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Psychosocial Determinants Related to Medication Taking Behaviors in Patients with Type II Diabetes

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Abstract

Recent estimates indicate that 21 million US adults live with Type II Diabetes Mellitus (T2DM). The management of the condition often requires patients to take multiple prescription medications to prevent disease progression; yet prescribed regimens themselves can become burdensome. Studies have shown that for patients with T2DM, the average regimen size ranges between four and ten chronic, daily medications. Since individuals with T2DM are also likely to have other comorbid chronic conditions, such as hypertension and hyperlipidemia, self-management can be quite complex.

To achieve the greatest therapeutic benefit from medications, patients with T2DM need to maintain a high level of adherence. This requires sufficient cognitive skills to organize how and when medications are taken in a consistent manner. Thus, the complexity of medication-related tasks can be formidable, arising from the sheer number of medications, the frequency of doses daily each is to be taken, route of administration, and many other facets. As regimen complexity increases, so does the risk a patient may unintentionally misuse a medication leading to harm or inadequate adherence leading to suboptimal treatment benefits. Prior studies have suggested patients with limited health literacy may be particularly at risk of making dosing errors and overcomplicating medication regimens. Most of the evidence to date has studied medication-taking behaviors in hypothetical scenarios, as opposed to examining how patients organize and dose their actual medication regimens. Thus, little is known about how lower health literate, community dwelling adults living with T2DM and other chronic conditions dose their daily medications and the frequency of unintentional dosing errors. Also unknown are which, if any,

demographic or psychosocial factors (e.g., mental health, patient activation, social support) are associated with difficulty managing overly complex dosing patterns.

Nonadherence and unintentional misuse of medications place patients at risk of subtherapeutic benefit and worsened clinical outcomes such as hypoglycemia. Complex regimens are also associated with preventable medication errors that can lead to adverse drug events. Patients with undertreated T2DM are at risk of serious health consequences such as heart attack or stroke. If patients with T2DM are found to have high levels of regimen complexity, then interventions tailored toward simplifying complex regimens or increasing additional support for patients with complex regimens would be an important pathway to reducing preventable negative outcomes. However, very few studies have examined the relationship between robust definitions of regimen complexity and diabetes outcomes.

In this dissertation, I conducted three studies using data collected from two parent studies of community dwelling adults with T2DM taking multiple medications. The first and second studies were conducted among a traditionally underserved population, primarily lower income, Hispanic participants with low health literacy. The first study described the relationship between age and limited English proficiency with regimen knowledge, dosing overcomplication, and dosing errors. The second study examined the association between the previously validated medication regimen complexity index (MRCI) and hemoglobin A1C. Finally, the third study explored the relationship between psychosocial determinants of health with perceived barriers to adherence among patients with polypharmacy.

Results from these studies revealed that one in five patients from traditionally underserved backgrounds overcomplicated the daily dosing of their medication regimens. Larger regimen size

was associated with increased risk of dosing overcomplication and worse regimen knowledge, while limited English proficiency was associated with increased risk of dosing errors. Regimen complexity, as measured by the MRCI across the entire medication regimen, was associated with higher A1C. Among patients contending with multimorbidity and polypharmacy, depression, poor health activation, and low levels of social support predicted increased barriers of adherence.

In summary, patients with multimorbidity and polypharmacy contend with significant skill-based and psychosocial barriers affecting their adherence and control of their diabetes. For interventions aimed at improving adherence and outcomes among complex patients to be effective, opportunities should be sought in clinical practice to routinely monitor how patients actually take their multi-drug regimens to ensure safe use, as well as to be aware of certain risk factors that may also adversely distract from proper dosing.

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Andrea Russell

List of Abbreviations

A1C	Glycated hemoglobin
ASK-12	Adherence Starts with Knowledge – 12
CHAI	Consumer Health Activation Index
CI	Confidence Interval
FQHC	Federally Qualified Health Center
GEE	Generalized Estimating Equations
GED	General Educational Development
HMO	Health Maintenance Organization
HS	High School
LEP	Limited English Proficiency
LS	Least Squares
M	Mean
MRCI	Medication Regimen Complexity Index
PROMIS	Patient-Reported Outcomes Measurement Information Service
REMIND	Regimen Education and Messaging in Diabetes
RR	Risk Ratio
SD	Standard Deviation
SDH	Social Determinants of Health
T2DM	Type 2 Diabetes Mellitus
US	United States

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A. Significance

1. The Challenges of Type II Diabetes Self-Management

According to the Centers for Disease Control (2017), 21 million Americans are currently diagnosed with Type II Diabetes Mellitus (T2DM). Patients with T2DM contend with highly challenging and complex self-care behaviors to optimally manage their condition. Many patients are required to make significant changes to longstanding habits regarding diet and physical activity as well as reducing unhealthy behaviors, such as tobacco and alcohol use. At the same time, patients are often tasked with daily monitoring of blood sugar, calculating the appropriate amount of insulin based on self-monitoring, and correctly dosing multiple diabetes-specific medications. In addition to T2DM challenges, multimorbidity is common, with as many as 86% of adults with T2DM diagnosed with at least two comorbid chronic conditions (Iglay et al., 2016).

The burden of T2DM and comorbid conditions is substantial, and successful self-management requires consequential time, energy, and daily vigilance. Thus, many patients encounter barriers when attempting to meet self-care demands resulting in nonadherence. Specifically, regarding medications, rates of adherence among patients with T2DM are highly variable but often low; studies have reported prevalence ranging between 38-93% for oral diabetes medications (Krass et al., 2015). Poor medication adherence in T2DM is associated with worse glycemic control, more frequent emergency department visits, more hospitalizations, and higher medical costs (Capoccia et al., 2016).

Prescription regimen size and complexity is a well-studied risk factor for nonadherence. In a large study conducted among commercially insured adults newly diagnosed with T2DM, the

mean number of medications taken by patients was 8.4 and about 52% were considered to have regimens of moderate or high complexity (Iglay et al., 2016). In a recent systematic review, polypharmacy was identified as a major risk factor for adverse events and medication-related problems leading to hospitalization (Al Hamid et al., 2014). Additionally, vulnerable patients (e.g., older adults, patients with depression or low health literacy) and traditionally underserved populations (e.g., lower income, Spanish-speaking) are at greater risk of nonadherence and negative outcomes (Bailey et al., 2014; Fan et al., 2016; Fernandez et al., 2017; Kirkman et al., 2015; O'Conor et al., 2018; Polonsky & Henry, 2016; Wroe, 2002). *Multimorbidity and complex drug regimens are barriers to management of T2DM, and traditionally marginalized patients are at increased risk of nonadherence and negative outcomes.*

2. Potentially Modifiable Barriers to Adequate Diabetes Self-Care

One key potentially modifiable factor associated with outcomes among patients with T2DM is unintentional nonadherence. Poor quality patient-provider communication regarding how patients should take medications, and variability in specificity of information, have been linked to poor adherence (Brundisini et al., 2015; Wolf et al., 2016). Patients with lower levels of knowledge about medication purposes, instructions, and how to prevent complications often experience challenges, especially with changing medication or upon onset of new problems (Brundisini et al., 2015). Studies have shown as many as half of adults misunderstand one or more instructions or warnings for how to safely take their medications (Davis et al., 2006; Wolf et al., 2006). In these scenarios where patients have naïve or inaccurate understanding of their regimens, there is a greater risk of missing doses or making medication errors.

Medication administration challenges due to complex regimens and inconsistent daily routines also have causal implications to nonadherence (Brundisini et al., 2015). Organizing medication schedules requires a significant amount of attention and skill, and patients often report forgetfulness, confusion and difficulty differentiating medications in the context of polypharmacy (Antoine et al., 2014; Nelson et al., 2018). Patients with complex regimens encounter challenges related to frequently changing prescriptions as well as concerns about drug interactions, side effects, and adverse events resulting from dosing errors (Bernhard et al., 2017; Russell et al., 2018). Highly variable daily routines and life disruption, which disproportionately affect patients with lower socioeconomic position, impair patients' ability to adhere to medication regimens (Brundisini et al., 2015). *Confusion about how to take medication, complex regimens and inconsistency in daily routines contribute to nonadherence to medication in patients with T2DM.*

3. Defining Medication Regimen Complexity

There are multiple attributes of medications regimens which contribute to complexity. The simplest definition of complexity is regimen size – how many prescribed medications an individual is expected to take on a routine basis. Beyond size, numerous studies among patients with T2DM have found that more frequent dosing (e.g., once vs twice daily) is associated with worse adherence for both oral route and injectable anti-diabetic agents (Dezii et al., 2002; Paes et al., 1997). Studies have also shown that patients have stronger preference for and better adherence to oral anti-diabetic medications compared to injectables (Balkrishnan et al., 2003; Cramer, 2004; Curkendall et al., 2013; Dibonaventura et al., 2010). Many T2DM patients, especially those with limited health literacy, have difficulty understanding the way instructions

for use are transcribed by pharmacies (Singh et al., 2018) and implementing simpler, patient-centered drug labels has been shown to increase proper medication use (Wolf et al., 2016).

The Medication Regimen Complexity Index (MRCI) quantifies complexity across the domains of regimen size, dosing frequency, route of administration, and auxiliary instructions into a single score (Hirsch et al., 2014). Studies have shown utilizing the MRCI can capture regimen complexity to a greater detail compared to regimen size alone. For instance, one study found that compared to patients with poorly managed hypertension, patients with poorly managed T2DM had the same mean number of medications but higher MRCI (Rettig et al., 2013). Utilizing the MRCI to measure regimen complexity offers a more robust estimate of complexity than any domain on its own.

A small number of studies have examined the relationship between MRCI and T2DM outcomes, finding that high diabetes-specific MRCI predicts glycemic control (Ayele et al., 2019; Yeh et al., 2017). However, the relationship between MRCI in the full regimen with glycemic control has been mixed. As other studies have demonstrated that patients with multimorbidity and polypharmacy have worse clinical outcomes compared to patients with fewer chronic conditions (McCoy et al., 2020), more knowledge is needed regarding how MRCI is associated with outcomes. *Medication regimen complexity as measured by the MRCI is a robust indicator of complexity, and preliminary findings suggest it is associated with worse glycemic control among patients with T2DM.*

4. Psychosocial Predictors of Barriers to Adherence in the Context of Polypharmacy

There is a large body of research on the individual and medication-related factors which influence adherence among patients with chronic illness (Gellad et al., 2011). Despite the knowledge gained to date, there are gaps worth attention.

Most research to date explores these factors in the context of a single disease state or class of medications (Kim et al., 2018), whereas less is known about the transdiagnostic factors which influence adherence in patients with polypharmacy. This is problematic as patients with multiple chronic conditions may have different needs or experiences arising from the formidable challenges associated with multi-drug regimens compared to patients with fewer chronic conditions. Knowledge about the specific challenges of this population will facilitate development of interventions targeting improvement of adherence in patients with polypharmacy.

Recent studies exploring modifiable barriers to adherence in the context of regimen complexity and polypharmacy have focused on regimen-based predictors of adherence (Smaje et al., 2018; Ulley et al., 2019; Yap et al., 2016) as opposed to psychosocial barriers. While it is crucial to understand and intervene at the level of the medication regimen, it is possible that adjustments to the regimen may not be sufficient if there are psychosocial barriers which influence patient adherence.

Experts have recommended that studies on adherence in adults with polypharmacy should explore adherence as a "complex, holistic process" with a focus on the specific challenges of multimorbidity and polypharmacy (Granata et al., 2020). Focus group data among small samples has identified common barriers to adherence among older adults with multimorbidity

which include knowledge about medications, beliefs about medication effectiveness, beliefs about the consequences of non-adherence, anxiety, physical limitations, limited self-efficacy, environmental challenges, limited resources, lack of specific goals, cognitive barriers, limited social support, and lack of routine (Patton et al., 2018). There are few studies to date, to our knowledge, which examine the relationship between sociodemographic and psychosocial factors with perceived barriers to adherence among patients contending with polypharmacy. *Certain patient characteristics, sociodemographic traits, and psychosocial factors reduce patient capacity to manage medications, and patients with these attributes and polypharmacy could be at high risk of having barriers to adherence.*

5. Conceptual Framework

The conceptual framework supporting Papers 1, 2 & 3 are informed by the Model of Medication Self-Management proposed by Bailey and colleagues (Bailey et al., 2013) illustrated in **Figure 1**, and the functional, patient-centered framework of Cumulative Complexity (Shippee et al., 2012) depicted in **Figure 2.** Across Papers 1, 2, & 3, medication taking behavior will be conceptualized as part of the patient workload of demands. In Paper 1, I will focus on how patients organize their medications as a form of self-care, specifically examining the prevalence of over-complicated daily medication dosing schedules among patients with low health literacy and limited English proficiency. In Paper 2, I will examine if medication regimen complexity, an aspect of the patient workload of demands, leads to worse clinical outcomes. I hypothesize that high regimen complexity will lead to poorer glycemic control among patients with T2DM.

