Anxiety in Rheumatoid Arthritis (RA):
Support for a Biopsychosocial Approach to the Management of RA

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Abstract

Anxiety is highly prevalent among patients with rheumatoid arthritis (RA). Although this co-occurrence is associated with a range of adverse functional, mental, and physical health outcomes (e.g., joint counts, disease activity, functional status, pain, and fatigue), the management of RA remains reliant on a biomedical approach. Guided by a biopsychosocial framework, this dissertation aimed to both clarify and add to the extant literature on comorbid anxiety in RA. Specifically, (1) I examined the possibility of distinct anxiety trajectory groups within an RA sample as well as unique correlates associated with group membership; and (2) I tested the feasibility and potential benefit of an accessible anxiety intervention among RA patients. Using a clinical sample of individuals with RA (N=154), Study 1 identified three distinct anxiety trajectory groups uniquely associated with a number of clinical indicators cross-sectionally and longitudinally. More severe anxiety was associated with worse indicators (i.e., functional disability, tender joint count, pain, and fatigue) and persistent moderate anxiety was associated with worsening fatigue. Study 2 supported the feasibility of an Internet-based cognitive-behavioral therapy (iCBT) intervention for anxiety (and depression) in RA patients (N=34) through recruitment, adherence, and qualitative patient feedback. Preliminary evidence of mental (i.e., anxiety, depression, and emotional distress) and physical (i.e., fatigue) improvements following participation in the intervention was also provided. Results of this dissertation hold important implications for the assessment and treatment of anxiety in the context of RA. To explain these implications, findings are discussed in relation to a stepped care model as to illustrate possible amendments to current Canadian healthcare practices.

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Dedication

This thesis is dedicated to my family. To my mother, Sabrina Parnham, thank you for passing down your curiosity and continuing to inspire my pursuit of knowledge. To my sister, Amy Blaney, thank you for always reminding me what actually matters, and also for making me laugh to the point of physical pain. To my father, John Blaney, who lived courageously with physical and mental health difficulties, thank you for inspiring me to push harder.

Table of Contents

List of Tables

Chapter 2

Chapter 3

List of Figures

Chapter 1

Chapter 2

Chapter 3

Chapter 4

List of Copyrighted Material/Contribution of Authors

Copyrighted Material

Blaney, C., Hitchon, C.A., Marrie, R.A., Mackenzie, C., Holens, P., & El-Gabalawy, R. (2021). Support for a non-therapist assisted, Internet-based cognitive-behavioral therapy (iCBT) intervention for mental health in rheumatoid arthritis. *Internet Interventions, 24,* 100385. doi: 10.1016/j.invent.2021.100385

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Contribution of Authors

` I, Ms. Caitlin Blaney, M.A., am the primary contributor to Studies 1 and 2. For Study 1, as first author, I was responsible for idea conception and design, literature searches, analysis and interpretation of the data, writing the first draft, and editing subsequent drafts of the manuscript. Contributions were also made by the following co-authors: Dr. Renée El-Gabalawy, Dr. Ruth Ann Marrie, Dr. Depeng Jiang, Dr. Corey Mackenzie, and Dr. Pamela Holens. Drs. El-Gabalawy, Marrie, Jiang, and Mackenzie provided input on study design, analysis, and interpretation of the data, with Dr. Jiang taking a particularly prominent role in terms of statistical support. The data was secondary data, collected by Dr. Marrie (therefore Dr. Marrie is also due credit in terms of idea conception). All five co-authors reviewed drafts of the manuscript.

For Study 2, as first author, I was responsible for idea conception and design, literature searches, data collection, analysis and interpretation of the data, writing the first draft, and editing subsequent drafts of the manuscript. Contributions were also made by the following co-authors: Dr. Renée El-Gabalawy, Dr. Carol Hitchen, Dr. Ruth Ann Marrie, Dr. Corey Mackenzie, and Dr. Pamela Holens. Additional contributions came from Dr. John Walker, Dr. Kristin Reynolds, and Ms. Gabrielle Logan. Dr. El-Gabalawy provided input on study design, analysis, and interpretation of the data. All co-authors plus Dr. Walker provided input on study design. Dr. Reynolds provided feedback when developing the treatment experience questions. Ms. Logan acted as second coder in the qualitative analysis. All five co-authors reviewed drafts of the manuscript.

Chapter 1: General Introduction

An Intersection Framework of Physical Health

An interdependent relationship between mental and physical health has become widely accepted. This recognition, however, did not come without resistance. The *mind-body problem* is a longstanding philosophical debate on the relationship between the physical body and mental state, specifically the degree to which they are linked. *Dualism* (i.e., the philosophical stance that the mind and body are separate entities, abiding by distinct principles) has long led the debate, and its predominance resulted in the development of the *biomedical model* that has shaped modern medicine. In accordance with the biomedical model, the human body can be understood entirely through principles of biological science: anatomy, physiology, biochemistry and physics (Mehta, 2011). Accordingly, illness (i.e., a physical condition) is conceptualized as a product of pathology (i.e., deviation in biological norms), typically derived from a single, biologically based cause (Mehta, 2011; Wade & Halligan, 2017).

The initial shift towards a more comprehensive ideology of health and illness can be, ironically, credited to staunch dualist René Descartes; his 17th century pineal gland hypothesis, which suggested communication between the mind and body was both continuous and essential (Shapiro, 2011), inherently challenged the concept of the body's functional autonomy from the mind. Science has since rigorously examined linkage between psychological and physical experience, resulting in the contemporary theoretical extension of the biomedical model i.e., the *biopsychosocial model* (Engel, 1977). First popularized in the 1970s, the reformed perspective emphasized the relevance of interaction effects between internal and external factors in the induction and maintenance of illness, specifically *biological*, *psychological*, and *social/environmental* factors (Fava & Sonino, 2008). Evidence for the contemporary framework has since accumulated (Wade & Halligan, 2017), gradually dismantling the tenets of dualism and diminishing the possibility of a single, pathological explanation in most circumstances of illness. And yet, despite the holistic conceptualization of health that has become mainstream today, changes in healthcare approaches lag; currently, the majority of health care expenditures remain allocated to biomedical approaches to care (Fava & Sonino, 2008; Kusnanto et al., 2018; Wade & Halligan, 2017).

