Relationship Between Medication Adherence and Health-Related Quality of Life in Subjects With COPD: A Systematic Review

Tamás Ágh MD PhD, Péterné Dömötör MSc, Zoltán Bárfai MD PhD, András Inotai PharmD PhD, Eszter Fujsz MD, and Ágnes Mészáros PharmD PhD

Introduction

Methods
- Literature Search and Eligibility Criteria
- Quality Assessment of the Included Studies

Results
- Search Results
- Methodological Quality
- Medication Adherence and HRQOL

Discussion
- Association Between Medication Adherence and HRQOL
- Future Studies and Recommendations
- Limitations
- Conclusions

BACKGROUND: Various aspects of medication adherence and health-related quality of life (HRQOL) have been studied in subjects with COPD. Nevertheless, little is known about the association between these factors. The aim of this study was to undertake a systematic review of the published literature focusing on the relationship between medication adherence and HRQOL in COPD. METHODS: A systematic literature search of English language articles was conducted in April 2013 using MEDLINE. No publication date limits were defined. All of the included studies were assessed for quality. RESULTS: Seven studies were included in the review. Three of the assessed studies found no correlation, and 3 studies described positive and 2 studies reported negative associations between medication adherence and HRQOL. The results indicate that an improved HRQOL may be a trigger for non-adherence in patients with COPD. CONCLUSIONS: The relationship between medication adherence and HRQOL may be dual. The effect of medication adherence on HRQOL might be a consequence of the effectiveness of therapy and the negative effects (ie, side effects, daily life limitation of therapy, social stigma) that it can generate. HRQOL might also influence the patterns of patients' drug use, as an increased HRQOL might trigger non-adherence. The dynamics between adherence and HRQOL might differ over time, as the negative effects of medication non-adherence might become dominant in the long term. Key words: chronic obstructive pulmonary disease; COPD; medication adherence; medication compliance; quality of life; patient outcome assessment; respiratory therapy. [Respir Care 2015;60(2):297–303. © 2015 Daedalus Enterprises]
Introduction

COPD is a major public health problem. The prevalence of COPD is increasing worldwide, resulting in a substantial economic burden. Medication adherence “refers to the act of conforming to the recommendations made by the provider with respect of timing, dosage and frequency of medication taking.” Medication non-adherence is common in COPD. Non-adherence reduces the clinical benefit of the therapy and accounts for many of the observed differences between the efficacy reported in randomized controlled trials (RCTs) and the effectiveness of the drug treatment achieved in real-world conditions. In RCTs, conditions are highly controlled, and the stringent follow-up protocol limits the occurrence of medication non-adherence; therefore, non-adherence rates derived from RCTs do not reflect an objective picture of medication adherence. Although the average rates of adherence to COPD medication in RCTs have been estimated to be ~70–90%, in real-world conditions, these rates are only in the range of 20–60%. The discontinuation of COPD therapy contributes to the increased frequency of exacerbations, number of hospitalizations, and mortality rate.

COPD impairs the health-related quality of life (HRQOL) markedly; patients experience substantial limitations in their daily life. HRQOL, one of the most important patient-reported outcomes, truly reflects the individual’s self-report on health status and well-being.

Medication adherence and HRQOL are 2 important indicators in determining the success of drug treatments. Although adherence and HRQOL have been studied intensively in COPD, less is known about the association between these factors.

The aim of this research was to undertake a systematic review of the published literature to gain a better understanding of the relationship between medication adherence and HRQOL in patients with COPD. Our hypothesis was that the association between medication adherence and HRQOL is dual. Therefore, the objective of this study was to evaluate not only the effect of medication adherence on HRQOL but also the impact of HRQOL on medication adherence. To our knowledge, no comprehensive review has been published on this topic to date.

Methods

Literature Search and Eligibility Criteria

A systematic literature search was conducted in April 2013 using MEDLINE (via PubMed) with the following search string: (compliance OR adherence OR persistence OR non-compliance OR non-adherence OR non-persistence OR noncompliance OR nonadherence OR nonper-
down of when and for what reason records were excluded from the review.

Five studies were prospective cohort studies, and two cross-sectional studies were also included. The earliest study dated from 1995, and the most recent was published in 2013. The included studies originated from Canada and the United States, Hungary, Japan, The Netherlands, and the United Kingdom. The population size varied between 1,122 and 9,851 subjects, with a mean age of 58 to 76 years. The general characteristics of the reviewed studies are presented in Table 1.