With Paper 3, I will perform analyses testing if select patient, cognitive, and psychosocial factors as elements of patient capacity are associated with self-reported barriers to adherence among patients with polypharmacy, T2DM, and co-existing conditions.

6. Summary

Over-complication of daily medication dosing schedules in patients with T2DM places patients at risk of unintentional nonadherence and poor clinical outcomes. Regimen over-complication, defined as taking medications more than four discrete times per day, has been understudied among vulnerable populations with racial or ethnic minority status, limited health literacy, low patient activation, and depressive symptoms. Examining the prevalence of over-complication and its impact on patient outcomes is worthwhile given that it is a potentially modifiable treatment factor.

B. Studies

Study 1. Regimen consolidation, knowledge, and dosing errors: the role of age, limited English proficiency, and regimen complexity

a. Introduction

Multi-drug regimens are increasingly common, with data showing that in the past 30 years the number of US adults taking multi-drug regimens (i.e., three or more medications) has roughly doubled across most age groups (American Academy of Actuaries, 2018; Centers for Disease Control 2018). With greater regimen complexity, proper medication use becomes more challenging. While the burden of treatment can make it difficult to remember to take medications

or find the most efficient daily dosing schedule to simplify medication-taking behaviors, added complexity may arise from the health system, through the manner in which patients are given adequate guidance to understand how to administer medications, be aware of benefits and risks, and how to optimally organize daily schedules (Bailey et al., 2013).

Complicated and variable medication use instructions are one of the health systems factors which have causal implications to poorer treatment understanding, medication scheduling and dosing (Guilcher et al., 2019; Russell et al., 2018). Research over the past two decades has highlighted that as many as half of adults may have inadequate understanding of their prescribed medications (Davis et al., 2006). Patients with limited health literacy and limited English proficiency are at heightened risk of misunderstanding medication information and making dosing errors (Bailey et al., 2012; Harris et al., 2017; Leyva et al., 2005; Masland et al., 2011).

Despite substantial evidence finding greater complexity of a prescribed medication regimen is difficult for patients, little is known about how patients actually take medications. As studies have shown limited English proficiency (Harris et al., 2017), older age (Bailey et al., 2020), and limited health literacy (Davis et al., 2006; Harris et al., 2017; Smith et al., 2015; Wolf et al., 2011) were associated with hypothetical overcomplication of medication dosing in an experimental setting, it is possible that overcomplication of actual regimens is a pathway through which regimen complexity influences outcomes. Only one study has reported on rates of dosing schedule overcomplication using patients' actual regimens, (Lindquist et al., 2014) finding that among a sample of primarily White, community-dwelling seniors with high education attainment, almost half overcomplicated the dosing schedule of their own medication regimens.

A better understanding of dosing challenges could guide health system interventions in how to help ensure patients are 'onboarded' to treatment and their dosing habits continually monitored.

This study is unique in that data on medication taking behavior was taken from a primarily Hispanic, majority Spanish-speaking, and predominantly limited health literacy sample of community-dwelling adults. We sought to fill these gaps in the research by: (1) describing medication regimens and real-world medication dosing behaviors, and (2) examine which, if any, sociodemographic or medication-related factors are associated with regimen consolidation, medication knowledge, and dosing errors.

b. Methods

Design and Sample. This secondary analysis used data from a clinical trial examining electronic health record enabled interventions intended to support safe and effective prescription drug use. Study participants were recruited from two Federally Qualified Health Centers (FQHCs), representing eleven clinical practices in Chicago, IL. Patients were eligible for the study if they were 21 years of age or older, diagnosed with T2DM, spoke English or Spanish, owned a cell phone with text message capabilities, took at least three chronic prescription medications, and were responsible for administering their own medication. Patients with visual, auditory, or cognitive impairments were excluded. Prior to data collection, approval for this study was obtained from the Northwestern University Institutional Review Board. Data collection occurred between February 2015 and December 2016.

Recruitment and Procedure. Prior to the study, letters were mailed to potentially eligible patients informing them about the study and allowing them to opt-out of being called for screening. Trained bilingual research assistants called potentially eligible patients, obtained verbal consent,

and confirmed patient eligibility. Interviews for primarily Spanish speaking participants were conducted in Spanish.

The trial was cluster-randomized at the level of the provider, such that patients whose care was managed by intervention-randomized physicians automatically received the intervention. Weekly chart reviews identified consented patients whose new medication or change in prescription triggered the receipt of the intervention materials (intervention group only) and the scheduling of the baseline interview (all participants). Medication instructions and materials were available in English and Spanish. The current analyses utilized data collected at a baseline telephone interview conducted one week after patient filled a study-related medication.

Measures. Baseline structured interviews also collected sociodemographic information including sex, race, ethnicity, primary language, education level, and income. Age and limited English proficiency were the primary independent variables. English proficiency was determined with the question, “How would you describe your ability to speak and understand English?” Participants who responded with *very poor, poor,* or *fair* were categorized has having limited English proficiency.

In addition, a medication regimen complexity score was determined for all participants prescription medications using the Medication Regimen Complexity Index (MRCI) developed by George and colleagues (George et al., 2004). The MRCI is a validated instrument that combines three components of complexity into a single score: (1) dose form, (2) frequency of dosing, and (3) administration instructions. Higher MRCI scores indicate greater regimen complexity.

Consolidated regimens were determined based on the number of distinct times the patient reported taking medication in a typical day. Regimen consolidation was examined as a continuous variable as well as a dichotomous variable, where four or fewer times per day was considered "consolidated" (Wolf et al., 2011).

Knowledge about medications was examined using questionnaire methods used by Wolf and colleagues in previous research (Wolf et al., 2005; Wolf et al., 2004; Wolf et al., 2011). Patients were asked to identify information for each of their medications from three categories: purpose, side-effects, and auxiliary instructions. Auxiliary instructions referred to warnings or restrictions on how to take the medicine, such as with food or drink. Each correct answer earned one point, with the maximum earnable points being three per medication. To be considered correct, the answer was required to be consistent with medication information content reviewed by pharmacists and medical doctors, including an endocrinologist, prior to the start of the study. For each participant, a knowledge percentage was obtained for each variable by dividing the number of correct answers by the number of medications in the patients' regimen. Individual participant percentages were averaged to describe the overall level of knowledge of all participants in the study.

Dosing errors were determined by comparing the instructions on each of the patients' prescription labels to their typical use for each of their medications. For each medication in the patients' regimen, errors were categorized as: dosing errors (incorrect number of pills in a single dose), frequency errors (incorrect times per day) or spacing errors (insufficient number of hours between doses). Each error earned one point toward a sum score of errors across the regimen,

with three being the maximum number of errors for an individual medication. Sum scores were examined as frequencies as well as converted to a binary outcome described as "any error."

Analysis. Descriptive statistics are reported for each sociodemographic variable, relevant covariates, and medication-related information. First, parametric and non-parametric tests were used as appropriate to examine the associations between sociodemographic variables and covariates with independent variables (age and English proficiency). Spearman correlations were used to examine the association between regimen complexity (number of chronic medications and MRCI score) and dosing schedules. Then, unadjusted models were conducted to examine the association between each independent variable predicting each dependent variable. Multivariate models controlled for sex, race/ethnicity, education, regimen size, and treatment arm. Generalized linear regression models specifying a Poisson distribution were used for count outcomes and logistic regression was used for binary outcomes. Generalized Estimating Equations (GEEs) using a Poisson distribution and log link were conducted for outcome variables repeated per participant to account for within-participant correlation. Risk ratios were calculated and reported for relevant outcomes to support data interpretation and reduce the likelihood of overestimating risk (Davis, 2002; McNutt et al., 2003; Zou, 2004). Analyses were performed using STATA version 16.1.

c. Results

A summary of participant characteristics is available in Table I. The sample was comprised of middle aged and older adults (mean age=56.8, SD=9.5, range: 32-81) and about one third were male (34.2%). Participants were diverse in terms of race and ethnicity, with the majority being Hispanic/Latino (73.4%) or Black (17.5%). Over half of study participants (59.0%) were

classified has having limited English proficiency and 89.0% participants had limited health literacy. Health insurance coverage was variable and included participants with government sponsored plans (Medicare+Medicaid: 11.7%, Medicare only: 17.8%, Medicaid only: 24.4%), private insurance (11.0%) or no insurance (35.0%). Almost half of the sample earned less than a high school degree (49.0%) and most had low income.

Compared to younger adults, participants aged 60 and older were more likely to have lower educational attainment ($p<.01$), Medicare insurance ($p<.001$), and larger medication regimens ($p<.001$). Participants with limited English proficiency were more likely to be Hispanic/Latino ($p<.001$), have lower income ($p=.04$), be uninsured ($p<.001$), and take smaller medication regimens ($p=.001$) compared to participants who were proficient in English.

Regimen Characteristics and Consolidation. Overall, participants reported taking 6.5 chronic pill-form prescription medications (SD=3.12, range: 2-26). Two thirds of participants (n=294) reported taking prescription medications on an as needed schedule (e.g., for pain) or in a non-pill (e.g., inhaler) form (mean=2.2, SD=1.34, range:1-8). More than half of participants (n=283) reported regularly taking over the counter medicines (mean= 2.0, SD=1.42, range:1-8). The average prescription medication regimen complexity score was 21.4 (SD=11.30, range: 6-83.5). Both regimen size, $\rho=0.35$ ($p<.001$) and MRCI score, $\rho=0.36$ ($p<.001$) were associated with more frequent dosing of medications.

Out of all 2,235 chronic pill-form medications participants reported, two-thirds were instructed to be taken once daily (64.3%) and about a third (27.6%) were prescribed twice daily. Variable medication instructions (e.g., “Take 1 capsule by mouth on day 1 then 1 capsule by mouth twice a day on day 2”) represented 1.9% of medication instructions. Three times daily

instructions (3.0%) or four times daily instructions (0.3%) were uncommon. At the regimen level, study participants (N=441) were prescribed all once daily (n=56), once and twice daily (n=311), up to three times daily (n=53) and four times daily (n=21). Participants demonstrated dosing medications an average of 3.2 times per day (SD=1.50, range: 1-9). **Figure 3** illustrates how three different patients, each with a 12 drug regimen, dosed their medications.

In unadjusted analyses (Table II), regimen size of between six and eight medications (RR=1.30, 95% CI:1.13-1.50, p<.001) and nine or more medications (RR=1.49, 95% CI:1.29-1.72, p<.001) was associated with more frequent dosing compared to smaller regimens. After controlling for covariates, the relationship between regimen size and dosing frequency was maintained in the adjusted models (6-8 medications: RR=1.31, 95% CI:1.13-1.52, p<.001; 9+ medications: RR=1.51, 95% CI: 1.30-1.76, p<.001).

Despite that only 1.6% of participants (n=7) were prescribed a medication instructed to be taken four times per day, nearly 20% of participants (n=76) dosed medication five or more times per day. No sociodemographic factors were associated with regimen consolidation in unadjusted or adjusted analyses. Additionally, larger regimen size predicted increased likelihood of poorly consolidated regimens for participants taking between six and eight medications and nine or more medications in both unadjusted (6-8 medications: RR= 1.30, 95% CI:1.13-1.50, p<.001; 9+ medications: RR=1.49, 95% CI: 1.29-1.72, p<.001) and adjusted analyses (6-8 medications: RR=1.31, 95% CI: 1.13-1.52, p<.001; 9+ medications: RR=1.51, 95% CI: 1.30-1.76, p<.001).

Medication Knowledge. On average, participants were able to correctly identify the purpose of 64.3% of the medications in their regimen, 21.4% of side effects, and 13.4% of

auxiliary instructions. Unadjusted analyses of sociodemographic data with knowledge (Table III) revealed adults with less than a high school degree (RR=0.81, CI: 0.71-0.94, p=.04), and those taking nine or more medications (RR=0.83, 95% CI: 0.71-0.97, p<.001) had worse knowledge of medications.

In multivariable analyses, lower education (RR=0.82, 95% CI: 0.70-0.96, p<.01) and regimen size of nine or more medications (RR=0.81, 95% CI: 0.68-0.94, p<.001) represented independent, statistically significant predictors of medication knowledge when compared to adults with higher education or fewer medications. Neither older age nor limited English proficiency were associated with medication knowledge.