The need to operate from a biopsychosocial framework is exemplified in circumstances of physical and mental health comorbidity. Overlap between physical and mental health

conditions is well supported in both cross-sectional (Dai et al., 2020; Daré et al., 2019) and longitudinal data (Blaney et al., 2020; El-Gabalawy et al., 2014), particularly when the physical health problem is chronic (Kusnanto et al., 2018). For example, among psychiatric patients, rates of chronic physical health conditions (e.g., cardiovascular disease, respiratory illness) are consistently elevated compared to the general population (Correll et al., 2017; Sokal et al., 2004; Sommer et al., 2021). Further, among chronic illness populations (e.g., multiple sclerosis, Parkinson's disease), mental health disorder prevalence estimates are routinely higher than those demonstrated by healthy controls (Grover et al., 2019; Marrie et al., 2014). Commonly referenced explanations for these comorbidities include psychological factors such as adverse experiences (Montgomery et al., 2013); social/environmental factors such as social support (e.g., frequency of social interactions; Ohrenberger et al., 2017) and social determinants of health (e.g., socioeconomic status; Kivimäki et al., 2020); and biological factors such as inflammatory processes (Bennett et al., 2018). However, these factors are rarely addressed comprehensively in disease treatment or considered in health care policy.

Accordingly, this dissertation aims to advocate for change in health care approaches to disease through an examination of a commonly reported co-occurrence: rheumatoid arthritis (RA), the most prevalent form of inflammatory arthritis (Firestein et al., 2003), and anxiety. Specifically, I focused on characterization of anxiety and health consequences over time, as well as a potential intervention opportunity to target anxiety among patients with RA.

Rheumatoid Arthritis

Clinical Description of Rheumatoid Arthritis

RA affects almost 20 million individuals globally (Safiri et al., 2019). Of 195 countries surveyed, Canada, Paraguay, and Guatemala demonstrated the largest increases in age-standardized prevalence and incidence rates of RA over the last three decades (Safiri et al., 2019). The disease is more common in women (at a 3:1 ratio; Tobón et al., 2010) and more prevalent with increasing age, although age of onset varies substantially from one person to another (Tobón et al., 2010). Some racial groups, such as Indigenous populations, demonstrate elevated diagnostic risk (Hitchon et al., 2020). However, while relevant in terms of risk, sociodemographic characteristics appear to be poor predictors of prognosis (Rupp et al., 2006a).

RA is a progressive autoimmune disease, typified by polyarthritis that originates in the smaller joints (e.g., hands, feet) and results in the gradual destruction of cartilage and bone

(Grondal et al., 2007; Silvagni et al., 2020). The most common symptoms include inflammation-induced joint swelling, pain, and morning stiffness lasting over an hour (Majithia & Geraci, 2007; Visser, 2005). RA is characterized by intermittent periods of lower disease activity, i.e., remission, relative to periods of higher disease activity (i.e., flares; Alten et al., 2011). Flares vary broadly in terms of intensity, frequency, and duration (Alten et al., 2011), yet worse flare patterns over time are associated with physical and functional deterioration as well as disease progression (Ajeganova & Huizinga, 2017; Markusse et al., 2015). Sustained remission (a definition that varies between contexts, but tends to involve a minimum of 6 months without flare; Ajeganova & Huizinga, 2017) is associated with lower risk of flares (Smolen et al., 2020).

Disease status is monitored through ongoing assessment of clinical indicators. Outcomes associated with RA can be initially divided into those pertaining to consequences of the disease on functioning (i.e., illness outcomes; Vetriglio et al., 2017) and those pertaining to disease pathophysiology (i.e., disease outcomes). Illness outcomes for RA include lower rates of employment (Sokka et al., 2010), greater likelihood of functional disability (Kronisch et al., 2016), reduced quality of life (Matcham et al., 2014), increased morbidity (Ramos et al., 2019), and increased disease-induced mortality (Pincus, Gibson, & Block, 2015). While the most common causes of death (circulatory system disease, cancer, and respiratory disease) mirror that of the general populations (Widdifield et al., 2018; van den Hoek et al., 2017), RA patients die approximately 3-10 years younger than their healthy counterparts (Tobón et al., 2010).

Disease outcomes can be further divided into clinician-assessed outcomes and patient-reported outcomes. Clinician-assessed outcomes include joints counts (swollen and tender, respectively) and indicators of circulating inflammation levels (Farheen & Agarwal, 2011). Accurate assessment of these outcomes is necessary for optimizing medical management of the disease yet they inconsistently correspond with (i) each other (Bechman et al., 2018; Hammer et al., 2019; Markusse et al., 2015; Silva et al., 2010); and (ii) patient goals in terms of patient-reported outcomes (Fleischmann et al., 2016). Patient-reported outcomes, including pain, fatigue, and functional status (Hewlett et al., 2005; Santos et al., 2019), demonstrate unique predictive power in terms of RA outcomes over time (Leigh & Fries, 1992; Markusse et al., 2015; Santos et al., 2019) and best predict treatment adherence (Fautrel et al., 2018); another routinely used measure is patient opinion of disease activity (Nikiphorou et al., 2016). Given growing emphasis on shared decision-making within patient care (Nikiphorou et al., 2016; Smolen et al., 2020;

Silvagni et al., 2020) and the evident complementary roles of both types of outcomes measures, contemporary management of RA involves consideration of both clinician-assessed and patient-reported outcomes.

