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Prospective Impact of Illness Uncertainty on Outcomes in Chronic Lung Disease

Karin F. Hoth, Ph.D.[1,2,3], **Frederick S. Wamboldt, M.D.**[1,2], **Matthew Strand, Ph.D.**[4,5], **Dee W. Ford, M.D., M.S.C.R.**[6], **Robert A. Sandhaus, M.D., Ph.D.**[1,7], **Charlie Strange, M.D.**[6], **David Bekelman, M.D.**[1,8,9], and **Kristen E. Holm, Ph.D., M.P.H.**[1,10]

[1]National Jewish Health, Department of Medicine, Denver, CO, United States

[2]University of Colorado School of Medicine at the Anschutz Medical Campus, Department of Psychiatry, Aurora, CO, United States

[3]University of Colorado School of Medicine at the Anschutz Medical Campus, Department of Neurology, Aurora, CO, United States

[4]National Jewish Health, Division of Biostatistics and Bioinformatics, Denver, CO, United States

[5]Colorado School of Public Health, Department of Biostatistics, Aurora, CO, United States

[6]Medical University of South Carolina, Division of Pulmonary and Critical Care Medicine, Charleston, SC, United States

[7]Clinical Director, Alpha-1 Foundation, Miami, FL, United States

[8]Eastern Colorado Health Care System, Department of Veterans Affairs, Denver, CO, United States

[9]University of Colorado School of Medicine at the Anschutz Medical Campus, Department of Medicine, Aurora, CO, United States

[10]Colorado School of Public Health, Department of Community and Behavioral Health, Aurora, CO, United States

Abstract

Objective—To determine which aspect of illness uncertainty (i.e., ambiguity or complexity) has a stronger association with psychological and clinical outcomes over a two year period among individuals with a genetic subtype of chronic obstructive pulmonary disease (COPD). Ambiguity reflects uncertainty about physical cues and symptoms, and complexity reflects uncertainty about treatment and the medical system.

Methods—407 individuals with alpha-1 antitrypsin deficiency-associated COPD completed questionnaires at baseline, 1- and 2-year follow-up. Uncertainty was measured using the Mishel Uncertainty in Illness Scale. Outcomes were measured using the Hospital Anxiety and Depression Scale, St. George's Respiratory Questionnaire, and MMRC Dyspnea Scale. Ambiguity and complexity were examined as predictors of depressive symptoms, anxiety, quality of life, and breathlessness using linear mixed models adjusting for demographic and health characteristics.

Results—Ambiguity was associated with more depressive symptoms ($b = 0.09$, $SE = 0.02$, $p < 0.001$) and anxiety ($b = 0.13$, $SE = 0.02$, $p < 0.001$), worse quality of life ($b = 0.57$, $SE = 0.10$, $p < 0.001$), and more breathlessness ($b = 0.02$, $SE = 0.006$, $p < 0.001$). Complexity did not have an

Corresponding Author : Karin Hoth, Ph.D. hothk@njhealth.org.

independent effect on any outcome. Interactions between ambiguity and time since diagnosis were not statistically significant.

Conclusions—Ambiguity was prospectively associated with worse mood, quality of life, and breathlessness. Thus, ambiguity should be targeted in psychosocial interventions. Time since diagnosis did not affect the association between ambiguity and outcomes, suggesting that the impact of ambiguity is equally strong throughout the course of COPD.

Keywords

Uncertainty; Mishel Uncertainty in Illness Scale (MUIS); Chronic Obstructive Pulmonary Disease (COPD); Alpha One Antitrypsin Deficiency (AATD)

Perceived uncertainty about current symptoms and future prognosis is an unavoidable part of living with a chronic illness. Uncertainty in Illness Theory states that uncertainty occurs when a person is unable to categorize the meaning of illness-related events, such as having difficulty interpreting their physical symptoms or predicting the likely outcome of treatment (Mishel, 1997). Higher levels of uncertainty have consistently been associated with worse mood and quality of life in chronic illness populations (Bailey, et al., 2009). Most studies have been cross sectional, have not investigated physical symptoms, and have treated uncertainty as a unitary construct. The most frequently-used measure of illness uncertainty has two subscales: 1) *ambiguity*: “cues about the state of the illness are vague and indistinct and tend to blur together and overlap,” and 2) *complexity*: “cues about the treatment and the system of care are multiple, intricate and varied” (Mishel, 1997; pages 8–9). The relative importance of each aspect of uncertainty may differ based on the illness or vary over time. Information about which aspect of uncertainty is most critical in a given situation can be used to tailor psychosocial interventions.