Dosing Errors. Overall, participants made 0.9 dosing errors (SD=1.25, range=0-9) and 48.1% of participants (n=217) made one or more dosing errors. Among participants who made errors, two thirds (65.0%) made a spacing error, almost half (46.5%) made frequency errors, and a third (32.7%) made dosing errors.

Limited English proficiency was a significant predictor of increased risk of making any dosing error in both unadjusted (RR=1.30, 95% CI: 1.07-1.58, p=02) and multivariable models (RR=1.57, 95% CI: 1.19-2.08, p<.01). No other sociodemographic variables or covariates were associated with risk of dosing errors.

d. Discussion

This is the first study to our knowledge that examines demonstrated daily dosing schedules using patients' actual regimens among adults from traditionally marginalized groups. In this unique sample with large representation of Hispanic/Latinx, Spanish-speaking patients the majority of

whom had limited health literacy, results indicated that patients taking more medications were more likely to overcomplicate dosing by taking medications more times per day than necessary. Adults with less than a high school degree and those with larger regimens had worse knowledge of medications compared to those with higher educational attainment and patients with smaller regimens. In addition, limited English proficiency was the only examined variable independently and significantly associated with an increased risk of making a dosing error.

While nearly all participants' medication regimens in this study consisted of medications to be taken no more than three times a day, one in five participants reported daily dosing schedules of five or more times per day. Considering how regimen complexity increases with age and declining functional health status, higher daily dosing schedules may place patients at greater risk of unintentional nonadherence and worse clinical outcomes. It is well known that patient adherence to medication improves when instructions specify the medication be dosed fewer times per day (Coleman et al., 2012; Srivastava et al., 2013), however nearly all the research in this area focuses on how medicines are instructed to be taken rather than how patients understand, interpret instructions, and ultimately dose their medications.

Larger regimen size was associated with worse knowledge about medications with regards to indication, side effect profile, and specific instructions for safe use. It is logical patients with more medications have more confusion about the details of each medication. This often stems from providers missing opportunities to counsel patients and poorly written materials providing supplementary education (Wali et al., 2016). Given the high risk of poor outcomes among patients with multidrug regimens, emphasis must be placed on providing adequate medication information to high risk patients. Health systems and providers are increasingly

seeking solutions to improve patient education, which are especially needed for patients with multi-drug regimens.

Another major finding of this research was that patients with LEP had smaller regimens but were more likely to demonstrate dosing errors compared to participants more proficient in English. Existing literature has demonstrated lack of bilingual providers, inadequate verbal interpreters, or poor written translation services are key factors which reduce patient understanding of medications (Bailey et al., 2009; Davis et al., 2019; Mutchler et al., 2007). However, even when language concordant labels and resources are available, health disparities persist (Fernández et al., 2017). One possibility is that translating prescription instructions is not enough and enhancing prescription instructions from both a cultural and health literate perspective is needed. Supporting this hypothesis is research which has shown enhanced, language concordant medication instructions improve prescription understanding, dosing, and regimen consolidation among patients with limited English proficiency (Bailey et al., 2012).

These findings have implications for clinical practice. Given the brevity of ambulatory care visits, regimen overcomplication is likely to go unnoticed (Shaw et al., 2014). Considering these findings, patients with large regimens may benefit from providers discussing how patients are dosing medications to see if the dosing schedule can be simplified. Resources for reviewing older adults' complex regimens currently exist. For instance, medication therapy management, which is available from most major health insurers and Medicare part D, provides annual medication regimen review to patients with multimorbidity. These programs have been associated with reduction in mortality, rates of hospitalization and stable medication cost (Hui et al., 2014; Welch et al., 2009), but have historically been underutilized (Rucker, 2012). Future

research should explore whether these programs reduce the complexity of actual medication dosing behavior and examine if more frequent dosing schedules are related to medication adherence.

This study had several limitations warranting discussion. First and most notably, data used in this analysis was taken from an interventional study designed to improve medication knowledge and promote regimen consolidation. Second, health literacy has been shown to be a major determinant of regimen consolidation in previous literature; in our sample, nearly all participants had limited health literacy and thus limited our ability to account for this factor. Relatedly, the sociodemographic traits of this diverse sample limit generalizability in terms of national population estimates. Whereas other studies examining regimen consolidation have used methods to objectively assess whether regimens could be consolidated, such as through medical provider review of regimens, we used only general benchmarks to define consolidation. However, our estimates of regimen consolidation in this case would skew toward conservative and supporting this benchmark is the consensus in medicine that most medication regimens can be consolidated into four or fewer doses per day. Lastly, participants demonstrated dosing was based on self-report of how they usually take their medications, and while these dosing methods have been based on prior work in many similar investigations, patients may not be accurate reporters.

e. Conclusions

These findings indicate that poorly consolidated regimens are relatively common, as approximately 20% of adults from traditionally underserved backgrounds reported dosing medication five or more times per day. This highlights the importance of assessing not only how

adults with multi-drug regimens are instructed to take medicine, but how adults with multi-drug regimens actually schedule the dosing of their prescription regimens as part of the medication self-management continuum. Patients with limited health literacy, from traditionally underserved backgrounds, and those with limited English proficiency may be the most likely to benefit from this review. As these services exist but are typically underutilized, efforts to expand or support uptake of these services may benefit community-dwelling adults.

Study 2. Moving from disease silos to multimorbidity: the impact of full regimen complexity on glycemic control

a. Introduction

Nearly 86% of adults with type II diabetes mellitus (T2DM) are diagnosed with at least two comorbid chronic conditions (Iglay et al., 2016). As medications are often a first line treatment of chronic disease, with increasing morbidity brings increasing likelihood of patients requiring multi-drug regimens. Studies have shown that for patients with T2DM, the average regimen size ranges between four and ten chronic, daily medications (Odegard & Capoccia, 2007). Research has consistently shown that larger regimens, increased dosing frequency (i.e., twice daily vs once daily), varied routes of administration (i.e., inhalers, injections), and additional instructions (i.e., take with food) are associated with poorer clinical outcomes among patients with chronic illness (Coleman et al., 2012). This is no exception for patients with T2DM, who commonly cite regimen complexity as a barrier to their self-management (Odegard & Capoccia, 2007).

For patients with multiple chronic conditions including T2DM, the ability to successfully manage their medications increases the likelihood of achieving better control of their chronic illnesses overall and glycemic control specifically, measured by hemoglobin A1C. Some studies have found that higher diabetes-specific medication regimen complexity predicts higher A1C levels in US populations (Yeh et al., 2017), and some non-US populations (Abdelaziz & Sadek, 2019; Ayele et al., 2019). Yet these studies have not found a relationship between regimen complexity using the entire regimen, including prescribed medications taken to manage other conditions. As patients with T2DM from traditionally underserved backgrounds, such as adults belonging to racial/ethnic minority communities and those with limited English proficiency, have

disproportionately worse clinical outcomes (Lanting et al., 2005), it is critical that research examines the impact of regimen complexity on outcomes among this population. To our knowledge no studies have found an association between overall medication regimen complexity and increased A1C, and few examine this association among diverse US populations.

The primary aim of this study was to describe medication regimen complexity of a diverse group of US adults with T2DM as well as other chronic conditions and who were taking at least three medications. We specifically sought to examine if higher regimen complexity, as measured by the medication regimen complexity index (MRCI), was associated with poorer A1C in an underserved, primarily Hispanic, low health literate, and majority Spanish-speaking population of adults with T2DM and multi-drug regimens.

b. Methods

Design and Sample. This secondary data analysis used data from a clinical trial examining electronic health record embedded interventions intended to support safe and effective prescription drug use. Study participants were recruited from two Federally Qualified Health Centers (FQHCs), representing eleven clinical practices in Chicago, IL. Patients were eligible for the study if they were 30 years of age or older, diagnosed with T2DM, spoke English or Spanish, owned a cell phone with text message capabilities, took at least three chronic prescription medications, and were responsible for administering their own medication. Patients with visual, auditory, or cognitive impairments were excluded. Prior to data collection, approval for this study was obtained from the Northwestern University Institutional Review Board. Data collection occurred between February 2015 and December 2016.

Recruitment and Procedure. Prior to the study, letters were mailed to potentially eligible patients informing them about the study and allowing them to opt-out of being called for screening. Trained bilingual research assistants called potentially eligible patients, obtained verbal consent, and confirmed patient eligibility. Interviews for primarily Spanish speaking participants were conducted in Spanish.

The trial was cluster-randomized at the level of the provider, such that patients whose care was managed by intervention-randomized physicians automatically received the intervention. Weekly chart reviews identified consented patients whose new medication or change in prescription triggered the receipt of the intervention materials (intervention group only) and the scheduling of the baseline interview (all participants). Medication instructions and materials were available in English and Spanish. The current analyses utilized data collected at a baseline telephone interview conducted one week after consented patients filled a study-related medication.

Measures. The primary independent variable of medication regimen complexity was calculated based on participants' daily prescription medication regimen. Regimen complexity was measured using the Medication Regimen Complexity Index (MRCI) developed by George and colleagues (George et al., 2004). The MRCI is a validated instrument that combines three components of complexity into a single score: (1) dose form, (2) frequency of dosing, and (3) administration instructions. Higher MRCI scores indicate greater regimen complexity. In this analysis, MRCI score was divided into four quartiles based on the data distribution. A score of less than 14 was considered low, 14-18.4 was moderate-low, 18.5-26 was moderate-high, and greater than 26 was high. These categorizations are like other studies finding the average MRCI

score among solid organ transplant patients was 18, and such patients are generally considered to have high regimen complexity (Przytula et al., 2014).

Baseline structured interviews collected sociodemographic information. Participants were classified has having limited English proficiency if they responded to the question "How would you describe your ability to speak and understand English?" with *very poor, poor,* or *fair.* Limited health literacy was determined using the brief subjective health literacy screener (Chew et al., 2004). Participants who answered *somewhat, a little bit, or not at all* to the question "How confident are you filling out forms by yourself" were classified as having limited health literacy. Frequency of medical visits was included in the model as an additional indicator of health status. This was assessed by participant self-report of the number of times they were seen by any outpatient provider in the last six months. Intervention arm was included as a control variable.

Hemoglobin A1C (A1C) was the outcome of interest. The closest A1C value available from six months prior or six months after the baseline interview was abstracted from the medical record.

Analysis. Descriptive statistics were calculated and reported for sociodemographic variables and covariates. Bivariate analyses examined the association between sociodemographic characteristics (age, sex, race/ethnicity, income, education, limited English proficiency, health literacy), regimen complexity, and other covariates with A1C. Associations identified as statistically significant ($p<0.05$) in the bivariate analyses and relevant covariates were included in the multivariable model. While significant, income was excluded from the multivariable model due to concern for over-adjustment. Linear regression was utilized for both the bivariate

and multivariable analyses. Standardized beta coefficients are presented. Analyses were performed using STATA version 16.1.

c. Results

Sample demographics and characteristics are available in Table IV. The average age of the 441 participants was 56.9 (SD=9.4) and most were female (65.8%). Most of the sample was Hispanic (73.4%), followed by non-Hispanic black (17.5%), and other (9.1%). The sample was diverse with respect to education, with about half of participants receiving less than a high school degree (5^{th} grade or lower: 13.6%; 6-8^{th} grade: 23.2%; 9-11^{th} grade: 11.3%). Most of the participants were low income, with only 11.8% earning more than $30,000 per year. Many participants had no insurance (35.0%) while others had Medicaid (24.4%), Medicare (17.8%), a combination of Medicare and Medicaid (11.7), or private insurance (11.0%). Most participants had limited English proficiency (59%). Participants described their health as good (32.9%), fair (50.9), or poor (16.2%).

Regimen Characteristics and Complexity. Participants took, on average, 7.80 (SD=3.53) medications. Among all the study participants, 5.9% (n=26) were taking no anti-diabetic medications, 29.5% (n=130) were taking one, 37.0% (n=163) were taking two, and 27.6% (n=122) were taking three or more. Nearly half of participants (n=205) were prescribed at least one injectable insulin.

The average prescription regimen MRCI score was 21.4 (SD=11.3, range: 6-83.5). Sample participant regimens and their associated MRCI score are available in Figure 4.

Hemoglobin A1C. Overall, clinical outcome data was available for 93.4% of participants (n=412) and the average A1C of the sample was 8.15 (SD: 1.96). About one third (35%) of

participants had an A1C of 8.5 or greater. There were no sociodemographic characteristics associated with likelihood of missing data.