Assessment Approaches for Rheumatoid Arthritis

Clinician-assessed outcomes often involve simple numerical equations. For example, there are 28 joints commonly considered in joint counts: 10 proximal interphalangeal joints and 10 metacarpophalangeal joints (in the hands), two wrist joints, two elbow joints, two shoulder joints, and two knee joints (Smolen et al., 1995). Swollen joints are enlarged due to surrounding inflammation, and tender joints produce pain for the patient (Hammer et al., 2019). With respect to inflammation, the two primary indicators considered in the assessment of RA disease activity are the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP; Park et al., 2016). The ESR is the rate at which red blood cells sediment over time, a process that speeds up during an inflammatory response (Osei-Bimpong et al., 2007) and CRP is a plasma protein that is released in response to the presence of inflammation (Kotulska et al., 2015). They are commonly assessed simultaneously, as CRP level is a more sensitive indicator of acute inflammation whereas ESR is thought to capture the general inflammatory state more appropriately (Wolfe, 1997).

Compared to clinician-assessed outcomes, approaches to the assessment of patient-reported outcomes are more heterogeneous. For example, pain has traditionally been assessed through visual analogue scales (VAS), ordinal scales, and verbal scales such as the McGill Pain Questionnaire and the Arthritis Impact Measurement Scale (Anderson, 2001). Fatigue has also been assessed through VAS and ordinal scales, as well as the Functional Assessment of Chronic Illness Therapy Scale and the Multidimensional Assessment of Fatigue scale (Hewlett et al., 2007). More recently, forms from the National Institutes of Health (NIH) Patient-Reported Outcomes Measurement Information System (PROMIS) have been validated and encouraged for the assessment of pain and fatigue in RA (Bartlett et al., 2015; Cella et al., 2010; Wohlfahrt et al., 2019). Functional status in RA is unique in that it is consistently measured with one instrument, specifically the Health Assessment Questionnaire (HAQ), which assesses disability in terms of daily activities such as dressing/grooming, hygiene, and activity (Linde et al., 2008). An abbreviated version of the measure (the modified Health Assessment Questionnaire/mHAQ) has also been developed (Maska et al., 2011). While the mHAQ demonstrates poorer

performance in high severity disease presentations relative to the HAQ, it is considered more advantageous in research settings due to its increased usability (Uhlig et al., 2006).

To thoughtfully capture both clinician-assessed and patient-reported variables, composite measures of disease activity have been developed as means of efficient, comprehensive assessment (Cordingley et al., 2014). The most empirically supported of these measures include the Disease Activity Score (DAS)-28, the Simplified Disease Activity Index, and the latter's modified version, the Clinical Disease Activity Index (CDAI; Gaujoux-Viala et al., 2012; Wohlfahrt et al., 2019). An advantage of the CDAI relative to the other two indices is it does not require laboratory tests (e.g., ESR for the DAS-28, CRP for the SDAI). As such, the CDAI allows for less bias due to patient variables (e.g., gender impacts inflammatory profiles, Kotulska et al., 2015) and greater ease in terms of routine assessment (Singh et al., 2011). These measures can be assessed as a single score or through their individual components in the evaluation of RA disease status.

Treatment Approaches for Rheumatoid Arthritis

The central target of treatment is sustained remission (Smolen et al., 2020), and current, comprehensive treatment involves patient education (e.g., on beneficial lifestyle changes such as smoking cessation), physical/occupational therapy, and drug therapy (Burmester & Pope, 2017; Majithia & Geraci, 2007). Drug therapy for RA has advanced substantially in the last several decades, given available medications and a more strategic approach to care (Fautrel et al., 2018; Wabe & Wiese, 2016). The strategy, dubbed "treat-to-target," is early diagnosis followed by aggressive pharmaceutical intervention, based off evidence indicating response to treatment is contingent on disease progression status (Majithia & Geraci, 2007; Wabe & Wiese, 2016; Wilsdon, 2017). First-line medical treatment is disease-modifying antirheumatic drugs (DMARDs), specifically methotrexate; if insufficient, combination therapy (often methotrexate with another DMARD) is attempted (Majithia & Geraci, 2007; Smolen et al., 2020; Wilsdon, 2017). Adjunctive corticosteroid therapy is often recommended in early RA with the hope use will not be prolonged (Crossfield et al., 2021). Biologics (e.g., adalimumab, etanercept, infliximab) are a final option, given they are associated with a greater risk of adverse consequences including infection (Majithia & Geraci, 2007). Upon sustained remission, it is recommended that DMARD use is tapered rather than stopped (Smolen et al., 2020).

While the advancements of the last two decades have improved treatment outcomes (Ajeganova & Huizinga, 2017), challenges to the medical management of RA remain. For example, within 18 months, 1 in 2 RA patients will be required to stop a new DMARD due to low efficacy or adverse effects, such as mouth sores, gastrointestinal symptoms, and impaired liver function (Berkun et al., 2004; Smolen et al., 2020); 20-30% of patients never reach remission (Smolen et al., 2020); and key patient concerns (e.g., fatigue) persist even among those who achieve remission (Scott et al., 2018). As such, adjustments in the management of RA appear warranted (Scott et al., 2018). The use of complementary alternative treatment (e.g., acupuncture, herbal/homeopathic medicine, meditation/yoga) is already common among RA patients (Contreras-Yáñez et al., 2020); more recently, incorporating alternative pharmacological options such as neuromodulators or antidepressants and/or non-pharmacological options such as cognitive-behavioural therapy (CBT) has proven effective for reducing pain and fatigue (Biddle & Softat, 2020). Taken together, a more holistic treatment approach to the management of RA is gaining support.