Methodological Quality

The included studies fulfilled the STROBE criteria between 64% and 81%. Details of the quality assessment are provided (see the supplementary materials at http://www.rcjournal.com). The majority of the studies described their scope, study design, settings, participants, variables, and measurements adequately. Hesselink et al were the only authors who did not clearly define the method for measuring adherence. No study provided information on missing data and how they dealt with. All of the reviewed studies described their statistical methods in detail; however, there was only one study that undertook a sensitivity analysis to examine the robustness of the results.

Medication Adherence and HRQOL

Medication adherence was measured in all included studies, but none of these assessed persistence. Medication adherence was analyzed by a self-reported questionnaire, counting the number of unused doses of medication, or an electronic monitoring method. Turner et al and Bosley et al used a self-reported questionnaire and electronic monitoring for measuring adherence simultaneously, but both groups considered the subjects to be adherent based on the results of the electronic monitoring only. Except for the studies conducted by Mochizuki et al and Bosley et al, most studies defined adherence as a dichotomous variable.

The questionnaires used to measure HRQOL differed between the studies. In most studies, a disease-specific instrument was used; only two studies measured generic HRQOL. The disease-specific St George Respiratory Questionnaire was the most commonly used quality-of-life instrument.

The association between adherence and HRQOL was evaluated in all included studies; however, only one study explored the effect of medication adherence on HRQOL, and one explored the impact of HRQOL on adherence. Detailed information on the measurements of adherence and HRQOL, the applied statistical methods, and the results on the association between adherence and HRQOL are summarized in Table 2.

Discussion

A comprehensive review of the relationship between medication adherence and HRQOL in patients with COPD was missing from the literature. Only seven relevant articles were found through our systematic literature search. The findings of the reviewed studies were heterogeneous; nevertheless, some demonstrated that the relationship between medication adherence and HRQOL may be dual and may be affected by multiple factors.

Association Between Medication Adherence and HRQOL

The evidence suggests that, in COPD, non-adherence to medication may not have a clear negative impact on HRQOL. Three studies found no correlation, whereas three studies described positive and two studies reported negative associations between adherence and HRQOL. This heterogeneity might be caused by several factors, such as differences in study design, study popu-
tion, therapy, adherence measurement methods, and HRQOL instruments.

Considering the fact that the different HRQOL questionnaires may assess different aspects of HRQOL, the type of HRQOL questionnaire could significantly influence the association between adherence and HRQOL. In the study conducted by Turner et al,16 3 different HRQOL instruments were used: the Sickness Impact Profile measured the effect of illness on daily functioning, the Profile of Mood States measured feelings and mood, and the Recent Life Changes Questionnaire measured changes in lifestyle. Turner et al16 found no correlation between adherence and HRQOL measured by the Sickness Impact Profile and Profile of Mood States; however, the non-adherent subjects reported significantly higher HRQOL scores on the Recent Life Changes Questionnaire. The number of the included studies was limited, and the types of HRQOL questionnaires were very heterogeneous in these; therefore, HRQOL could be used only in a broad sense to interpret the association between medication adherence and HRQOL. In this broad concept, HRQOL has been defined as the patient’s subjective perception of the impact of the disease and its treatment(s) on daily life, physical/psychological/social functioning, and well-being.19

The effect of medication adherence on HRQOL can be derived from the effectiveness of the pharmacologic therapy and the negative effects that it can generate. Medication adherence improves a patient’s HRQOL by reducing the symptoms, disease progression, and frequency and severity of exacerbations. Aside from the treatment-related side effects, there might be other factors as well by which adherence could impair a patient’s HRQOL, such as a daily life limitation of therapy and the social stigma of using inhalers in public. Patients with moderate-to-severe COPD are generally treated with combination therapy, and most respiratory medications are dosed several times daily. Therefore, COPD treatment regimens might significantly impact a patient’s daily life.17 Patients with COPD are mostly treated with inhalation medication; however, the perceived social stigma associated with using inhalers in public might also affect HRQOL.20