Bivariate analyses revealed greater MRCI score was associated with higher A1C (<14: 7.66, SD=1.67; 14-18.4: 2.11, SD=2.11; 18.5-26: 8.43, SD=2.16; >26: 8.16 (1.69). More frequent medical visits within a six month period were associated with lower A1C (p=.04) while younger age (p<.01), male sex (p=.001), higher income (p<.01), and insurance type (p=.001) was associated with higher A1C.

In multivariable analyses controlling for study arm, participants with higher MRCI scores had higher A1C (MRCI quartiles: 14-18.4: β=-.244, p<.001; 18.5-26: β=-.246, p<.001; >26: β=-.278, p<.001). When compared to participants with one visit in the last six months, participants attending five or more visits in the same timeframe were more likely to have lower A1C (β=-.162, p=.01). There remained a statistically significant difference in A1C based on insurance type. Lower A1C was observed in participants with government insurance, including Medicare+Medicaid (β=-.180, p=.003), Medicare alone (β=-.204, p=.001), or Medicaid alone (β=-.165, p=.008), compared to participants with self-pay or no insurance. Male sex (β=-.153, p=.003), remained an independent predictor of higher A1C. We tested for interactions, but these were not significant.

d. Discussion

We sought to understand the association between the Medication Regimen Complexity Index and hemoglobin A1C among a traditionally underserved sample of community-dwelling adults contending with type 2 diabetes. Participants in this study were primarily Hispanic, over half had limited English proficiency and nearly all had low health literacy and low

socioeconomic status. Our results indicated greater MRCI, fewer outpatient healthcare visits, male sex, and insurance type were independently associated with poorer hemoglobin A1C.

This is the first study to our knowledge to link higher full regimen MRCI score to higher A1C, but two prior studies found no association (Ayele et al., 2019) or an inverse association (Yeh et al., 2017). The latter was a study among 365 primarily Hispanic patients from one FQHC in Napa, California. In the study, while higher diabetes-specific MRCI was associated with worse A1C control, higher full regimen MRCI was significantly associated with better A1C control. The authors of the study hypothesized this unexpected finding may have been related to the effect of non-diabetic agents, commonly prescribed to patients with T2DM, on blood sugar levels. Our study supports the opposite conclusion, therefore future studies should seek to replicate these findings.

Our findings add support to literature suggesting that medication regimen complexity irrespective of condition is associated with health outcomes. A systematic review and meta-analysis from 2018 found evidence that higher MRCI score was associated with medication adherence, adverse drug events, emergency department visits, hospitalization, readmission, and mortality (Alves-Conceição et al., 2018). To date there is little evidence for disease-specific outcomes and full regimen MRCI score, though there was one study conducted among patients with chronic obstructive pulmonary disease which found higher full regimen MRCI was associated with more frequent disease exacerbations, higher patient-reported symptom frequency, and poorer walking ability (Negewo et al., 2017). Additionally, among older adults in a residential care facility, full regimen MRCI was associated with more frailty and dementia severity (Chen et al., 2019). Appreciating the full burden of treatment faced by patients may

better convey the risk for inadequate medication adherence or self-management capacity, a call which has been echoed by researchers studying medication regimen complexity (Linnebur et al., 2014).

In this analysis, a threshold effect was observed between MRCI and A1C, such that a score of 14 or more was associated with higher A1C and the magnitude of the effect was relatively consistent across the upper quartiles. The original validation of the MRCI did not include clinically meaningful cutoffs, therefore studies analyzing the MRCI categorically have created their own definitions of low, moderate, or high complexity using sample distributions. Thus, there is considerable variability due to heterogeneity between studies. A few studies have presented data supporting MRCI clinical cutoffs for other disease characteristics (Ferreira et al., 2015) and hospital readmission (Olson et al., 2014; Willson et al., 2014), but none have been published to our knowledge regarding clinical outcomes.

These findings have important clinical implications. Research consistently shows that simplifying regimens when clinically appropriate improves self-management in terms of medication adherence (Elnaem et al., 2020). Thus, clinicians may wish to consider factoring in dosing frequency, route of administration, and administration instructions in the benefit/risk calculation when caring for patients with complex regimens. For patients with high regimen complexity where the ability to simplify regimens is not possible, additional interventions may be needed to support chronic disease self-management. Periodic assessments from pharmacists may also promote medication reconciliation, particularly for patients who may see multiple specialists or whose providers are affiliated with multiple health systems. The MRCI score would also have utility if it could be readily calculated for review by clinicians. Practically, the

MRCI takes between two and eight minutes for an independent rater to calculate, which would not fit into busy clinic workflows. One study successfully leveraged their existing electronic health record to automate the calculation of MRCI score (McDonald et al., 2013), making using the tool a more realistic option for providers.

An unexpected finding emerging from this data was more frequent outpatient visits was associated with better A1C, though this is consistent with research highlighting that regular outpatient primary care follow-up is associated with fewer emergency department visits and hospitalizations (Rose et al., 2019). Previous studies have shown that patients with higher levels of health activation have better health outcomes, therefore one possibility is these patients had higher levels of activation. Alternatively, it is possible that patients were previously at risk and have been more closely monitored by their healthcare system.

Limited English proficiency was also not found to be associated with blood sugar control. While these findings have been demonstrated in the literature previously (Brown et al., 2005; Pérez-Stable et al., 1997; Tocher & Larson, 1998), researchers have also found that patients with LEP had improved glycemic control when transitioning from language discordant providers to language concordant providers (Parker et al., 2017). Our findings could be a reflection on the capability of Chicago-area FQHCs which are designed to treat low income and Hispanic populations by providing culturally competent care.

This study had limitations. We chose to identify regimen consolidation as taking medications four or fewer discrete times per day as this is a simple cutoff grounded in clinically meaningful standards. However, it is possible this underestimates the frequency of overcomplicating regimen dosing by taking medications more times per day than necessary (i.e., a patient taking

medications three times per day when they could consolidate as twice daily). The generalizability of our study is limited given this population was comprised of mostly Hispanic, Spanish speaking patients with low socioeconomic status and health literacy. However, these populations are often under-represented in research. As this study examined a single clinical outcome, other clinical outcomes important to primary care populations such as blood pressure control and cholesterol were not examined. Additionally, hypoglycemia has been increasingly targeted as a major outcome of interest among patients with T2DM, but this data was not collected as part of our study. Given that the parent dataset included a trial which intervened at the level of prescription instructions, the intervention could have influenced the findings. The likelihood this strongly influenced our results is low as the fidelity of the intervention was limited and our multivariable models controlled for intervention arm.

As noted above, future research should seek to consolidate different cutoffs recommendations into a more global or clinically meaningful manner. A large study, among sociodemographic and clinically diverse patients with multimorbidity examining multiple health outcomes would be helpful to characterize an overall, clinically meaningful MRCI threshold. In addition, it may be useful to compare the MRCI to other measures of regimen complexity to further characterize the tools validity.

e. Conclusion

Higher full regimen MRCI and more frequent outpatient healthcare utilization were independently associated with poorer hemoglobin A1C among a sample of primarily Spanish-speaking, Hispanic adults in Chicago, IL. Interventions to simplify both diabetic and nondiabetic medications may improve A1C. Medication regimen complexity, as measured by the MRCI,

could be used as a tool to identify patients who could benefit from additional support with medication taking behavior, such as meeting with pharmacists.

Study 3. Barriers to adherence among patients with multimorbidity and polypharmacy

a. Introduction

The prevalence of middle aged and older adults living with multiple chronic conditions has steadily risen over the past decades, with most recent estimates indicating 47% of adults aged 45-64 and 77% of adults 65 and over have at least three chronic conditions (King et al., 2018). Patients with multiple chronic conditions contend with formidable self-management roles including communication with insurers or providers, attending frequent medical appointments, managing complex medication regimens, and engaging in healthy behavior change (e.g., smoking cessation, weight loss, improved nutrition).

As medications are often the first line treatment of chronic conditions, polypharmacy has increased alongside multimorbidity. According to the most common definition of polypharmacy (i.e., taking five or more chronic medications), between 1999 and 2012 the prevalence of middle age and older adults with polypharmacy has nearly doubled from 8% to 15% (Kantor et al., 2015). Adherence to multi-drug regimens can be challenging, and prior studies have cited approximately half of individuals with any chronic condition demonstrate taking less than 80% of their treatment as prescribed (World Health Organization, 2003).

While there is ample research on medication adherence, most studies investigating barriers to adherence have focused on a specific chronic condition or treatment whereas fewer explore adherence in the context of polypharmacy from a transdiagnostic perspective. Clinicians and researchers have documented the drawbacks to viewing chronic diseases in silos. There is a concern that results based on single chronic conditions are not always generalizable (Fortin et al.,

2006) and clinical guidelines based on one disease are insufficient to optimally treat patients with multimorbidity (Wallace et al., 2015).

In this study, we sought to explore psychosocial factors associated with barriers to adherence among a cohort of middle age and older adults contending with multiple chronic conditions and subsequent polypharmacy.

b. Methods

Design and Sample. This secondary data analysis used data collected from the ongoing Regimen Education and Messaging in Diabetes (REMinD) study launched in January 2018. The REMIND study is a large clinical trial examining electronic health record enabled interventions intended to support safe and effective prescription drug use. Study participants were recruited from two health centers, the General Internal Medicine clinics at Northwestern Memorial HealthCare in Chicago, IL, and Mt. Sinai Medical Center in New York, New York. Patients were eligible for the study if they were 21 years of age or older, diagnosed with T2DM, spoke English or Spanish, owned a cell phone with text message capabilities, took at least five chronic prescription medications, and were responsible for administering their own medication. Patients with visual, auditory, or cognitive impairments were excluded. This research was reviewed and approved by the institutional review boards at Northwestern University and Mt. Sinai Medical Center.

Recruitment and Procedure. The trial was cluster-randomized at the level of the provider, such that patients whose care was managed by intervention-randomized physicians automatically received the intervention. Weekly chart reviews identified consented patients who were potentially eligible for the study. Trained research assistants called potentially eligible

patients, obtained verbal consent, and confirmed patient eligibility. This study uses data collected at a baseline in-person interview, conducted one week after the participant filled their study-related medication.

Measures. Sociodemographic and health-related factors including age, sex, race, ethnicity, income, education, health status, and number of chronic conditions were collected. Depressive symptoms were measured using the 4-item Patient-Reported Outcomes Measurement Information Service (PROMIS) Short Form for Depression (Cella et al., 2010). Higher scores indicate greater symptom severity. The sum score on the measure is converted into a t-score. The t-scores categorize the severity of depression as follows: none to slight (less than 55), mild (55.0-59.9), moderate (60.0-69.9) and severe (70 or over). Previous research has identified T-scores 60 and over are associated with clinically meaningful depressive symptoms (Choi et al., 2014), and for this analysis, the variable was collapsed into two categories, none-mild (less than 59.9) and clinically significant.

Health activation was measured using the Consumer Health Activation Index (CHAI), a measure specialized for use among diverse populations (Wolf et al., 2018). Scores for each item are summed with a possible range of 0-100. Higher scores indicate higher patient activation, and established categories label patients as having low (0-79), moderate (80-94), or high (95-100) activation.

Health literacy was assessed with the Newest Vital Sign, a health literacy screener validated for use in primary health care populations (Weiss et al., 2005). The measure consists of six questions about a nutrition label, which require individuals to use literacy and numeracy skills. Each correct answer earns one point. The total score ranges between 0-6, with individuals

categorized as having likely limited (0-2), possibly limited (3-4) or adequate health literacy (5-6).

A brief, validated scale was used to measure adequacy of social support (Woloshin et al., 1997). The scale consists of two questions: (1) “In the last 6 months, have you needed any kind of extra help at home because your health kept you from taking care of yourself or doing what you usually do?” and (2) [If yes] “Of the help you got at home, would you say you got: all you needed, most you needed, some you needed, only a little, or none of the help you needed?” Participants who reported they needed no additional help or reported receiving sufficient help (i.e., all or most of the help needed) were classified as having adequate social support.

Self-report of regimen adherence was measured using the Adherence Starts with Knowledge 12-item questionnaire which assesses an individuals’ perceived barriers to adherence in domains of beliefs, behaviors, and forgetfulness using a Likert scale response option (Matza et al., 2009). Higher scores suggest greater difficulties with adherence. Participants were characterized as perceiving the item as a barrier if they answered in the top 40% of the scale (i.e., answered “agree” or “strongly agree” to item 1).