Anxiety

Clinical Description of Anxiety

Anxiety, while diverse by nature, can be loosely defined as excessive fear with behavioural consequences (APA, 2013). Anxiety is the most common mental health presentation within the general population (Statistic Canada-Health Analysis Division, 2012), with evidence suggesting more than 1 in 10 people meet criteria for clinically significant anxiety in a given year and almost 1 in 5 people will meet criteria within their lifetime (Anxiety Disorders Association of Canada, 2003; Somers et al., 2006). Anxiety is more common in women (Donnell et al., 216) and the age of onset is typically among younger adults (i.e., early 20s; de Lijster et al., 2017). Individuals with anxiety are more likely to have lower education levels (Bjelland et al., 2008). Although convoluted by diagnostic biases (Neighbors et al., 2003), data suggests some racial groups, such as Indigenous peoples, are at increased risk of elevated anxiety symptoms (Smith et al., 2006). North Americans as a whole demonstrate the highest rate of maladaptive anxiety internationally (Remes et al., 2016), although this assessment is potentially confounded as well (e.g., by social norms, language differences, etc.; Hofmann & Hinton, 2014).

The past decade has brought a rise in research interest on anxiety, likely due to a greater recognition of its' adverse functional outcomes (Ravindran & Stein, 2010; Remes et al., 2016).

Consequences of anxiety on functioning include worse employment outcomes (i.e., rates of employment, career progression, work productivity; Waghorn et al; 2005), reduced quality of life (Sherbourne et al; 2010), increased morbidity (e.g., approximately 50% of patients with clinically significant anxiety levels meet criteria for depression; Demyttenaere & Heirman, 2020; Hofmeijer-Sevink et al., 2012), and increased mortality by both natural (e.g., disease) and unnatural (e.g., suicide) causes (Meier et al., 2016).

The construct of anxiety can be conceptualized in a variety of ways, including Aaron Beck's cognitive theory. This derivative of the biopsychosocial model involves four self-perpetuating components: physiological factors, cognitive factors, behavioural factors, and emotional factors (Deary et al., 2007). According to cognitive theory, a situation (e.g., noticing an irregular ache) may generate a physiological experience (e.g., increased heart rate), evoking a cognitive experience (e.g., "What if I am sick?"), resulting in a behavioural response (e.g., getting into bed), leading to an emotional consequence (e.g., fear), which only furthers physiological disturbances. As illustrated, a feedback loop is created. It should be noted anxiety exists on a continuum, from low or appropriate levels of anxiety that could be considered adaptive (e.g., the "fight or flight" response experienced when a bear enters your campground) to anxiety that has likely entered the aforementioned feedback loop and is considered maladaptive, or *clinical*. Position on the anxiety continuum will be partially dependent upon *trait anxiety*, defined as an individual's reaction tendencies in a range of situations, and levels of *state anxiety*, a transitory experience in response to stress (Endler et al., 2001). From this point on in the dissertation, mention of anxiety should be considered interchangeable with the term clinical anxiety i.e., the more severe, maladaptive presentation of anxiety. Some common symptoms of anxiety include excessive worry, avoidance, and physical manifestations such as sweating, trembling, heart palpitations and nausea (Craske et al., 2009).

Anxiety is designated as clinically significant in one of two ways: through the determination of specific anxiety disorders and through identifying the presence/severity of anxiety symptoms common to multiple anxiety disorders. Traditionally, the former approach has been favoured. A formal anxiety disorder diagnosis requires certain criteria, outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM), are met (when the diagnosis is made in Canada). There were seven core DSM-Fourth Edition (DSM-IV) anxiety disorders addressed by the Public Health Agency of Canada (Public Health Agency of Canada, 2016).

These disorders are: generalized anxiety disorder (GAD), social phobia/social anxiety disorder, specific phobia, panic disorder, agoraphobia, obsessive-compulsive disorder (OCD), and posttraumatic stress disorder (PTSD; APA, 2000). OCD and PTSD were then formally re-conceptualized in 2013 and re-categorized into their own subgroups, obsessive-compulsive and related disorders and trauma-and-stressor related disorders, respectively (APA, 2013). The clinical presentations, however, are both still characterized by a foundation of anxiety and alterations in arousal and fear avoidance and therefore remain relevant in anxiety research and treatment (Asmundson, 2019).

Assessment Approaches for Anxiety

Anxiety symptoms are often evaluated with self-report measures. Some of the most commonly used measures include the Beck Anxiety Inventory (BAI; Beck et al., 1988), the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS; Zigmound & Snaith, 1983), and the Generalized Anxiety Disorder 7-item scale (GAD-7; Spitzer et al., 2006). More recently, PROMIS forms have been validated for the assessment of anxiety (and depression; Cella et al., 2010). Anxiety test bank items pertain to fear (e.g., feelings of panic), anxious misery (e.g., dread), hyperarousal (e.g., restlessness) and related somatic symptoms (Cella et al., 2010). While demonstrating correlations with legacy measures (Cella et al., 2010; Sunderland et al., 2018), advantages of the PROMIS system include: a collaborative, interdisciplinary development process; extensive testing for establishing norms; reduction in floor and ceiling effects; and domain-specific (as opposed to disease-specific) test banks with standardized scoring, as to allow for comparisons across populations and studies (Bevans et al., 2014). Ultimately, the PROMIS system provides a "universal language" for assessing anxiety symptoms (Bevans et al., 2014). The diagnosis of a specific anxiety disorder requires more comprehensive clinical evaluation. Certain diagnostic tools, such as the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM) Axis I Disorders (SCID; First et al., 1997), have been developed to support and objectify this diagnostic process. As to align with the evolving DSM, the SCID is revised as new DSM editions are released.