Not only can adherence affect HRQOL, but HRQOL may also impact medication adherence.21 Ágh et al17 found that an improved HRQOL was a trigger for non-adherence in subjects with COPD. They suggested that a patient’s decision to adhere and to what extent is a personal trade-off between the benefits and negative effects of the therapy at any given time, which is consistent with the view of

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Study Design (Follow-Up)</th>
<th>Study Population Characteristics</th>
<th>Medication Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ágh et al17</td>
<td>Hungary</td>
<td>Cross-sectional study</td>
<td>n = 170; mean age, 64 y; 42% male; FEV1, 64% of predicted; GOLD stages I/II/III/IV; 23/52/21/4%</td>
<td>Short-acting and long-acting β agonists, short-acting and long-acting anticholinergics, inhaled corticosteroids, theophylline, combinations</td>
</tr>
<tr>
<td>Bosley et al12</td>
<td>United Kingdom</td>
<td>Prospective cohort (4 wk)</td>
<td>n = 11; mean age, 64 y; 36% male; FEV1 % of predicted, ND; GOLD stages I/II/III/IV, ND</td>
<td>Bronchodilators (all by nebulizer)</td>
</tr>
<tr>
<td>Corden et al13</td>
<td>United Kingdom</td>
<td>Prospective cohort (4 wk)</td>
<td>n = 82; mean age, 65 y; 54% male; FEV1 % of predicted, ND; GOLD stages I/II/III/IV, ND</td>
<td>Short-acting and long-acting β agonists, short-acting anticholinergics, corticosteroids (all by nebulizer)</td>
</tr>
<tr>
<td>Hesselink et al14</td>
<td>The Netherlands</td>
<td>Prospective cohort (2 y)</td>
<td>n = 120 (COPD); mean age, 58 y; 58% male; FEV1, 61% of predicted; GOLD stages I/II/III/IV, ND</td>
<td>Anti-inflammatory agents</td>
</tr>
<tr>
<td>Mochizuki et al15</td>
<td>Japan</td>
<td>Prospective cohort (12 wk)</td>
<td>n = 44; mean age, 76 y; 73% male; FEV1, 55% of predicted; GOLD stages I/II/III/IV, 0/64/36/0%</td>
<td>Transdermal tulobuterol patch, inhaled salmeterol</td>
</tr>
<tr>
<td>Takemura et al18</td>
<td>Japan</td>
<td>Cross-sectional study</td>
<td>n = 55; mean age, 69 y; 73% male; FEV1, 68% of predicted; GOLD stages I/II/III/IV, 24/54/16/1%</td>
<td>Long-acting muscarinic antagonists, short-acting and long-acting β agonists, inhaled corticosteroids</td>
</tr>
<tr>
<td>Turner et al16</td>
<td>Canada, United States</td>
<td>Prospective cohort (1 y)</td>
<td>n = 985; mean age, 61 y; 81% male; FEV1, 41% of predicted; GOLD stages I/II/III/IV, ND</td>
<td>Bronchodilators (all by nebulizer)</td>
</tr>
</tbody>
</table>

GOLD = Global Initiative for Chronic Obstructive Lung Disease
ND = not determined
Bosley et al\textsuperscript{12} that adherence is related to the current health status of the patient and is not dependent on previous experience of illness. The initiation of a pharmacologic therapy in newly diagnosed COPD patients might significantly improve their HRQOL; however, later, this HRQOL improvement due to medical treatment might be smaller and could be detected only in the long term.\textsuperscript{22} Therefore, if patients have previously been treated for longer durations, the benefits from medication non-adherence might temporarily outweigh the effects of the disease deterioration in the short term. The dynamics between adherence and HRQOL might differ over time. The negative effects of a patient’s non-adherence could become more and more significant over a longer time horizon.

Psychiatric disorders such as depression and anxiety are highly prevalent in patients with COPD.\textsuperscript{23} Psychiatric comorbidities influence the relationship between medication adherence and HRQOL. Evidence suggests that depression...
is linked to non-adherence and HRQOL impairment.\textsuperscript{12,24} Therefore, a patient’s psychiatric comorbidity might affect the relationship between these factors.

**Future Studies and Recommendations**

Overall, the methodology of the reviewed studies was not entirely appropriate to evaluate the relationship between adherence and HRQOL in COPD patients; therefore, it would be important to develop recommendations for future studies in this area.