Analysis. Descriptive statistics were calculated for all variables as appropriate. Bivariate analyses using one-way ANOVA evaluated associations between all covariates and the outcome of barriers to adherence. Covariates that were statistically significant in bivariate analyses were then included in multivariable generalized linear models. Results were presented as Least-Square means (LSM) with 95% confidence intervals (CIs). Analyses were performed using STATA version 16.1.

c. Results

Sample characteristics are available in Table VII. Overall, 585 participants were enrolled in Chicago, IL (n=308) and New York, NY (n=277).. The average age was 61.7 years (SD=10.6) and most participants were female (n=353). There was considerable racial and ethnic diversity, with a similar percentage of Caucasian (n=267) and African-American participants (n=265) as well as 31.8% of the sample identifying as Hispanic. A third of the sample achieved less than a high school degree (n=113) or a high school degree/GED (n=100). Nearly half of the sample reported earning less than $20,000 per year.

Approximately one in five participants reported having limited social support (n=109) and a similar percentage had clinically meaningful depressive symptoms (n=105). About two-thirds of participants had limited health literacy (n=397) and patient activation levels in the low (n=311) or moderate (n=228) range. Most participants rated their health as good (n=238) or fair (n=217). On average, participants were taking 11.0 (SD=4.9) medications daily.

Barriers to Adherence. One fifth (20.0%, n=117) of patients endorsed having no barriers to adherence, whereas 25.0% reported one and 55.0% cited having two or more barriers (see Table VIII). The most reported adherence issues were forgetting doses (n=235) and taking medicines more than once per day (n=216). Participants also frequently cited not having their medicine with them (n=158), lack of timely refills (n=117), and taking medication differently than prescribed (n=125) as barriers. Cost issues, uncollaborative relationships with providers and stopping medications due to perceived lack of benefit were the least reported concerns by participants.

In bivariate analyses (shown in Table IX), older age (p<.001), higher income (p<.01), adequate social support (p<.001), clinically meaningful depression (p<.001), and higher patient activation (<.001) were associated with fewer barriers to adherence.

In multivariable analyses (Table X) controlling for age, sex, race, ethnicity, number of chronic conditions, and health status, we found that social support, depression, and level of patient activation were independently associated with barriers to adherence. Participants with greater social support had fewer barriers to adherence (Adequate: LSM=24.0, 95% CI: 23.5, 24.5 vs Limited: LSM=25.5, 95% CI: 24.4, 26.6). Those endorsing symptoms consistent with clinically meaningful depression had more barriers (Depression: LSM=26.0, 95% CI: 24.9, 27.1 vs Minimal Depression: LSM=23.9, 95% CI: 23.4, 24.4). Lower levels of patient activation were linked to higher barriers to adherence (Low: LSM=25.9, 95% CI: 25.3, 26.5 vs High: LSM=21.4, 95% CI: 19.8, 23.0).

d. Discussion

Among middle age and older adults, all with diabetes among other chronic conditions, and contending with formidable polypharmacy, adherence barriers were highly prevalent. Those who were more depressed, less activated, and with inadequate social support were at greater risk of having more regimen adherence concerns. Income and health literacy were not associated with adherence in multivariable models, and the relationship between education and barriers to adherence were mixed.

In our sample, depressive symptoms affected one in five participants and clinical levels of depression were associated with worse adherence, which has been demonstrated in prior systematic reviews and meta-analyses (Choi & Smaldone, 2018; Gonzalez et al., 2008). Reviews

have identified a moderate association between depression and some self-care behaviors (i.e., appointment attendance, medication adherence) and experts have hypothesized that the underlying features which drive the association are the clinical features of depression including social withdrawal, disengagement from important activities, avoidance, lack of energy, and negative future expectations. Research has shown that treating depression in the context of chronic health issues results in small but significant improvements in glycemic control, likely in part result to improved medication adherence (van der Feltz-Cornelis et al., 2021). More qualitative research is needed to explore how depression may present differently in patients with multimorbidity and polypharmacy as opposed to patients with comparatively higher health status, in order to inform psychological treatment in these settings.

Most participants in this study endorsed having low to moderate health activation, which was associated with more barriers to adherence, whereas there was no association with health literacy. One possible reason for an unobserved relationship is that we had a sample with relatively high educational attainment. However, prior studies have been mixed with regards to the association between health literacy and medication adherence (Berkman et al., 2011; Miller, 2016). Nonetheless, it may impart that educational interventions are not warranted, as these would be expected to increase understanding but not engagement (Hibbard, 2017). Multifaceted interventions are needed that help patients clarify their priorities, address motivation, and regimen fatigue due to sustained exposure to polypharmacy if they are expected to improve outcomes among patients with low health activation. These programs have been shown to be acceptable among older patients with multiple chronic conditions (Feder et al., 2019).

We found that limited social support was associated with more barriers to adherence. Past research has shown that social support, particularly functional support consisting of practical assistance, is associated with medication adherence in general medical populations (Magrin et al., 2015; Scheurer et al., 2012) and among patients with polypharmacy (Lozano-Hernández et al., 2020). Social support is considered a protective factor in the presence or lack of stressors (Cohen & Wills, 1985; Ford et al., 1998). It has been hypothesized to improve adherence by aligning the patients' emotions, attitude, and mindset with adaptive health behavior (Berkman, 1984; Maeda et al., 2013; Shumaker & Hill, 1991; Wallston et al., 1983), accountability (Lewis & Rook, 1999; Umberson, 1987), and through receipt of tangible assistance (Berkman, 1984; DiMatteo, 2004). Functional support through practical assistance for the patient with polypharmacy may involve transportation (e.g., driving patients to appointments, picking up medication from the pharmacy), informational support (e.g., participating in care coordination, communicating symptoms with providers between appointments), medication support (e.g., organizing medications in the pillbox, reminding patients to take medication), healthy lifestyle choices (e.g., cooking healthy meals, going on walks), or medical support (e.g., changing dressings). Inadequate social support may influence adherence through stress (Revicki & May, 1985), and patients with multimorbidity and contending with formidable self-management challenges may be at heightened risk. In such cases, connecting patients with resources such as home health, psychotherapy, and financial aid may be necessary to reduce adherence barriers.

Despite longstanding data supporting socioeconomic factors as a prominent social determinant of health among patients with T2DM (Hill-Briggs et al., 2020), there was no meaningful relationship between income or education with barriers to adherence in this study.

These findings are like the results of a systematic review examining patient factors associated with anti-diabetic medications (Krass et al., 2015). Key findings included that of nine studies assessing education and adherence, eight found no association and one found a negative association. Among studies assessing socioeconomic status, three found no association, two found a negative association, and one found a positive association with adherence. These data suggest that adherence is likely not the primary pathway through which low income affects health outcomes, despite that some providers have biases regarding the compliance of patients with lower incomes (van Ryn & Burke, 2000; Woo et al., 2004).

This study had limitations. It was cross-sectional so we are unable to explore how our variables may change over time. Similarly, we cannot infer causality between regimen complexity and A1C values. Our study was conducted in two urban settings, so while diverse in terms of income, race, and ethnicity, these findings may not be generalizable to smaller cities or rural areas. We examined adherence with one subjective measure as objective measures of adherence were not available in the existing dataset. However, we were unable to find another study examining adherence to medications using the ASK-12 in patients with T2DM, therefore this is a significant contribution to the literature. The ASK-12 is also limited in that there are no well-established clinically meaningful cutoffs or units of meaningful difference, therefore the ability to translate these findings for practical use in clinical settings is difficult. We were not able to look at the relationship between psychosocial determinants and more intermediary clinical outcomes such as A1C. Lastly, this data was collected from an interventional study intended to promote adherence among patients receiving the intervention. It is possible that

patients receiving the intervention endorsed fewer barriers to adherence, though we controlled for study arm in the multivariable models.

Future research should seek to replicate these findings using other established measures of patient activation and medication adherence. Moving forward primary care practices should seek ways to routinely monitor adherence among those patients with more complex regimens. Brief depression screeners, like the Patient Health Questionnaire-2, are already routinely administered and tracked in the medical record. Applying this model to health activation and social support needs could further promote case finding and intervention.

e. Conclusions

In a sample of community dwelling adults with type II diabetes taking five or more chronic medications, clinical levels of depressive symptoms, low patient activation, and low levels of social support were associated with increased barriers to adherence. Historically, individually tailored interventions have shown to improve adherence and outcomes for patients with depression and low health activation. As patients with polypharmacy endorse contending with multiple barriers to adherence, interventions may need to be multifaceted to obtain the greatest benefit.

C. Discussion

1. Summary of Findings

a. Study 1 Aim and Hypotheses

Study 1 described the actual medication dosing behaviors of a diverse sample of Hispanic, Spanish-speaking adults with limited health literacy and examined the sociodemographic or medication-related factors associated with regimen consolidation, medication knowledge, and dosing errors. It was hypothesized that older patients and those with limited English proficiency would have worse knowledge of medications, more frequent dosing errors, and have less consolidated regimens.

b. Study 1 Findings

Although only 21 out of 441 participants were prescribed a medication instructed to be taken 4 times per day, nearly 20% of participants had consolidated regimens sub optimally, defined as having dosed their regimen 5 or more times a day. Intuitively, individuals taking more medications had more daily doses. Neither age nor English proficiency were independently associated with unconsolidated regimens.

Overall, knowledge was variable in the sample, with participants on average being able to name the purpose of 65% of their medications, 21% of associated side effects, and 13% of auxiliary or special instructions. Adults with less than a high school degree and those with larger regimens had worse knowledge of medications. Again, English proficiency and age were not independently associated with regimen knowledge in multivariable models.

Limited English proficiency was the only examined variable that was significantly associated with demonstrated dosing errors.

c. Study 2 Aim and Hypotheses

The aim of Study 2 was to characterize medication regimen complexity among a diverse group of US adults with T2DM. It was hypothesized that greater regimen complexity, measured by the medication regimen complexity index, would be associated with poorer hemoglobin A1C.

d. Study 2 Findings

Study participants took an average of 7.8 medications. The majority (94%) were taking at least one anti-diabetic agent, and about half were prescribed at least one injectable insulin. The average MRCI score was 21.4 (SD=11.3, range: 6-83.5). The average A1C of the sample was 8.15 (SD=1.96) and about a third (35%) of participants had an A1C of 8.5 or greater. Our results indicated greater MRCI, fewer outpatient healthcare visits, male sex, and insurance type were independently associated with poorer hemoglobin A1C.

e. Study 3 Aim

The aim of Study 3 was to explore psychosocial factors associated with barriers to adherence among a cohort of middle age and older adults contending with multiple chronic conditions and subsequent polypharmacy.

f. Study 3 Findings

In our sample of 585 adults with T2DM, multimorbidity and polypharmacy, most participants (80%) endorsed having at least one barrier to adherence and 20% cited having four or more barriers. Forgetfulness and having medications that needed to be taken more than once daily were the most cited barriers. Issues of medication cost, poor patient-provider alliance, and perceptions of medication ineffectiveness were endorsed infrequently relative to the other items.

Clinically significant depression, low health activation, and poor social support were all associated with barriers to adherence when controlling for covariates.

2. Overall Discussion of Findings

This dissertation examined the relationship between sociodemographic and medication regimen characteristics with patient outcomes among high risk and traditionally underserved adults with T2DM, multimorbidity, and polypharmacy. Complex medication regimens in this population are common and these patients experience a significant burden of overcomplicated dosing schedules, depression, poor social support, and limited health activation. These factors were observed to influence a range of outcomes including knowledge, dosing error frequency, and glycemic control.

Although the burden of regimen complexity is well known, the ways in which patients may further complicate their regimens through poorly consolidated dosing systems is less well understood. One of the most novel findings was that 20% of participants may have unnecessarily and possibly unknowingly overcomplicated their medication regimens. For patients taking injectable insulin therapies, or other non-pill medications for other chronic conditions, the level of complexity is even greater. The way patients take medications at home is not well understood as it is rarely assessed, therefore providers may not be aware their patients are at risk for overcomplicating the dosing schedule of their regimens.

This research adds support to the literature finding that organizing and dosing more complex medication schedules can be a formidable task. Unfortunately, not all patients have the capacity to impart the requisite vigilance when taking medication. Limited social support, depression, and low health activation were common among patients with complex regimens and

were all associated with perceived barriers to medication adherence. While efforts to simplify regimens and consolidate doses can improve adherence, these interventions alone will not be enough for patients without a healthy mindset.

Although significant research attention in recent years has focused on examining racial and ethnic health disparities in patients with T2DM, in our study, no single sociodemographic subgroup was especially vulnerable to overcomplicating medication dosing schedules, limited knowledge of medications, or dosing errors. The only sociodemographic predictor independently associated with dosing errors was limited English proficiency. Other studies have identified a relationship where patients with LEP and/or limited health literacy demonstrated poorer understanding of medication instructions (Masland et al., 2011) and more dosing errors in hypothetical scenarios (Harris et al., 2017). To reduce these disparities, previous research has shown that language concordant prescription labels reduce dosing errors for patients with LEP (Bailey et al., 2012). These identified gaps and the benefits of intervention aimed to reduce disparities highlight the importance of incorporating culturally sensitive medication information to patients from multicultural backgrounds.