There are advantages to both conceptual approaches (i.e., assessing for symptoms versus disorders) when determining clinically significant anxiety. For example, many empirically supported interventions are disorder-specific, with targets (cognitive, behavioural, pharmacological, etc.) tailored for a particular mental health condition (Gutner & Presseau,

2019; Titov et al., 2015). However, a categorical approach to the assessment of anxiety is problematic for several reasons. Given that anxiety is an adaptive response in many circumstances, determination of the threshold for clinical anxiety is multifactorial (e.g., cultural context), which opens classification to bias (Aquin et al., 2017). Similarly, given anxiety disorders (as well as other psychiatric conditions) are highly comorbid with other mental health presentations, identification of a primary diagnosis is open to bias (Bystritsky et al., 2013; Snowden, 2003). Comorbidity can also result in several co-existing subsyndromal presentations; although the DSM does not recognize these presentations, clinical impairment from these symptom manifestations is apparent (Möller et al., 2016). Finally, as anxiety symptom trajectories evolve, time might reveal that a presentation initially defined with one label (e.g., panic disorder) is better defined by another label (e.g., OCD), resulting in a preliminary identification error (Bystritsky et al., 2013). Given these diagnostic challenges, assessment is moving towards transdiagnostic, symptom-based models (Bystritsky et al., 2013; Clark et al., 2017; Endler et al., 2001; McGorry et al., 2020). For example, the Hierarchical Taxonomy of Psychopathology (HiTOP) is a hierarchy-based, alternative model to DSM diagnosis that conceptualizes mental health presentations through transdiagnostic dimensions of psychological dysfunction (e.g., obsession, blame externalization, reality distortion; Kotov et al., 2021). Accordingly, transdiagnostic treatments, based on evidence-based practices for common treatment goals in the context of poor mental health, are growing in popularity (Hoffman & Hayes, 2019; Titov et al., 2015). These treatments better allow for real world nuance, such as comorbidity (e.g., co-occurring anxiety and depression) and patient individuality (e.g., symptom etiology, symptom course; Hoffman & Hayes, 2019).

Treatment Approaches for Anxiety

The most empirically supported treatment approach for reducing anxiety symptoms is participation in psychotherapy (Butler et al., 2006). Anxiety, both in terms of symptoms and specific disorders, is treated with a variety of psychological approaches, including interpersonal therapy (Cuijpers et al., 2016), mindfulness-based therapy (Hofmann et al., 2010), and CBT (Olatunji et al., 2010), among others. The latter is the most extensively investigated and validated of the psychotherapeutic treatment approaches for reducing anxiety (Butler et al., 2006). The effectiveness of CBT has been demonstrated with large effect sizes using numerous psychological measures of anxiety, both immediately following treatment (Watts et al., 2015)

and up to a year post-treatment (DiMauro et al., 2013). Pharmacotherapy is also an effective treatment approach (Ravindran & Stein, 2010), however, CBT is typically considered advantageous to medications (e.g., greater long-term efficacy, fewer side effects) when treating anxiety disorders (Roshanaei-Moghaddam et al., 2011). While a two-pronged approach, involving CBT and pharmacotherapy, is common in practice, evidence suggests combined therapy might attenuate the long-term effects of psychotherapy (e.g., through minimizing opportunity to extinguish fears; Otto et al., 2006); as such, CBT remains the gold-standard treatment for anxiety at present.

While traditionally implemented in both individual therapy and group therapy settings, there is support for the adaptation of CBT therapy into online formats as well (Christensen et al., 2014). The approach translates well to an online platform given that CBT is based on therapist-guided learning and skills practice (Musiat & Tarrier, 2014). Online options offset some of the traditional barriers to care including high costs, long-waiting lists, limited availability of health care resources, and access concerns (Dear et al., 2013). Although effect sizes vary dependent on intervention characteristics (e.g., outcomes are typically better when programs include therapist involvement; Andersson & Cuijpers, 2008), the effectiveness of online CBT interventions for reducing the severity of anxiety symptoms has been well-established, using both disorder-specific (Dugas et al., 2010; Hobfoll et al., 2016; Wims et al., 2010) and transdiagnostic anxiety protocols (Powell et al., 2013; Proudfood et al., 2003). Of note, intervention targets remain a relevant consideration in transdiagnostic interventions e.g., psychosis-focused interventions appear to be less effective for the reduction of anxiety symptoms than anxiety-focused interventions, despite symptom overlap such as fear (Waller et al., 2013). Altogether, the evidence supports transdiagnostic yet targeted CBT interventions for anxiety, while endorsing online formats as a promising treatment option.

Comorbid Anxiety and Rheumatoid Arthritis

Clinical Description of Comorbid Anxiety and Rheumatoid Arthritis

Discussion of anxiety in RA is highly warranted, as mental health comorbidity is both common in RA and relatively overlooked in terms of treatment (VanDyke et al., 2004). This is particularly true with anxiety (Fiest et al., 2017). As reviewed by Ryan and McGuire (2016), investigations of mental health comorbidity in RA began with anecdotal evidence of disproportionately high levels of psychological disorders among RA patients. Formal assessment

was initially limited by the overlap of symptoms between RA and various presentations of poor mental health, such as fatigue (Creed et al., 1990). However, as the clinical implications of mood disorders in RA became increasingly recognized, psychological measures were developed and validated for use within RA populations (e.g., the Hospital Anxiety and Depression Scale [HADS]; Chandarana et al., 1987). The early research focus was on depressive symptomatology (Ang et al., 2005; Nenova et al., 2013; Nikolaus et al., 2013), and as such, the relationship between depression and RA has been well-documented.