In the long term, evidence from real-world settings could provide more reliable data regarding the association between medication adherence and HRQOL compared with RCTs. Real-world studies assess effectiveness in unselected populations; subjects are under routine care, taking open-label treatment, with no additional visits, allowing an objective assessment of medication adherence. A study in real-world settings, preferably with a minimum of a 1-y study period and regular screening visits (eg, quarterly), would be desirable.

There are a number of ways to measure adherence; nevertheless, there is no accepted standard because each method has its strengths and limitations.\textsuperscript{4} The easiest way to assess adherence is to collect information from the subjects themselves through questionnaires. However, self-reporting methods might overestimate adherence. The retrospective analysis of prescription refill data is rapid and inexpensive but does not provide information on medication intake or inhaler use directly. Pill counting and canister weighing are widely used methods of adherence assessment, especially in clinical trials; pill counting is limited to oral medications, but canister weighing can be used for inhalers as well. These approaches assess only the quantity of the medication removed from the canister without any indication of ingestion or inhalation. Electronic monitoring methods for measuring adherence can provide more objective data about medication use than the aforementioned methods. Pill bottles, inhalers, and nebulizers can all be fitted with electronic recording devices. The evidence suggests that although the underuse of medications seems to be one of the largest problems in the management of COPD, overuse is also common.\textsuperscript{3} To be able to separate and identify both types of medication non-adherence, it would be of great value to define adherence as a categorical variable (ie, full adherer, partial adherer, partial non-adherer, over-user) or a continuous variable instead of as a dichotomous variable (adherent vs non-adherent).

Regarding the assessment of HRQOL, generic and disease-specific instruments may capture complementary information. Disease-specific instruments seem to be more sensitive for the clinical measures of COPD. However, generic questionnaires capture more broad aspects of health but are less sensitive to clinical changes.\textsuperscript{25} For this reason, the optimal situation would be for generic (eg, EQ-5D health questionnaire) and disease-specific (eg, St George Respiratory Questionnaire) measures to be used simultaneously to monitor a patient’s HRQOL.

To understand fully the dynamics of adherence and HRQOL, it would be important to also assess how other factors such as disease symptoms, disease severity, side effects, and the patient’s satisfaction (understanding the social and psychological impact of medical therapy) and psychological status (eg, depressive symptoms, anxiety) influence the nature of their relationship. The evidence suggests that there is only a weak correlation between lung function and HRQOL.\textsuperscript{26} As recommended by the Global Initiative for Chronic Obstructive Lung Disease (http://www.goldcopd.org/uploads/users/files/GOLD_Report_2013-Feb13.pdf, Accessed October 1, 2013), the assessment of disease severity should be based not only on a spirometric assessment but also on the patient-reported outcome instruments (eg, breathlessness measurement using the Modified British Medical Research Council Questionnaire, COPD Assessment Test, Clinical COPD Questionnaire, and Borg scale).

A univariate statistical analysis is important but not sufficient for evaluating the association between medication adherence and HRQOL. Therefore, a univariate analysis needs to be complemented with a multivariate analysis.

**Limitations**

Our findings should be considered in light of the following limitations. Our systematic review identified only studies published in English and in peer-reviewed journals, and our search was limited to MEDLINE. We included studies that evaluated the relationship between medication adherence and HRQOL. However, we acknowledge the importance of oxygen therapy and other non-pharmacologic interventions in COPD, such as physical activity, nutrition, and other lifestyle recommendations. The association between adherence to these interventions and HRQOL would also require evaluation.

**Conclusions**

The association between medication adherence and HRQOL may be dual. The effect of medication adherence on HRQOL might be a consequence of the effectiveness of the therapy and the negative effects (ie, side effects, daily life limitation of therapy, social stigma) that it can generate. In contrast, the level of HRQOL, may also influence the patterns of patients’ drug use; an increased HRQOL may trigger non-adherence. In addition, the dynamics between adherence and HRQOL might differ over time. In the short term, the benefits could be dominant, whereas in the long term, the negative effects of medication non-adherence might become dominant. There is a clear need...
for rigorous research to better understand the dynamics between adherence and HRQOL in COPD. Such data would be critically important for optimal COPD management and should also be considered when integrating medication adherence into health-economic evaluations (eg, adherence interventions).

REFERENCES