Associations between polypharmacy, symptom burden, and quality of life in patients with advanced, life-limiting illness, PI: Schenker

Background and Significance

Polypharmacy, defined by the World Health Organization as "the administration of many drugs at the same time or the administration of an excessive number of drugs," is an increasingly common public health problem. Fifteen percent of all adults in the United States use ≥ 5 prescription drugs.[1] Polypharmacy is associated with poor health outcomes, including medication non-adherence, adverse drug effects, and worse quality of life in elderly population- and primary care-based cohorts.[2,3] Polypharmacy is particularly burdensome near the end of life, as patients "accumulate" medications to treat life-limiting illness and its associated symptoms, prevent age-related diseases, and control non-life threatening comorbidities. In an analysis of medication burden among a cohort of adults with advanced, life-limiting illness, participants took an average of 11.5 (SD 5) medications, and the most commonly-used medications were for primary disease prevention (e.g. anti-hypertensives), not symptom management.[4]

The relationship between polypharmacy, symptom burden, and quality of life among patients with life-limiting illness is of particular concern for several reasons. First, many of the medications used are for preventing diseases which, given patients' remaining life expectancies, may never occur. Second, even medications for secondary prevention may be of limited effectiveness given patients' limited prognoses. Third, many patients have co-morbidities, such as hepatic or renal disease, that increase the risk of medication side effects. Finally, patients near the end of life may be on medications with significant side effects, such as anticholinergics. To date, however, associations between polypharmacy, symptom burden and quality of life in patients with life-limiting illness are not well understood.

The long-term goal of our research is to improve seriously-ill patients' quality of life. The goal of this project is to explore associations between polypharmacy and patient-centered outcomes in a cohort of patients with advanced, life-limiting illness. We will analyze longitudinal data from the Safety and Benefit of Discontinuing Statin Therapy in the Setting of Advanced, Life-Limiting Illness trial.[5] Understanding the relationship between polypharmacy, symptom burden and quality of life is significant because polypharmacy is an increasingly prevalent and *modifiable* risk factor among patients with serious illness. This proposal is highly feasible because we capitalize on an existing PCRC dataset and our research group includes experts in palliative care, health services research, pharmacy, and biostatistics. Our approach is innovative because we include a mediation analysis to explore hypothesized causal relationships between polypharmacy, symptom burden, and quality of life. We propose the following specific aims:

Aim 1. Assess the association between polypharmacy, symptom burden, and quality of life in a cohort of adult patients with advanced, life-limiting illness. Hypothesis: Polypharmacy is associated with higher symptom burden and worse quality of life.

Aim 2. Assess the potential causal effects of symptom burden on the association between polypharmacy and quality of life in patients with advanced, life-limiting illness. Hypothesis: Symptom burden will mediate the effect of polypharmacy on quality of life.

Research Plan

Overview and conceptual framework: This study explores the relationship between polypharmacy, symptom burden, and quality of life in the setting of advanced, life-limiting illness. We will use longitudinal data collected as part of a multi-center, pragmatic clinical trial.[5] Our conceptual model, based on work by Marcum et al,[6] posits that polypharmacy leads to higher symptom burden (related to therapeutic failure/medication non-adherence, adverse drug events, and increased medication side effects), and higher symptom burden in turn leads to worse quality of life.

Sample: The sample includes 381 adult patients with a life-limiting illness (estimated life expectancy between 1 month and 1 year and a recent deterioration in functional status) who were receiving statin therapy at the beginning of the trial. For this analysis, we will include all participants with medication use, quality of life, and symptom burden data available from at least one time point.

Measures: Patient-centered outcomes (including medication use, quality of life, and symptom burden) were measured longitudinally at baseline, 2, 4, 8, 12, 16, 20, and 24 weeks. Consistent with previous analyses,[5] we will create a single variable to quantify polypharmacy at each time point by combining measures of the number of nonstatin medications taken regularly, number of nonstatin medications taken as needed on ≥ 50% of days in the prior week, and number of nonstatin medications taken as needed on <50% of days in the prior week. We will also categorize medications by class and indication (symptom management vs disease management). We will assess quality of life using the McGill Quality of Life Questionnaire (total score range 0-10) and symptom burden using the Edmonton Symptom Assessment Scale (total score range 0-90). Covariates measured at baseline include age, sex, race, ethnicity, education, insurance, primary diagnosis, Charlson Comorbidity Index, performance status, enrollment in hospice, and enrollment in palliative care.

Analysis plan: We will first evaluate the statistical properties of polypharmacy, symptom burden, and quality of life, including potential outliers, distribution, and missing data. We will define polypharmacy groups (low, medium, high) based on distribution of the data. For aim 1, we will compare symptom burden and quality of life by polypharmacy group. We will then fit mixed effect linear regression models to account for clustering effect of observations within the same patient by including a random effect for patient. We will include polypharmacy, randomization group and covariates known to be associated with symptom burden and quality of life as fixed effects. For Aim 2, we will conduct regression-based path analysis to investigate the mediation relationship. We will use the bias-corrected bootstrapping method to test for mediation effects of symptom burden on quality of life. Based on empirical sample sizes estimates in the literature, we should have more than adequate (> 80%) power to identify mediation.[7]

Budget

We request $50,000. This amount will also allow us to (1) support 10% effort for the principal investigator (Dr. Schenker) and 5% effort for our pharmacist (Dr. Pruskowski) and biostatistician (Dr. Park) co-investigators; (2) employ a data analyst (200 hours at $56/hour); (3) allow Dr. Schenker and Dr. Park to meet with PCRC staff in Denver ($2500 for airfare, hotel and incidentals for two); and (4) allow Dr. Schenker to present study findings at one PCRC meeting ($1200 for airfare, hotel and incidentals for one). We have generously allotted 10% time to ensure that Dr. Schenker is able to lead efforts to publish and present these findings.

Timeline

	Q1 (Jul-Sep 2017)	Q2 (Oct-Dec 2017)	Q3 (Jan-Mar 2018)	Q4 (Apr-Jun 2018)
Data use agreement and travel to PCRC	X			
Data analysis		X	X	
Manuscript preparation				X
Presentation of key findings				X
Preparation of future grant proposals				X

References

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