Approximately 10-40% of RA patients meet criteria for major depressive disorder (Hitchon et al., 2020; Margaretten et al., 2011; Matcham et al., 2013), with prevalence studies suggesting approximately 30-50% of RA patients endorse clinically significant depressive symptoms (Covic et al., 2012; Matcham et al., 2013). The incidence of depression is approximately 1.5 times that of age-, sex-, and geographically-matched controls (Marrie et al., 2017). Depression has been shown to exacerbate illness outcomes, resulting in higher rates of disability (Iaquinta & McCrone, 2015; Jamshidi et al., 2016; Rupp et al., 2006b), reduced quality of life (Bazzichi et al., 2005; Beşirli et al., 2020; Guerrero-López et al., 2017), and higher rates of morbidity (Wolfe & Michaud, 2009) and mortality (Ang et al., 2005) compared to RA patients without depression.

In terms of disease correlates, depression has been associated with worse joint counts (Kwiatkowska et al., 2018; Ng et al., 2020), serum inflammation levels (Cheon et al., 2018; Kojima et al., 2009; Zhang et al., 2017), composite scores of disease activity (Borges et al., 2017; Cheon et al., 2018; Gomez et al., 2019; Imran et al., 2015; Kwiatkowska et al., 2018; Zhang et al., 2017), pain (Edwards et al., 2011; Melikoglu & Melikoglu, 2010; Rathburn et al., 2013; Sariyildiz et al., 2013; Soósová et al., 2017; Zhang et al., 2017), fatigue (Cheon et al., 2018; Nikolaus et al., 2013; Sariyildiz et al., 2013; Stebbings et al., 2010), and functional status (Imran et al., 2015; Kwiatkowska et al., 2018; Sariyildiz et al., 2013; Soósová et al., 2017; Zhang et al., 2017). There is also evidence of temporal impacts, with depression associated with worsened joint counts (Matcham et al., 2016a; Matcham et al., 2018a), serum inflammation levels (Matcham et al., 2018a), composite scores of disease activity (Cadena et al., 2003; Hider et al., 2009; Kuijper et al., 2018; Leblanc-Trudeau et al., 2015; Rathburn et al., 2013; Sautner et al., 2020), pain (Edwards et al., 2011; Jamshidi et al., 2016; Kekow et al., 2011; Rathburn et al.,

2013), fatigue (Feldthusen et al., 2016; van Hoodmoed et al., 2010; Kekow et al., 2011;), and disability (Karpouzas et al., 2017; Morris et al., 2011; Sautner et al., 2020) over time.

Estimates of anxiety in RA are even higher than those pertaining to depression (El-Miedany & El Rasheed, 2002). Studies suggest 25-70% of RA patients meet criteria for an anxiety disorder (El-Miedany & El Rasheed, 2002; Matcham et al., 2018b), as many as 85% of patients have clinically significant anxiety symptoms (Soósová et al., 2017), and the incidence of anxiety is also increased relative to age-, sex-, and geographically-matched controls (Marrie et al., 2017). Of note, more patients than not exhibit symptoms of both anxiety and depression, as these mental health presentations are highly comorbid (Covic et al., 2012; Isik et al., 2007). Patients with comorbid anxiety and RA are more likely to be female and of lower socioeconomic status (SES; Watad et al., 2017). Preliminary investigations of RA samples suggest anxiety is associated with worse illness outcomes such as increased disability (Börsbo et al., 2008; Jamshidi et al., 2016), reduced quality of life (Beşirli et al., 2020; Guerrero-López et al., 2017), and increased mortality (Marrie et al., 2018).

In terms of disease correlates, anxiety has been associated with worse joint counts (i.e., tender joint count; Brahem et al., 2017; Ng et al., 2020), serum inflammation levels (Cordingley et al., 2014; Liu et al., 2012), composite scores of disease activity (Borges et al., 2017; Cadena et al., 2003; Goma et al., 2019), pain (Jamshidi et al., 2016; Zhang et al., 2017), fatigue (Lapčević et al., 2017; Mancuso et al., 2006; Nikolaus et al., 2013; Stebbings et al., 2010), and functional status (Brahem et al., 2017; Soósová et al., 2017). Although fewer longitudinal studies of co-occurring anxiety and RA exist compared to cross-sectional investigations (Fiest et al., 2017; Ødegård et al., 2007), anxiety in RA has been shown to predict worse joint counts (i.e., tender joint count; Matcham et al., 2016a) and composite scores of disease activity (Kuijper et al., 2018) as well as greater pain (Kekow et al., 2011; Ødegård et al., 2007), fatigue (Kekow et al., 2011; Mancuso et al., 2006) and functional disability (more specifically, the anxiety-related construct, anxiety sensitivity; Bernstein et al., 2019) over time. However, several studies have contradicted these findings as well, instead demonstrating no effect of anxiety on disease outcomes (e.g., Beşirli et al., 2020; Matcham et al., 2016a; Walter et al., 2018).

Comorbidity Theories

Prior to conceptualizing comorbid anxiety and RA from a biopsychosocial perspective, it can be helpful to understand the most prominent theories of comorbidity previously applied or

applicable to anxiety in RA. Comorbidity theory tends to fall into one of three camps: shared common pathways, shared risk factors, and one-directional causation (Marrie & Bernstein, 2021). Evidence of all three is detailed below.

Biological Theories. Inflammation is central to all biological theories of psychological comorbidity in RA. With the accumulation of immunological studies on both RA and psychological distress over the last two decades (Lumley et al., 2011), commonality in the inflammatory profiles of patients with RA and individuals with clinical anxiety is well documented (Marrie & Bernstein, 2021). Specifically, both patient groups tend to exhibit elevated concentrations of inflammation-inducing cell-signalling molecules produced by the immune system, collectively referred to as pro-inflammatory cytokines (McInnes et al., 2016). Two prominent cytokines that characterize the peripheral inflammation associated with RA are interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), both of which have been connected to clinical anxiety (Chae et al., 2016; McInnes et al., 2016; O'Donovan et al., 2010; Steptoe et al., 2001; Wohleb et al., 2014). As such, it can be speculated that RA is a physical health manifestation of this inflammatory dysfunction, whereas anxiety is a mental health manifestation of the same inflammatory processes. In support of this inflammation-based hypothesis, mood and anxiety improvements have been documented when RA is treated with immunomodulating drugs (e.g., some biologics; Ingegnoli et al., 2020) and neuroinflammation has been found in animal models of RA (Süβ et al., 2020).