In our studies, larger regimen size was associated with more doses taken over the course of the day and inversely related to patient knowledge. The former may be intuitive, and the latter finding is consistent with studies showing patients in primary care with limited health literacy have worse medication knowledge (Davis et al., 2006; Persell et al., 2010; Wolf et al., 2011). Our results suggest patients with limited health literacy and complex regimens are at even higher risk. According to the model of medication self-management, for a patient to be able to safely use and benefit from medications, they need to be able to understand the purpose of their

medications and how to safely take them (Bailey et al., 2013). Many of the patients in our study struggled to identify not only their prescribed medications' indication for use, but their side effects and auxiliary instructions. Mismanagement of complex regimens may be a driver of worse outcomes among patients with multimorbidity, and efforts to simplify regimens and provide education are warranted.

3. Implications

Barriers to adherence were common among patients with polypharmacy, with 20% of participants endorsed having four or more barriers to adherence. As poor adherence places patients at greater risk for subtherapeutic benefit and negative outcomes, these findings have implications for how to best reduce complexity and promote medication adherence among patients with multimorbidity and polypharmacy. First, encouraging physicians to deprescribe when clinically appropriate may improve adherence, but this may not be possible for many adults. Patients with polypharmacy often also have multiple specialists, and due to time and resource constraints, these providers are not routinely in close contact. In many cases, the burden of communicating the recommendations of specialists with other providers is left up to the patient, who may have misconceptions about clinical recommendations from providers. Efforts to improve care coordination through patient-centered (i.e., patient-centered medical home) and team-based (i.e., nurse coordinator) approaches may take the burden off patients and physicians to communicate this information. Additionally, pharmacists may be well-positioned to review treatment regimens, and such services are offered, although underutilized, by Medicare Part D in the form of medication therapy management (Viswanathan et al., 2015).

Patients need more support around how to safely dose their regimens in the least complicated way. It should not be presumed that patients are finding the simplest way to dose medication, and routine monitoring using tools which assess how patients are dosing their medications is needed. Better methods for assessing misconceptions (i.e., fear of drug interactions) which may cause patients to unnecessarily complicate their dosing schedule are needed. Systemic change using scalable interventions through health system initiatives and public policy are an important step that has been gaining attention in the last 10 years. The Universal Medication Schedule (UMS) seeks to eliminate variability in prescription instructions and consolidate daily, chronic pill form regimens into four or fewer doses per day. This model has been endorsed by the Institute of Medicine (2008) and in a white paper from the National Council for Prescription Drug Programs (2013). In 2007, California passed legislation to implement enhanced drug labeling using the UMS (California Patient Medication Safety Act of 2007) and efforts are underway in Wisconsin to implement enhanced drug labeling (Wisconsin Literacy Project). Studies are currently being conducted to leverage the electronic health record to automate the UMS at the system level (Bailey et al., 2017; O'Conor et al., 2019).

When inadequate systems or barriers to taking medicine are identified, there are several practical options to improve adherence. Standard pillbox organizers and blister packs of pre-dosed medications have been shown to improve adherence (Conn et al., 2015; Zedler et al., 2011). Technology enhanced pill organizers have become more sophisticated, and some are able to prompt dispensing medications at proper times. However, the acceptability of these devices among older patients, who are more likely to contend with not only polypharmacy, but limited technology literacy is mixed. Some patients describe being hesitant to adopt these devices (Choi,

2019; Conn et al., 2015) whereas others have shown enthusiasm, particularly if there is assistance for using the device (Reeder et al., 2013). Further, text reminders have been shown to double the odds of medication adherence (Thakkar et al., 2016), but studies often do not explicitly investigate these interventions with older patients and those with polypharmacy.

Third, screening for regimen complexity and psychosocial determinants of health fall within the scope of patient-centered and team-based care models in primary care settings (Schottenfeld, 2016). Such models have been lauded for identifying and treating the unique problems of the patient and improving coordination of care, efficiency, and patient satisfaction. One major opportunity may be utilizing pharmacists to have a greater role collaborating with providers (i.e., providing up to date drug information, guidelines) and services directly to patients including medication counseling, risk/benefit review, and medication reviews (Manolakis & Skelton, 2010). In terms of mental health, studies have shown older patients prefer to receive mental health care in a primary care setting (Chen et al., 2006) and are more likely to follow through with referrals in this setting (Speer & Schneider, 2003). Health psychologists or social workers would be well-positioned to deliver brief interventions designed to treat mental health symptoms, problem solve barriers to adherence, serve as a social support, help patients set and progress toward goals for wellbeing and address health behaviors.

4. Limitations

This research was a secondary data analysis of an interventional study which was designed to improve factors which we were directly examining. The intervention was designed based on principles of health literacy, so it is possible that participants in the study benefitted and

our results are conservative. Future research to confirm these findings in a study designed to examine these specific hypotheses is needed.

Studies 1 and 2 were conducted among a low income, primarily Hispanic population and Study 3 was conducted among patients with polypharmacy. This limits our ability to generalize findings to patients with fewer chronic conditions, taking fewer medications or a broader sociodemographic population. Additionally, in studies 1 and 2, we were unable to examine the impact of health literacy on outcomes of daily dosing schedules, knowledge, dosing errors, and MRCI given that most of the sample had limited health literacy.

5. Final Conclusions

Complex medication regimens are becoming increasingly common as the population ages. If interventions are to be truly patient-centered, healthcare providers and teams need to consider evaluating not just whether patients are taking their prescribed treatment, but how. Specifically, an accurate understanding of patients' organizing and taking of multi-drug regimens can uncover unintentional dosing errors that could then be readily corrected to promote safety and optimal outcomes. Physicians are an ideal interventionist but may need support from other allied health professionals due to time constraints. Team-based care models could be leveraged to address other complex social determinants of health in the context of multimorbidity and polypharmacy.

Tables

Table I. Sample characteristics from Study 1

Variable	n=441 (%)
Sociodemographic	
Age, mean (SD)	56.9 (9.4)
Age	
<50	103 (23.4)
50-59	167 (37.9)
60+	171 (38.8)
Sex	
Male	151 (34.2)
Female	290 (65.8)
Race/Ethnicity	
Hispanic	332 (73.4)
Non-Hispanic Black	77 (17.5)
Other	40 (9.1)
Education	
Less than HS	210 (49.0)
HS graduate/GED	114 (27.0)
More than HS degree	105 (24.9)
Income	
Less than $15,000	205 (51.4)
$15,000-$30,000	147 (36.8)
More than $30,000	47 (11.8)
Insurance	
Medicare+Medicaid	50 (11.7)
Medicare	76 (17.8)
Medicaid	104 (24.4)
Private/HMO	47 (11.0)
Self-pay/None	149 (35.0)
English Proficiency	
Proficient	181 (41.0)
Limited	260 (59.0)
Health Literacy	
Adequate	47 (11.2)
Limited	372 (89.0)

Regimen Size	
3-5	121 (27.4)
6-8	171 (37.9)
9+	149 (33.0)

Table II. Bivariate and multivariable models for continuous daily dosing schedule outcome

Variable	**Daily dosing schedule** mean (SD)	p value	**Unadjusted model RR (95% CI)**	**Adjusted model RR (95% CI)**
Sociodemographic				
Age		.255		
<50	3.02 (1.34)		1.00 (ref)	1.00 (ref)
50-59	3.31 (1.60)		1.10 (0.95, 1.26)	1.03 (0.89, 1.19)
60+	3.30 (1.49)		1.10 (0.95, 1.26)	0.98 (0.84, 1.13)
Sex		.174		
Male	3.31 (1.54)		0.93 (0.84, 1.05)	0.98 (0.87, 1.10)
Female	3.10 (1.42)		1.00 (ref)	1.00 (ref)
Race/Ethnicity		.934		
Hispanic	3.24 (1.50)		0.98 (0.81, 1.17)	0.95 (0.76, 1.18)
Non-Hispanic Black	3.20 (1.61)		0.97 (0.78, 1.20)	1.06 (0.84 1.32)
Other	3.31 (1.38)		1.00 (ref)	1.00 (ref)
Education		.117		
Less than HS	3.40 (1.50)		1.06 (0.89, 1.27)	1.06 (0.91, 1.24)
HS graduate/GED	3.04 (1.55)		1.11 (0.96, 1.29)	0.95 (0.81, 1.12)
More than HS degree	3.18 (1.42)		1.00 (ref)	1.00 (ref)
English Proficiency		.144		
Proficient	3.11 (1.50)		1.00 (ref)	1.00 (ref)
Limited	3.33 (1.50)		1.07 (0.96, 1.19)	1.15 (0.99, 1.34)
Covariates				
Regimen Size		<.001		
3-5	2.45 (1.02)		1.00 (ref)	1.00 (ref)
6-8	3.27 (1.38)		**1.30 (1.13, 1.50)*** **	**1.31 (1.13, 1.52)*** **
9+	3.73 (1.71)		**1.49 (1.29, 1.72)*** **	**1.51 (1.30, 1.76)*** **

$^{*}p < .05$
$^{**}p < .01$
$^{***}p < .001$

Table III. Generalized estimating equation models including risk ratios with 95% confidence intervals for knowledge and dosing error outcomes

	Sum Knowledge Score		**Any Dosing Error**	
Variable	**Unadjusted RR (95% CI)**	**Adjusted RR (95% CI)**	**Unadjusted RR (95% CI)**	**Adjusted RR (95% CI)**
Age				
<50	–	–	–	–
50-59	0.94 (0.81, 1.10)	0.95 (0.81, 1.10)	0.94 (0.69, 1.30)	0.97 (0.70, 1.34)
60+	0.90 (0.77, 1.05)	0.94 (0.81, 1.10)	0.84 (0.61, 1.16)	0.85 (0.61, 1.18)
Gender				
Female	–	–	–	–
Male	1.01 (0.89, 1.14)	1.06 (0.94, 1.20)	0.93 (0.72, 1.19)	0.93 (0.71, 1.20)
Race/Ethnicity				
Hispanic	0.92 (0.75, 1.12)	0.96 (0.77, 1.20)	1.17 (0.76, 1.81)	0.90 (0.54, 1.50)
Black	0.99 (0.79, 1.25)	0.94 (0.75, 1.19)	1.16 (0.71, 1.91)	1.27 (0.76, 2.11)
Other	–	–	–	–
Education				
Less than HS	**0.81 (0.71, 0.94)***	**0.82 (0.70, 0.96)***	1.03 (0.76, 1.39)	0.88 (0.62, 1.24)
HS graduate/GED	0.93 (0.80, 1.09)	0.93 (0.79, 1.09)	1.02 (0.73, 1.44)	0.95 (0.67, 1.34)
Higher than HS degree	–	–	–	–
English Proficiency				
Proficient	–	–	–	–
Limited	0.91 (0.81, 1.02)	0.95 (0.81, 1.11)	**1.33 (1.03, 1.72)***	**1.65 (1.14, 2.39)***
Regimen Size				
3-5	–	–	–	–
6-8	0.95 (0.82, 1.10)	0.94 (0.81, 1.10)	1.03 (0.74, 1.43)	1.05 (0.76, 1.47)
9+	**0.83 (0.71, 0.97)****	**0.81 (0.68, 0.94)****	0.89 (0.64, 1.24)	0.98 (0.69, 1.39)

CI: confidence interval; RR, risk ratio; HS, high school
$^{*}p < .05$
$^{**}p < .01$
$^{***}p < .001$

Table IV. Sample characteristics from Study 2

Variable	Sample
	n=441 (%)
Sociodemographic	
Age, mean (SD)	56.9 (9.4)
Age	
<50	103 (23.4)
50-63	235 (53.3)
64+	103 (23.4)
Sex	
Male	151 (34.2)
Female	290 (65.8)
Race/Ethnicity	
Hispanic	332 (73.4)
Non-Hispanic Black	77 (17.5)
Other	40 (9.1)
Education	
5th grade or lower	60 (13.6)
6-8th grade	102 (23.1)
9-11th grade	50 (11.3)
HS graduate/GED	119 (27.0)
More than HS degree	110 (24.9)
Income	
Less than $15,000	205 (51.4)
$15,000-$30,000	147 (36.8)
More than $30,000	47 (11.8)
Insurance	
Medicare+Medicaid	50 (11.7)
Medicare	76 (17.8)
Medicaid	104 (24.4)
Private/HMO	47 (11.0)
Self-pay/None	149 (35.0)
English Proficiency	
Proficient	181 (41.0)
Limited	260 (59.0)
Health Literacy	
Adequate	47 (11.2)