Chronic obstructive pulmonary disease (COPD) is characterized by breathlessness and airflow limitation that is not fully reversible; thus, treatment focuses on managing symptoms and maintaining quality of life. Patients must recognize and appropriately interpret their symptoms to take inhaler medications and seek evaluation for acute exacerbations. The primary known genetic risk factor for COPD is alpha-1 antitrypsin deficiency (AATD). Patients with AATD-associated COPD are clinically similar to patients with non-AATD COPD except they are likely to be younger and may have the option of augmentation therapy. Two studies have previously examined uncertainty in COPD. The first was based on a sample of 26 hospitalized patients (Small & Graydon, 1992, 1993). The second tested an intervention to manage uncertainty (Jiang & He, 2012). The authors found a reduction in uncertainty and improvement in anxiety, depression and quality of life in the intervention group.

The current study examines the relative importance of ambiguity and complexity for outcomes over a two year period in more than 400 patients with AATD-associated COPD. The primary objective was to determine whether ambiguity or complexity has a stronger impact on depressive symptoms, anxiety, quality of life, and breathlessness. A prior study found ambiguity to be more strongly related to negative outcomes in Hepatitis C (Bailey, et al., 2009), and based on this we hypothesized that ambiguity would also be more important in COPD. The secondary objective was to determine whether the impact of ambiguity and complexity differs based on length of time since diagnosis. This objective was exploratory to determine whether uncertainty has more of an impact on outcomes when patients are initially adjusting to illness or whether the impact is greater when patients have lived longer with illness.

Methods

Participants and Procedures

The protocol was approved by the IRBs at National Jewish Health and the Medical University of South Carolina. Data were collected via questionnaires mailed to adult members of the Alpha-1 Foundation Research Registry (Alpha-1 Research Program, 2012) with physician-diagnosed COPD. This study was granted a waiver of informed consent. The overarching aim was to examine social and perceptual factors that affect adjustment in AATD-associated COPD. Baseline questionnaires were mailed to 1727 people and returned by 621 (36%). Follow-up data were collected each year for two years. Individuals were excluded as follows: indicated no COPD (n=22), death (n=27) or lung transplant (n=7) during the study, returned only baseline questionnaire (n=68), and missing data (n=90). To be included individuals needed to have complete data for uncertainty and all covariates and have complete data for one dependent variable at two time points. Responses from 407 individuals were used.

Measures—*Illness uncertainty* at baseline was measured with the Mishel Uncertainty in Illness Scale for Adults (Mishel, 1997). Items are rated on a 5-point scale with higher scores indicating more uncertainty. The *ambiguity* subscale has 16 items that address cues about the state of the illness (e.g., ability to determine whether the illness is getting better or worse). The *complexity* subscale has 12 items that address cues about treatment and the system of care (e.g., purpose of treatment is clear). Cronbach's alpha was 0.88 for ambiguity and 0.79 for complexity.

Symptoms of depression and anxiety were measured at each time point by the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983). Subscale scores for depression and anxiety range from 0 to 21 with higher scores indicating more symptoms. Cronbach's alpha for depression ranged from 0.79 to 0.80 and anxiety ranged from 0.83 to 0.86.

Health-related quality of life (HRQL) was measured at each time point with the St. George's Respiratory Questionnaire (SGRQ; Jones, Quirk, & Baveystock, 1991). The 50 items were summed and weighted to create a total score ranging from 0 to 100, with higher scores indicating worse HRQL. Cronbach's alpha ranged from 0.93 to 0.94.

Breathlessness was measured at each time point by the Modified Medical Research Council Dyspnea Scale (MMRC; Fletcher et al., 1959). This single-item 5-point scale predicts 5-year survival in COPD (Nishimura et al., 2002). A higher score indicates more breathlessness.