Dysregulation of a common biological pathway provides a mechanistic explanation for the above findings, with the most plausible pathway being the hypothalamic-pituitary-adrenal (HPA) axis. The immune system and the nervous system are in continuous, bidirectional communication, primarily through the HPA axis (Ingegnoli et al., 2020). All means of communication are beyond the scope of this dissertation, however, key points will be reviewed. Going one direction, systemic inflammation interacts with the HPA axis at multiple sites, leading to an overproduction of cortisol, a hormone correlated with anxiety symptomatology (O'Donovan et al., 2010; Silverman et al., 2005). Cortisol produces consequences on several neurotransmitter systems in the brain (Ingegnoli et al., 2020) e.g., serotonin, a neurochemical linked to anxiety (e.g., Pum et al., 2009; Steinberg et al., 2019) as well as glucocorticoid levels, which regulate neuronal transmission and synaptic changes associated with mental health symptoms (Numakawa et al., 2014). Conversely, the central nervous system regulates the

immune system via hormonal effects on the HPA axis as well as direct innervation of organs within the immune system such as lymph nodes and the spleen (Eskandari et al., 2003; Schiller et al., 2021; Wrona, 2006). Taken together, chronic excitation of the HPA axis might, at minimum, contribute to mental health symptoms in the context of RA. Support for this includes various forms of abnormal HPA axis activity among RA patients (Jessop & Harbuz, 2005) as well as among individuals with elevated anxiety (Taget & Nemeroff, 2020).

An alternate, possibly conjunctive, explanation for inflammation commonalities between RA patients and individuals with anxiety is shared risk factors with biological consequences, including genetics and adverse experiences. In reference to the former, a genome-wide association study provided evidence of pleiotrophy, where one phenotypic expression appears to be PTSD and another RA (Stein et al., 2016). In reference to the latter, early adverse events (e.g., childhood physical trauma), linked to the later development of any anxiety disorder (Copeland et al., 2018) as well as RA (Spitzer et al., 2013), are also associated with HPA axis dysregulation (Klaassens et al., 2009; Kuhlman et al., 2015) and systemic inflammation (Baumeister et al., 2016). Additional hypotheses will likely emerge in time, as the biological mechanisms of comorbidity represent an area of research still in its infancy.

Psychological/Behavioural and Social/Environmental Theories. Historically, psychological theories of mental and physical health comorbidity were largely framed as one-directional. For example, illness places unique demands (e.g. increased dependence, reduced physical capability) on preexisting coping resources, which might aggravate or instigate psychiatric conditions (Edmondson, 2014; Vallerand et al., 2019). Alternatively, mental health symptoms can be framed as a product of identity disruption (Golub et al., 2014), due to aspects of illness such as functional limitations (e.g., sexual function; Tristano, 2014) and changes in body image (Jenkinson, 2009). According to both explanations, mental health symptoms (i.e., anxiety) are a consequence of illness (i.e., RA). Behavioural theories (different than psychological theories, although they are sometimes collapsed) of comorbidity, on the other hand, tend to focus on shared risk factors. For example, smoking is both a risk factor for adult-onset anxiety (e.g., panic disorder; Isensee et al., 2003) and the development of RA (e.g., RA is twice as likely in smokers relative to non-smokers; Chang et al., 2014).

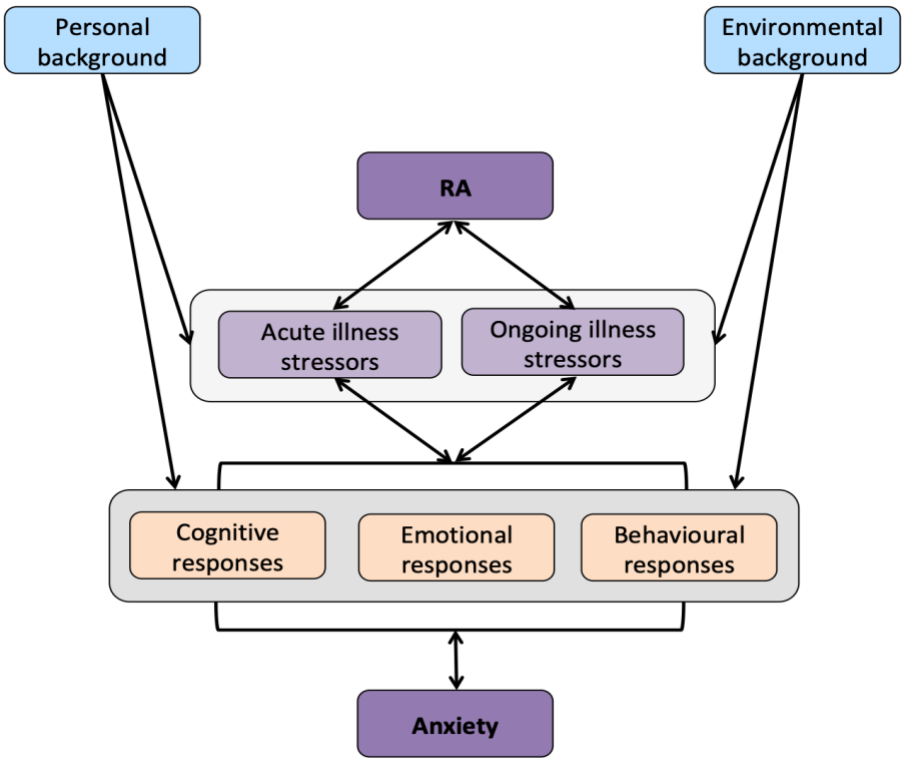
Social theories are best used to explain the exacerbation of physical and mental health outcomes during comorbidity, specifically through shared social dynamics (i.e., shared

