robinson WM. High treatment burden in adults with cystic fibrosis: challenges to disease self-management. J Cyst Fibros. 2009; 8:91–96. [PubMed: 18952504]

2. Eakin MN, Bilderback A, Boyle MP, et al. Longitudinal association between medication adherence and lung health in people with cystic fibrosis. Am J Respir Crit Care Med. 2011; 10:258–264.

3. Daniels T, Goodacre L, Sutton C, et al. Accurate assessment of adherence: self and clinician report versus electronic monitoring of nebulizers. Chest. 2011; 140:425–432. [PubMed: 21330381]

4. Shi L, Liu J, Koleva Y, et al. Concordance of adherence measurement using self-reported adherence questionnaires and medication monitoring devices. Pharmacoeconomics. 2010; 28:1097–1107. [PubMed: 21080735]

5. Krishnan JA, Bender BG, Wamboldt FS, et al. Adherence to inhaled corticosteroids: an ancillary study of the Childhood Asthma Management Program clinical trial. J Allergy Clin Immunol. 2012; 129:112–118. [PubMed: 22104610]

6. Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. J Clin Epidemiol. 1997; 50:105–116. [PubMed: 9048695]

7. 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; 40:1280–1288. [PubMed: 16868217]

8. Geller DE, Kesser KC. The I-neb Adaptive Aerosol Delivery System enhances delivery of alpha1-antitrypsin with controlled inhalation. J Aerosol Med Pulm Drug Deliv. 2010; 23(Suppl 1):S55–S59. [PubMed: 20373910]

9 ■■. Ball R, Southern KW, McCormack P, et al. Adherence to nebulised therapies in adolescents with cystic fibrosis is best on week-days during school term-time. J Cyst Fibros. 2013; 12:440–444. This article uses data from electronic medication monitors to illustrate patterns of adherence that may impact patient care. [PubMed: 23369661]

10 ■. Nasr SZ, Chou W, Villa KF, et al. Adherence to dornase alfa treatment among commercially insured patients with cystic fibrosis. J Med Econ. 2013; 16:801–808. This article utilizes large database to demonstrate an association between adherence to dornase alpha and shorter length of stays. [PubMed: 23506540]

11. Zindani GN, Streetman DD, Streetman DS, Nasr SZ. Adherence to treatment in children and adolescent patients with cystic fibrosis. J Adolesc Health. 2006; 38:13–17. [PubMed: 16387243]

12. Modi AC, Marciel KK, Slater SK, et al. The influence of parental supervision on medical adherence in adolescents with cystic fibrosis: developmental shifts from pre to late adolescence. Children's Healthcare. 2008; 37:78–92.

13. Briesacher BA, Quittner AL, Saiman L, et al. Adherence with tobramycin inhaled solution and healthcare utilization. BMC Pulm Med. 2011; 11:5. [PubMed: 21251275]

14. Hansen, LG., Chang, S. White paper. Ann Arbor, MI: Truven Health Analytics; 2012. Health research data for the real world: The MarketScan databases.

15. Wertz DA, Chang CL, Stephenson JJ, et al. Economic impact of tobramycin in patients with cystic fibrosis in a managed care population. J Med Econ. 2011; 14:759–768. [PubMed: 21942462]

16. Haynes RB, Ackloo E, Sahota N, et al. Interventions for enhancing medication adherence. Cochrane Database Syst Rev. 2008:CD000011. [PubMed: 18425859]

17. Savage E, Beirne PV, Ni CM, et al. Self-management education for cystic fibrosis. Cochrane Database Syst Rev. 2011:CD007641. [PubMed: 21735415]

18. George M, Rand-Giovannetti D, Eakin MN, et al. Perceptions of barriers and facilitators: self-management decisions by older adolescents and adults with CF. J Cyst Fibros. 2010; 9:425–432. [PubMed: 20846910]

19. Bregnballe V, Schiotz PO, Boisen KA, et al. Barriers to adherence in adolescents and young adults with cystic fibrosis: a questionnaire study in young patients and their parents. Patient Prefer Adherence. 2011; 5:507–515. [PubMed: 22114464]

20. Gamble J, Stevenson M, Heaney LG. A study of a multilevel intervention to improve nonadherence in difficult to control asthma. Respir Med. 2011; 105:1308–1315. [PubMed: 21511454]

21. Joseph CL, Ownby DR, Havstad SL, et al. Evaluation of a web-based asthma management intervention program for urban teenagers: reaching the hard to reach. J Adolesc Health. 2013; 52:419–426. [PubMed: 23299008]

22. Sawicki GS, Ren CL, Konstan MW, et al. Treatment complexity in cystic fibrosis: trends over time and associations with site-specific outcomes. J Cyst Fibros. 2013

23. Glasgow RE, Bull SS, Gillette C, et al. Behavior change intervention research in healthcare settings – a review of recent reports with emphasis on external validity. Am J Prev Med. 2002; 23:62–69. [PubMed: 12093425]

24. Glasgow RE, Chambers D. Developing robust, sustainable, implementation systems using rigorous, rapid and relevant science. Clin Transl Sci. 2012; 5:48–55. [PubMed: 22376257]

KEY POINTS

- Adherence to chronic pulmonary medication is approximately 50% among individuals with CF.
- Recent research has demonstrated an association between low medication adherence and an increase probability of pulmonary exacerbations, and increased healthcare utilization and cost.
- Interventions are needed to improve medication adherence to improve patient health and overall quality of life.

Table 1

Use of MarketScan data to examine association between adherence and outcomes

Author	Measure of adherence	Outcome definition	Result
Nasr *et al.* [10■]	MPR of dornase alpha	Exacerbation defined as a medical claim for hemoptysis, pneumothorax, acute asthma, acute respiratory infection, pneumonia, influenza, acute respiratory failure, or bronchospasm; or the presence of a pharmacy claim for oral or intravenous antibiotics	Higher adherence was associated with shorter hospital stays but not associated with lower utilization or cost
		Healthcare costs	
		Hospital length of stay	
Briesacher *et al.* [13]	Number of cycles of inhaled tobramycin solution dispensed	Frequency of hospitalizations	Individuals who were dispensed greater than four cycles of inhaled tobramycin had fewer hospitalizations
		Total healthcare costs	Higher adherence was associated with less outpatient costs but total costs were not different due to the costs of the prescriptions
Wertz *et al.* [15]	Number of cycles of inhaled tobramycin solution dispensed	Healthcare utilization	High adherence was associated with fewer physician visits and hospitalizations
		Total healthcare costs	Increases in prescription costs for high adherent group were offset by reductions in inpatient costs

MPR, medication possession ratio.