Data Analysis

Data were analyzed using linear mixed models (PROC MIXED) in SAS 9.3. These models account for the correlation within participants over time and permit inclusion of participants with partially missing outcome data. 68% of the 407 participants had outcome data at all three time points. Several combinations of random effects for subjects and error covariance structures were compared using the Akaike Information Criterion (AIC). The best overall fit was an UN error covariance structure (which allows the variance at each wave and the covariance between waves to be different) without a random intercept or random time effect. Models were fit using restricted maximum likelihood estimation with a two-sided significance level of 0.05.

For the primary objective, four linear mixed models were fit in which both ambiguity and complexity were included: one to predict depression, one for anxiety, one for HRQL, and one for breathlessness. All models included as covariates the demographic and health

characteristics listed in Table 1, and also included a fixed effect for time. Given that spirometry was not available, oxygen use was included as a proxy for illness severity as long-term oxygen therapy is recommended for patients with severe hypoxemia (Global Initiative for Obstructive Lung Disease, 2011). These models test the independent effect of each component of illness uncertainty, after accounting for the effect of the other component of illness uncertainty and all covariates. These models did not include any interaction terms.

The secondary objective was to determine whether the impact of ambiguity and complexity differ based on length of time since diagnosis. Two diagnoses are relevant: AATD (genetic predisposition identified) and COPD (lung disease diagnosed). For each dependent variable, four models were fit that included an interaction term (total of 16 models). Models included the predictors used above and interactions for: ambiguity x years since AATD diagnosis and x COPD diagnosis, and complexity x years since AATD diagnosis and x COPD diagnosis.

Results

Characteristics of Participants

Individuals who were removed from the sample did not differ from those included on age, gender, relationship status, education, tobacco exposure, oxygen use, or augmentation therapy use ($p>0.05$). The two groups did not differ on complexity, but those who were removed reported more ambiguity ($t_{(df=218)}=2.69$, $p<0.01$). Individuals who were removed reported more depression ($t_{(df=291)}=3.54$, $p<0.001$) and anxiety ($t_{(df=294)}=3.35$, $p=0.001$), worse HRQL ($t_{(df=578)}=2.92$, $p<0.01$), and more breathlessness ($t_{(df=327)}=2.96$, $p<0.01$) at baseline.

Demographic characteristics are presented in Table 1. Regarding uncertainty, the mean baseline ambiguity score was 35.4 (SD=10.5) and complexity score was 25.6 (SD=6.9). The Pearson correlation between ambiguity and complexity was 0.70, indicating 49% shared variance. With regard to outcomes, the sample means were stable over time. Sample means for depression were: 5.2 (SD=3.4), 5.2 (SD=3.4), and 5.3 (SD=3.5), for baseline, year 1 and year 2 respectively. For anxiety the sample means were: 6.2 (SD=3.7), 6.1 (3.9). 5.7 (SD=3.9)]. For HRQL the sample means were: 47.1 (SD=18.5), 45.9 (SD=19.3), and 46.0 (19.7). For breathlessness the sample means were: 2.8 (1.1), 2.8 (1.2). and 2.9 (1.2).

Results of Linear Mixed Models

Ambiguity was a highly significant predictor of all four outcomes ($p<0.001$; Table 2), while complexity was not a significant predictor of any outcome ($p>0.05$). This indicates that ambiguity has a significant effect independent of complexity (and the demographic and health characteristics included). Greater ambiguity was associated with worse outcomes throughout the two-year study. Expanded online materials contain results for all covariates in Table 2.

In all 16 models tested whether the impact of ambiguity and complexity differs by length of time since diagnosis, the interaction term was not significant ($p>0.05$). Thus, years since diagnosis did not moderate the relationships of ambiguity and complexity with outcomes.