Limited	372 (89.0)
Num MD Visits	
1	88 (20.4)
2	162 (37.6)
3-4	108 (25.1)
5+	73 (16.9)

Table V. Bivariate models examining regimen characteristics and health-related factors with blood sugar

Variable		A1C	
		Mean (SD)	p value
Age	<50	8.68 (2.12)	<.01
	50-63	8.08 (1.94)	
	64+	7.77 (1.70)	
Sex	Male	8.53 (2.10)	.001
	Female	7.94 (1.85)	
Race	Hispanic	8.24 (2.01)	.35
	Black	7.88 (1.88)	
	Other	7.90 (1.52)	
Education	5th grade or lower	8.15 (1.98)	.34
	6-8th grade	7.89 (1.81)	
	9-11th grade	8.15 (1.88)	
	HS graduate/GED	8.24 (2.05)	
	More than HS degree	8.28 (2.00)	
Income	Less than $15,000	7.93 (1.97)	<.01
	$15,000-$30,000	8.10 (1.87)	
	More than $30,000	8.98 (1.86)	
Insurance	Medicare+Medicaid	7.60 (1.76)	<.01
	Medicare	7.67 (1.83)	
	Medicaid	7.98 (1.75)	
	Private/HMO	8.36 (1.73)	
	Self-pay/None	8.65 (2.15)	
English Proficiency	Proficient	8.06 (1.97)	.56
	Limited	8.20 (1.95)	
Health Literacy	Adequate	7.76 (1.70)	.18
	Limited	8.18 (1.99)	
MRCI	<14	7.66 (1.67)	.02
	14-18.4	8.43 (2.11)	
	18.5-26	8.43 (2.16)	
	>26	8.16 (1.69)	
Number of MD visits (past 6 months)	1	8.55 (2.15)	.04
	2	8.18 (1.79)	
	3-4	8.11 (2.07)	

5+	7.63 (1.69)

Table VI. Multivariable models examining regimen characteristics and health-related factors with blood sugar

Variable		A1C
		Standardized β
Age	<50	---
	50-63	-.070
	64+	-.057
Sex	Male	.153**
	Female	---
Race	Hispanic	.152
	Black	.095
	Other	---
Education	5th grade or lower	-.049
	6-8th grade	-.167*
	9-11th grade	-.071
	HS graduate/GED	-.039
	More than HS degree	---
Insurance	Medicare+Medicaid	-.180**
	Medicare	-.204**
	Medicaid	-.165**
	Private/HMO	-.038
	Self-pay/None	---
MRCI	<14	---
	14-18.4	.244***
	18.5-26	.246***
	>26	.278***
Number of MD visits (past 6 months)	1	---
	2	-.077
	3-4	-.088
	5+	-.163**

p<.05*, p<.01**,p<.001***

Table VII. Sample characteristics from Study 3

Variable	Entire Sample
	n=585 (%)
Study site	
Northwestern (Chicago, IL)	308 (52.7)
Mt. Sinai (New York, NY)	277 (47.4)
Age, mean (SD)	61.7 (10.6)
Age	
<45	28 (4.8)
45-54	112 (19.2)
55-64	213 (36.4)
65+	232 (39.7)
Sex	
Male	232 (39.7)
Female	353 (60.3)
Race	
Black	265 (45.3)
White	267 (45.6)
Other	53 (9.1)
Ethnicity	
Hispanic	186 (31.8)
Non-Hispanic	396 (67.7)
Education	
Less than HS degree	113 (19.4)
HS graduate/GED	100 (17.2)
More than HS	370 (63.5)
Income	
<20K	274 (47.8)
20-39K	125 (21.8)
>40K	174 (30.4)
Social Support	
Adequate	476 (81.4)
Limited	109 (18.6)
Health Literacy	
Adequate	188 (32.1)
Limited	397 (68.9)
Patient Activation	

High	46 (7.9)
Moderate	228 (39.0)
Low	311 (53.2)
Depressive symptoms	
None-mild	480 (82.1)
Clinically meaningful	105 (18.0)
Health Status	
Excellent/Very Good	70 (12.0)
Good	238 (40.7)
Fair	217 (37.1)
Poor	60 (10.3)
Regimen size, mean (SD)	11.0 (4.9)

Table VIII. Adherence Starts with Knowledge 12 items and response patterns descriptive statistics

Ask-12 Item	**Perceived as Barrier n (%)**
Inconvenience/Forgetfulness	
I just forget to take my medicines some of the time.	235 (40.2)
I run out of my medicine because I don't get refills on time.	117 (20.0)
Taking medicines more than once a day is inconvenient.	216 (36.9)
Treatment Beliefs	
I feel confident that each one of my medicines will help me.	42 (7.2)
I know if I am reaching my health goals.	62 (10.6)
I have someone I can call with questions about my medicines.	66 (11.3)
My doctor/nurse and I work together to make decisions.	33 (5.6)
Behavior *How frequently have you:*	
Taken a medicine more or less often than prescribed?	125 (21.4)
Skipped or stopped taking a medicine because you didn't think it was working?	52 (8.9)
Skipped or stopped taking a medicine because it made you feel bad?	64 (10.9)
Skipped, stopped, or taken less medicine because of the cost?	32 (5.5)
Not had medicine with you when it was time to take it?	158 (27.1)

Table IX. Bivariate analyses of sociodemographic and psychosocial factors with barriers to adherence

Variable	Barriers to Adherence mean (SD)	p
Age		<.001
<45	27.0 (7.20)	
45-54	26.2 (6.67)	
55-64	24.1 (6.24)	
65+	23.4 (5.71)	
Sex		
Male	24.1 (6.04)	0.41
Female	24.5 (6.42)	
Race		
Black or African American	24.9 (6.20)	0.09
White	23.8 (6.15)	
Other	24.4 (7.00)	
Ethnicity		
Hispanic	24.3 (6.37)	0.9
Non-Hispanic	24.5 (6.06)	
Socioeconomic		
Income		
<20K	24.9 (6.47)	<.01
20-39K	24.8 (5.73)	
>40K	23.1 (6.01)	
Education		
Less than HS	24.4 (5.90)	0.23
HS grad	23.3 (6.62)	
More than HS	24.5 (6.22)	
Social Support		
Adequate	23.6 (6.03)	<.001
Limited	27.6 (6.28)	
Depression		
None-Mild	23.6 (5.93)	<.001
Clinically Meaningful	27.7 (6.73)	

Patient Activation		
High	20.0 (4.5)	<.001
Moderate	22.1 (5.49)	
Low	26.7 (6.08)	
Health Literacy		
Adequate	24.7 (6.51)	0.31
Limited	24.2 (6.15)	

Table X. Multivariable analyses of sociodemographic and psychosocial factors with barriers to adherence

Variable	Barriers to Adherence LS means (95% CI)	p value
Socioeconomic		
Income		
<20K	24.5 (23.8, 25.2)	0.35
20-39K	24.5 (23.6, 25.5)	0.4
>40K	23.8 (22.8, 24.7)	---
Education		
Less than HS	24.0 (22.8, 25.1)	0.27
HS grad	23.2 (22.1, 24.2)	0.02
More than HS	24.7 (24.1, 25.3)	---
Psychosocial		
Social Support		
Adequate	24.0 (23.5, 24.5)	---
Limited	25.5 (24.4, 26.6)	0.03
Depression		
None-Mild	23.9 (23.4, 24.4)	---
Clinically Meaningful	26.0 (24.9, 27.1)	<.01
Patient Activation		
High	21.4 (19.8, 23.0)	---
Moderate	22.7 (21.9, 23.4)	0.16
Low	25.9 (25.3, 26.5)	<.001

Model controlled for age, sex, race, ethnicity, number of chronic conditions and health status

Figures

Figure 1. Model of Medication Self-Management

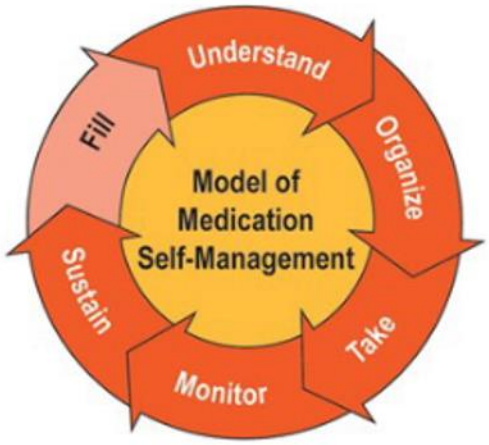

Figure 2. Model of Cumulative Complexity

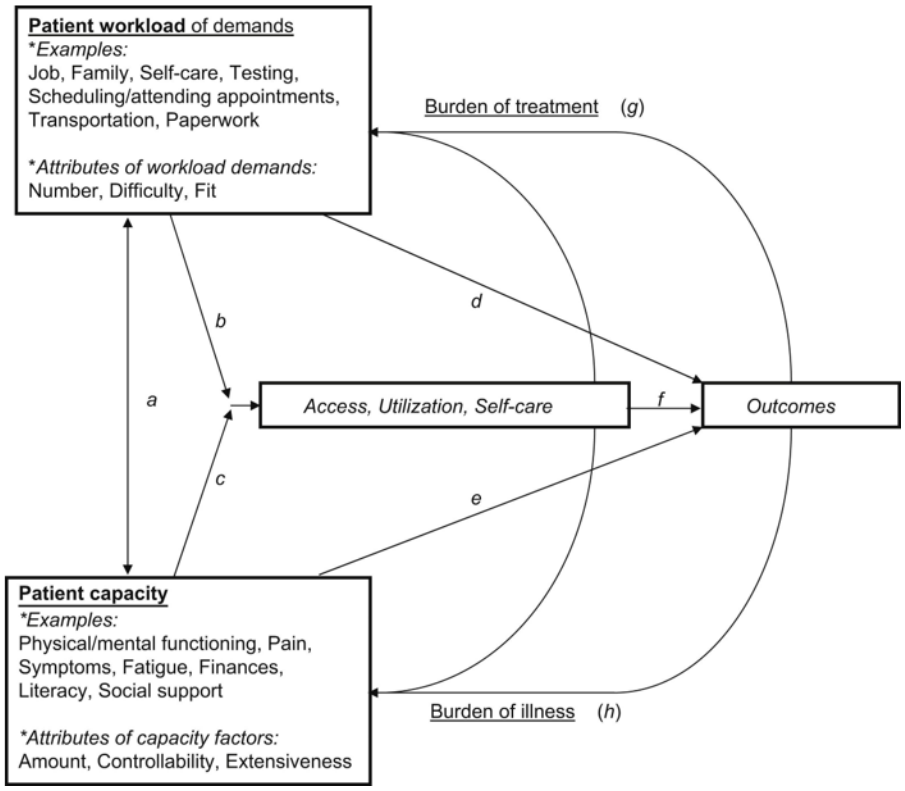

Figure 3. Sample dosing schedules from three patients with 12-drug regimens

Hour	Patient #1	Patient #2	Patient #3
3:00			
4:00			
5:00			
6:00			
7:00			
8:00			
9:00			
10:00			
11:00			
12:00			
13:00			
14:00			
15:00			
16:00			
17:00			
18:00			
19:00			
20:00			
21:00			
22:00			
Doses	**2**	**5**	**8**

Figure 4. Sample medication regimens with MRCI score

Patient	MRCI	Medication Name	Instructions
#1	7	lisinopril-hydrochlorothiazide	take one tablet by mouth once a day
		sitagliptin/metformin	take one tablet by mouth twice a day
		atorvastatin	take one tablet by mouth once a day
#2	14	glipizide	take 2 tablets by mouth before breakfast and in the evening before dinner
		metformin hcl	take one tablet by mouth twice daily
		levothyroxine	take one tablet by mouth one time daily
		aspirin ec	take one tablet by mouth one time daily
		fenofibrate	take one tablet by mouth one time daily
#3	18.5	metformin	take 1 tablet twice a day
		levothyroxine	take 1 tablet by mouth every morning before a meal
		lisinopril-hydrochlorothiazide	take 1 by mouth daily
		sertraline	take 1 tablet by mouth every day
		ranitidine	take one tablet by mouth daily
		albuterol	take as needed two puffs
#4	26	fluoxetine	take one capsule by mouth daily
		lisinopril	take one tablet by mouth daily
		rosuvastatin	take one tablet by mouth daily
		sitagliptin/metformin	take one tablet by mouth twice daily
		esomeprazole	take one capsule by mouth daily
		Levemir	inject 65 units at night daily
		NovoLog	inject 12-20 units 15 minutes before eating