Discussion

Uncertainty about physical symptoms (i.e., ambiguity) consistently predicted depression, anxiety, quality of life, and breathlessness over a two-year period among individuals with AATD-associated COPD. In contrast, uncertainty about treatment and the healthcare system (i.e., complexity) did not have an independent effect on any of these outcomes. A direct clinical implication is that interventions designed to minimize distress among individuals

with AATD-associated COPD should focus on coping with uncertainty about physical cues rather than clarifying information about treatment and the healthcare system. This study also examined whether length of time since diagnosis moderates the effect of ambiguity and complexity. Number of years since diagnosis did not have a linear influence on the relationship between the components of uncertainty and outcomes. Results suggest that interventions to address uncertainty are equally important for individuals soon after diagnosis when they are initially adjusting to illness and later when patients have lived longer with their illness.

The relative importance of ambiguity as compared to complexity in COPD may be understandable given the variable course of respiratory symptoms and the need to understand and respond to symptoms to carry out appropriate treatment. If a patient is having difficulty interpreting physical cues, they may be less apt to respond to symptoms by taking their inhaler at appropriate times or by seeking evaluation and treatment for acute exacerbations. Breathlessness is a nonspecific symptom and therefore more open to interpretation than discrete symptoms in other illnesses (e.g., localized pain). In a sample of individuals with COPD, high scores for ambiguity may reflect, in part, that patients do not understand the mechanisms that drive their experience of breathlessness. Many of these mechanisms are not readily observable via routine lung function tests (e.g., dynamic hyperinflation, oxygen desaturation). In this population, it may be important for medical professionals to help patients better understand the multiple causes of breathlessness and strategies that can be used to reduce breathlessness.

Limitations of the current study must be considered. Objective measures of COPD severity were not included; however, oxygen use and AATD genotype were included in all models as proxies of disease severity. The sample was reduced from non-response, and respondents may not represent the entire AATD-associated COPD population. Furthermore, individuals with more ambiguity and worse outcomes were more likely to be excluded. This limited analyses to an investigation of the impact of uncertainty on outcomes among individuals who were relatively well adjusted. The impact of uncertainty on breathlessness was statistically significant, although the clinical significance for any one individual is not clear based on this finding alone. There are likely subgroups of individuals for whom uncertainty does have a clinically significant impact on breathlessness. Future studies should examine individual differences that may moderate the association between uncertainty and outcomes, such as health literacy and negative thinking.

The current study extended prior research by examining the impact of different components of uncertainty on four psychological and clinical outcomes, including the primary physical symptom of COPD (i.e., breathlessness). Outcomes were prospectively measured over a two-year time period and participants were recruited from a nation-wide disease registry that provided access to a large, geographically diverse sample. Due to the wide range in length of time since diagnosis in this sample, it was possible to examine whether the impact of uncertainty on outcomes differs based on length of time since diagnosis.

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Table 1

Demographic and Health Characteristics of the Sample at Baseline (N=407)

Variable	M (SD)	Minimum	Maximum
Age (years)	59.6 (9.5)	32	84
Length of time since AATD diagnosis (years)	12.0 (7.6)	0	39
Length of time since COPD diagnosis (years)	12.1 (7.5)	0	40

Variable	N (%)
Gender (% male)	212 (52.1)
Relationship Status (% coupled)	318 (78.1)
Highest Level of Education Completed	
Grade 12 or less	121 (29.7)
College 1 to 3 years	141 (34.6)
College graduate degree or more	145 (35.6)
Lifetime Tobacco Exposure	
Never Smoked	130 (31.9)
1 to 20 pack years	151 (37.1)
More than 20 pack years	126 (31.0)
Genotype	
Severely deficient	347 (85.3)
(ZZ, SZ, FZ, P-Null, Z-Null, ZPlowell, ZMmalton, and ZMheerlen) Not severely deficient (MZ, MS, M-Null, and SS)	29 (7.1)
Unknown	31 (7.6)
Currently using Oxygen for COPD	203 (49.9)
Has Undergone Augmentation Therapy	323 (79.4)

Note: Pack-years= (average # of cigarette packs per day) × (# of years smoked)

Table 2

Results of Linear Mixed Models for Psychological and Clinical Outcomes of COPD*

	Outcomes			
Predictors	**Depression b (SE), p**	**Anxiety B (SE), p**	**HRQL b (SE), p**	**Breathlessness b (SE), p**
Ambiguity	0.09 (0.02), <0.001	0.13 (0.02), <0.001	0.57 (0.10), <0.001	0.02 (0.006), <0.001
Complexity	0.01 (0.03), 0.636	−0.01 (0.03), 0.713	0.01 (0.15), 0.958	0.003 (0.009), 0.770
Age	−0.02 (0.02), 0.144	−0.08 (0.02), <0.001	−0.26 (0.09), 0.002	−0.01 (0.005), 0.273
Years Since AATD was Diagnosed	−0.005 (0.02), 0.841	−0.03 (0.03), 0.189	−0.07 (0.12), 0.585	0.01 (0.007), 0.277
Years Since COPD was Diagnosed	0.01 (0.02), 0.713	0.03 (0.03), 0.242	0.40 (0.13), 0.002	0.02 (0.007), 0.004
Gender				
Male	Reference	Reference	Reference	Referents
Female	0.01 (0.28), 0.974	0.88 (0.33), 0.007	2.17 (1.53), 0.156	0.07 (0.087), 0.395
Relationship Status				
Single	Reference	Reference	Reference	Reference
Coupled	0.08 (0.34), 0.808	−0.32 (0.38), 0.401	−3.59 (1.80), 0.047	−0.05 (0.103), 0.598
Education	Overall p = 0.042	Overall p = 0.780	Overall p = 0.051	Overall p = 0.169
Grade 12 or less	0.88 (0.35), 0.013	0.20 (0.41), 0.620	4.58 (1.92), 0.018	0.20 (0.109), 0.071
College 1 to 3 years	0.30 (0.33), 0.370	−0.07 (0.38), 0.856	3.05 (1.80), 0.091	0.14 (0.103), 0.172
College graduate or more	Reference	Reference	Reference	Reference
Lifetime Tobacco Exposure	Overall p = 0.122	Overall p = 0.422	Overall p = 0.417	Overall p = 0.107
Never smoked	Reference	Reference	Reference	Reference
1 to 20 pack years	0.65 (0.35), 0.063	0.34 (0.41), 0.398	2.06 (1.90), 0.280	0.18 (0.109), 0.094
More than 20 pack years	0.64 (0.36), 0.077	0.55 (0.42), 0.191	2.47 (1.98), 0.212	0.23 (0.112), 0.044
Genotype	Overall p = 0.024	Overall p = 0.352	Overall p = 0.009	Overall p = 0.008
Severely deficient	Reference	Reference	Reference	Reference
Not severely deficient	1.01 (0.61), 0.098	0.16 (0.70), 0.824	5.83 (3.35), 0.083	−0.31 (0.189), 0.100
Unknown	1.27 (0.52), 0.015	0.87 (0.60), 0.149	7.90 (2.80), 0.005	0.38 (0.162), 0.020
Oxygen Use				
No	Reference	Reference	Reference	Reference
Yes	1.47 (0.29), <0.001	0.14 (0.33), 0.675	12.31 (1.55), <0.001	0.91 (0.089), <0.001
Augmentation Therapy Use				

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	Outcomes			
Predictors	**Depression b (SE), p**	**Anxiety B (SE), p**	**HRQL b (SE), p**	**Breathlessness b (SE), p**
No	Reference	Reference	Reference	Reference
Yes	−0.52 (0.40), 0.198	0.24 (0.47), 0.611	1.95 (2.20), 0.378	−0.12 (0.127), 0.360
Time	Overall p = 0.617	Overall p = 0.017	Overall p = 0.454	Overall p = 0.384
Baseline	−0.10 (0.15), 0.524	0.45 (0.17), 0.008	0.61 (0.65), 0.344	−0.03 (0.047), 0.540
1-year follow-up	0.05 (0.13), 0.708	0.40 (0.17), 0.022	−0.16 (0.51), 0.761	−0.07 (0.048), 0.169
2-year follow-up	Reference	Reference	Reference	Reference

*Note that ambiguity and complexity were entered simultaneously in all four models. All models adjust for age, number of years since AATD was diagnosed, number of years since COPD was diagnosed, gender, relationship status, highest level of education completed, lifetime tobacco exposure, genotype, oxygen use, and augmentation therapy use. All models also include a fixed effect for time (treated as a categorical variable).