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Curriculum Vitae

1. PERSONAL INFORMATION

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2. EDUCATION

2016-present Doctoral Candidate, Clinical Psychology
Northwestern University, Feinberg School of Medicine
Department of Psychiatry and Behavioral Sciences
Behavioral Medicine Clinical and Research Emphasis
Primary Research Mentor: Michael Wolf, PhD, MPH

2016-2018 Master of Science in Clinical Psychology
Northwestern University, Feinberg School of Medicine

2008-2012 Bachelor of Science in Psychology, *Cum Laude*
Minors in General Business, Sexuality
Studies
The Ohio State University

3. CLINICAL EXPERIENCE

2019-Present **The Ohio State University Wexner Medical Center**
Health Psychology Internship
Women's Health: *Supervised by Kristen Carpenter, PhD*
Transplant Psychology: *Supervised by Kristin Kuntz, PhD*
Chronic Pain: *Supervised by Jose Moreno, PhD*
Cardiac Behavioral Health: *Supervised by Cheryl Carmin, PhD*

2019-2020 **University of Chicago Medicine**
Psychosocial Oncology: *Supervised by Yasmin Asvat, PhD*

2018-2019 **Northwestern Memorial Hospital**
Consult/Liaison: *Supervised by Shirley Baron, PhD*
Sleep Medicine: *Supervised by Jennifer Mundt, PhD*
Transplant Psychology: *Supervised by Zeeshan Butt, PhD*
Neuropsychological Testing: *Supervised by Brian Griffin, PhD and Erica Sieg, PsyD*

2017-2018 **Illinois Masonic Medical Center, Behavioral Health Services**
General Outpatient Mental Health: *Supervised by Melissa Hernandez, PhD*

4. PROFESSIONAL AND RESEARCH EXPERIENCE

2014-present **Northwestern University Feinberg College of Medicine** (Chicago, IL)
Michael Wolf, PhD, MPH – Health Literacy and Learning Program
Research Study Coordinator/Graduate Research Assistant

2018-2020 *Inger Burnett-Ziegler, PhD*
Graduate Research Assistant

2018-2020 **University of Illinois at Chicago** (Chicago, IL)
Sylvia Herbozo, PhD – Body Image and Eating Behaviors Lab
Graduate Research Assistant

2012-2016 **Northwestern University Feinberg College of Medicine (**Chicago, IL)
Marla Clayman, PhD
Research Assistant

2011-2012 **The Ohio State University – Psychology Department** (Columbus, OH)
Janice Keicolt-Glaser, PhD – Stress and Health Lab
Undergraduate Research Assistant

Jen Cheavens, PhD – Mood and Personality Disorders Lab
Undergraduate Research Assistant

Per Sederberg, PhD – Computational Memory Lab
Undergraduate Research Assistant

2009-2010 **Northwest Counseling Services – Older Adult Program** (Columbus, OH)
Student Intern

5. COMMUNITY SERVICE

2014-2016 *Imerman Angels 1-on-1 Cancer Support*
Volunteer Cancer Support Specialist

2013-2014 *Big Brothers, Big Sisters of Chicago*
Big Sister

2011-2012 *ServCorps at Ohio State University*
Student Volunteer Coordinator

6. AWARDS, HONORS, DISTINCTIONS

2016-2018 **Amgen, Inc.** (Thousand Oaks, CA)
Supervisor: Meredith Smith, PhD
Pre-doctoral Fellowship in Risk Communication

2012 Graduation *Cum Laude*

2011-2012 Deans' List (Spring)
2010-2011 Deans' List (Autumn, Winter, Spring)
2009-2010 Deans' List (Autumn, Winter, Spring)

7. SCHOLARLY BIBLIOGRAPHY

Peer Reviewed Publications

1. Newman A, Herbozo S, **Russell AM**, Eisele H, Zasadzinski L, Sanchez-Johnson L. Interventions to increase adherence in bariatric surgery patients: a systematic review. *Under review at the Journal of Health Psychology.*

2. Bailey SC, Serper M, Opsasnick L, Persell SD, O'Conor R, Curtis LM, Benavente JY, Wismer G, Batio S, Eifler M, Zheng P, **Russell A**, Arvanitis M, Ladner DP, Kwasny MJ, Rowe T, Linder JA, Wolf MS. Changes in COVID-19 Knowledge, Beliefs, Behaviors, and Preparedness Among High-Risk Adults from the Onset to the Acceleration Phase of the US Outbreak. (2020) *Journal of General Intern Medicine*. 2020 Sep 1:1–8. https://doi.org/ 10.1007/s11606-020-05980-2

3. O'Conor R, Opsasnick L, Benavente JY, **Russell AM**, Wismer G, Eifler M, Marino D, Curtis LM, Arvanitis M, Lindquist LA, Persell SD, Bailey SC, Wolf MS. Knowledge and Behaviors of Adults with Underlying Health Conditions during the Onset of the COVID-19 U.S. Outbreak: The Chicago COVID-19 Comorbidities Survey. (2020) *J Community Health*.

4. **Russell AM**, Mullen RJ, Morrato E, Smith MYS. Quality of reporting on risk minimization evaluation studies: a systematic review. (2020) *Drug Saf.* https://doi.org/ 10.1007/s40264-020-00905-8

5. Wolf MS, Serper M, Opsasnick L, O'Conor RM, Curtis LM, Benavente JY, Wismer G, Batio S, Eifler M, Zheng P, **Russell AM**, Arvanitis M, Ladner D, Kwasny M, Persell SD, Rowe T, Linder JA, Bailey SC. Awareness, attitudes, and actions related to COVID-19 among adults with chronic conditions at the onset of the US outbreak: A cross sectional survey. (2020) *Ann Intern Med,* https://doi.org/ 10.7326/M20-1239

6. McCarthy DM, **Russell AM**, Eifler MR, Opsasnick LA, Lyden AE, Gravenor SJ, Montague E, Hur SI, Cameron KA, Curtis LM, Wolf MS. (2019). Implementation fidelity of a patient-centered prescription label to promote opioid safe use. *Saf,* https://doi.org/ 10.1002/pds.4795

7. **Russell AM,** Smith SG, Bailey SC, Belter LT, Pandit AU, Hedlund LA, Bojarski EH, Rush SR, Wolf MS. (2018). Older Adult Preferences of Mobile Application Functionality Supporting Medication Self-Management. *J Health Commun,* 23(12):1064-1071. https://doi.org/ 10.1080/10810730.2018.1554728

8. **Russell AM,** Patel DA, Curtis LM, Kim KY, Wolf MS, Rowland ME, McCarthy DM. (2018). Test-retest reliability of the Newest Vital Sign health literacy instrument: in person and remote administration. *Patient Educ Couns.* https://doi.org/ 10.1016/j.pec.2018.11.016

9. Chan H, **Russell AM,** Smith MY. (2018) What's the quality of drug safety information for patients? *Pharmacoepidemiol Drug Saf,* 27(9), 969-978. https://doi.org/ 10.1002/pds.4614

10. Mullen RJ, Duhig J, **Russell A**, Scarazzini L, Lievano F, Wolf MS. (2018). Best-practices for the design and development of prescription medication information: A systematic review. *Patient Educ Couns*, 101(8), 1351-1367. https://doi.org/ 10.1016/j.pec.2018.03.012

11. Smith MY, **Russell AM**, Bahri P, Mol PGM, Frise S, Freeman E, Morrato EH. (2017). The RIMES Statement: A Checklist to Assess the Quality of Studies Evaluating Risk Minimization Programs for Medicinal Products. *Drug Saf*, 41(4), 389-401. https://doi.org/ 10.1007/s40264-017-0619-x

12. McCarthy DM, Courtney DM, Lank PM, Cameron KA, **Russell AM**, Curtis LM, Kim KY, Walton SM, Montague E, Lyden AL, Gravenor SJ, Wolf MS. (2017). Electronic medication complete communication strategy for opioid prescriptions in the emergency department: Rationale and design for a three-arm provider randomized trial. *Contemp Clin Trials*, 59, 22-29. https://doi.org/ 10.1016/j.cct.2017.05.003

13. **Russell AM,** Harper MH, Galvin KM, Clayman ML. (2016). A comparison of heterosexual and LGBTQ cancer survivors' outlooks on relationships, family building, possible infertility, and patient-doctor fertility risk communication. *J Cancer Surviv*, 10(5), 935-942. https://doi.org/ 10.1007/s11764-016-0524-9

Publications (Other)

1. Smith MS, Chan HW, Strauss C, Hockley K, Russell AM. (2018). Medicinal Product Benefit-Risk Management: The Role of Patient Input. Regulatory Focus.

Publications (Under Review)

1. Lovett, RM, Opsasnick L, Russell AM, Yoon E, Weiner-Light S, Serper M, Bailey SC, Wolf MS. Prevalence and consequences of clinically relevant anxiety and depressive symptoms amidst COVID-19 among adults with chronic conditions.
2. O'Conor R, Eifler M, Russell AM, Opsasnick L, Arvanitis M, Pack A, Curtis L, Benavente J, Wolf MS. Caregiver Involvement in Managing Medications among Older Adults with Multiple Chronic Conditions. Under review at the Journal of the American Geriatrics Society.

Presentations

1. **Russell AM**, Opsasnick L, Wismer G, O'Brien M, Bailey SC, Wolf MS. Medication Taking Behavior among Adults with Type 2 Diabetes and Polypharmacy. *Accepted for poster presentation at the Society for Behavioral Medicine Annual Meeting 2020. Poster presented virtually due to COVID-19 outbreak.*

2. **Russell AM,** Mullen RJ, Morrato E, Smith MYS. Quality of reporting on risk minimization evaluation studies: a systematic review. *Oral presentation at the International Conference on Pharmacoepidemiology & Therapeutic Risk Management on August 26, 2018.*

3. **Russell AM,** O'Conor R, Benavente JY, Curtis LM, Wolf MS. Health Literacy and Adjustment to Increasing Comorbidity: An Exploratory Analysis. *Poster presentation at the Society for General Internal Medicine Annual Meeting on April 13, 2018.*

4. **Russell AM,** Patel DA, Curtis LM, Kim KY, Wolf MS, Rowland ME, McCarthy DM. Test-retest reliability of the Newest Vital Sign health literacy instrument: in person and remote administration. *Oral presentation at the International Conference on Communication in Healthcare/Health Literacy Annual Research Conference on October 10, 2017.*

5. Clayman M, **Russell AM**. Impact of decision partner presence on decision discussions in metastatic breast cancer oncology visits. *Oral presentation at the International Conference on Communication in Healthcare/Health Literacy Annual Research Conference on October 10, 2017.*

6. **Russell AM,** Clayman M. Fertility risk discussions and preservation decisions among male and female cancer patients. *Oral presentation at the American Public Health Association Annual Meeting November 1, 2015.*

7. **Russell AM**, Patel DA, Curtis LM, Rowland ME, Wolf MS, McCarthy DM. Changes in newest-vital-sign score among opioid prescribed patients before and after emergency department discharge. *Poster session at the Health Literacy Annual Research Conference on October, 13 2016.*

8. **Russell AM**, Bailey S, Smith S, O'Conor R, Wolf M. Patient preferences and desired functionality of mobile applications promoting medication self-management among older adults. *Poster session at the Health Literacy Annual Research Conference on November 2, 2015.*

9. del Salto G, Walia A, Curtis L, Nowicki C, Serrano E, Patel D, **Russell A**, Jacobson K, Parker R, Rittner S, Rachman F, Matusik M, Taitel M, Wolf, M. Introducing the eUMS Trial: Promoting safe use and adherence to multi-drug regimens. *Poster session at the Health Literacy Annual Research Conference on November 2, 2015.*

10. **Russell AM**, Davis T, Arnold C, Vadaparampil S, Wolf M, Clayman M. Impact of family member presence on decision discussions in metastatic breast cancer oncology visits. *Oral presentation at the International Conference on Communication in Healthcare. October 28, 2015.*

11. Clayman M, Harper M, Williams A, Pumarino J, **Russell A,** Galvin K. Retrospective examination of cancer patients' communication with physicians about fertility. *Oral presentation at the EACH International Conference on Communication in Healthcare. September 29, 2014.*

12. Clayman M, Harper M, Williams A, Pumarino J, **Russell A**, Galvin K. Just one in a list: the experiences of young women with cancer learning about potential fertility loss. *Oral presentation at the International Shared Decision Making Conference. June 17, 2013.*