pathways), whereas environmental theories are able to address etiology in comorbid conditions (i.e., shared risk factors). Beginning with social theories, living with RA has been associated with adverse social consequences (e.g., removal from the workplace; Klak et al., 2016) and low social support predicts adverse physical health outcomes (e.g., pain intensity, pain interference) in the context of chronic pain (Meints & Edwards, 2018). Similarly, anxiety demonstrates an adverse impact on interpersonal relationships (e.g., through increased social avoidance; Wu et al., 2013) and low social support is associated with more severe anxiety (Wang et al., 2018). Therefore worsened outcomes of both RA and anxiety, as a consequence of shared poor social support, fits conceptually during co-occurrence; the hypothesis is strengthened by demonstrated linkage between lower social support, more severe pain, and more severe depression in RA (Brandstetter et al., 2017; Costa & Gouveia, 2013). Coming from an alternate angle, certain environmental theories of RA and anxiety can be used to explain their high co-occurrence; for example, low childhood socioeconomic status appears to be a shared risk factor given its association with the development of both RA (Park et al., 2013) and adult anxiety (Morrissey & Kinderman, 2020).

As means of amalgamating important considerations, several relevant theories have been recently integrated into one primarily psychosocial framework (Dekker & Groot, 2018). This model, illustrated in Figure 1.1, was developed with the intention of conceptualizing psychological adjustment to illness in accordance with the World Health Organization (WHO) International Classification of Functioning, Disability and Health (ICF) framework of health (Dekker & Groot, 2018). The ICF, an increasingly recognized conceptual model in medicine, has already been applied to RA (Pfaller et al., 2020; Stucki & Cieza, 2004). I will use Dekker & Groot's model to conceptualize anxiety (as opposed to adjustment difficulties broadly) in the context of RA. The model speaks to both etiology and maintenance of co-occurring anxiety and RA.

Figure 1.1

Dekker & Groot's (2018) World Health Organization (WHO) International Classification of Functioning, Disability and Health (ICF) Framework for Psychological Adjustment to Illness, Applied to Anxiety in the Context of RA



The model delineates *acute stressors* (e.g., beginning an initial medication trial) from *ongoing stressors* (e.g., uncertainty about the future) due to illness. These stressors are met with three types of responses, occurring in interactive parallel (Dekker & Groot, 2018); these responses (highlighted in orange) involve both psychological and behavioural factors. Adaptive *cognitive responses* include self-efficacy, whereas an example of a maladaptive cognitive response is catastrophizing. Adaptive *emotional responses* include emotional awareness/openness, whereas a maladaptive emotional response might be alexithymia-like (i.e., involving minimal expression of painful emotions). Adaptive *behavioural responses* include daily movement, whereas a maladaptive behavioural response might be a sedentary lifestyle. Support for the relevance of these responses in co-occurring anxiety and RA has been previously established. Catastrophizing is associated with adverse health outcomes (e.g., greater disability; Sinclair, 2001) and higher levels of anxiety (Ryan & McGuire, 2016) in RA. Alexithymia is associated with worse disease outcomes (e.g., higher inflammation; Chimenti et al., 2019) and

greater anxiety in RA (Ryan & McGuire, 2016). Sedentary behaviour predicts worse health outcomes in both healthy individuals (e.g., inflammation) and patients with RA (e.g., pain; Fenton et al., 2018), and has been associated with anxiety universally (Allen et al., 2019). These psychological and behavioural responses appear to, at the very least, maintain co-occurrence and exacerbate outcomes; plausibly, these responses help explain the onset of anxiety in RA as well.

The model positions two factors as moderators of how illness stressors (both acute and ongoing) are experienced and what responses are elicited: *personal background* and *environmental background* (Dekker & Groot, 2018). Personal background may include personality structure and perceived social support, whereas environmental background might include socioeconomic status; through these variables (highlighted in blue), social and environmental factors are incorporated into the model. Aside from relevant associations previously mentioned pertaining to social support and socioeconomic status, suitability of this portion of the model when conceptualizing anxiety in RA is supported by: links between personality dysfunction and both RA (Blaney et al., 2020) and anxiety (e.g., Skodol et al., 2014); and associations between certain sociodemographics (e.g., highest education level achieved) and both RA (Liao et al., 2009) and anxiety (Bjelland et al., 2008; Erickson et al., 2016) i.e., higher education is a protective factor for both conditions. These social and environmental factors appear to speak to both etiology and maintenance.

The authors acknowledged the existence of bidirectional pathways in their model, but refrained from including a greater discussion of these complex relationships for the purpose of clarity (Dekker & Groot, 2018). Bidirectionality, however, in the relationship between anxiety and RA, is widely acknowledged (Aquin et al., 2017; Dekker & Groot, 2018; Ingegnoli et al., 2020; Kekow et al., 2011). When framing anxiety in RA with the ICF model, *mutual maintenance* (i.e., bidirectional impacts due to shared maintaining factors; Sharp & Harvey, 2001) is highly apparent. An additional example of relevant mutual maintenance, not illustrated in *Figure 1*, includes peripheral inflammation associated with RA dysregulating neurotransmitters implicated in anxiety, resulting in the increased release of peripheral inflammation (Ingegnoli et al., 2020). Ultimately, the relationship between anxiety and RA should be viewed as complex, likely synergistic, and in need of both biological and psychological treatment considerations.

Gaps in the Literature

While our understanding of mental health in RA and other immunological disorders is advancing rapidly, there remain significant gaps; among other factors, these gaps impede the shift towards a biopsychosocial approach to care. Anxiety being poorly understood relative to depression in RA is a particularly pertinent gap. A driving factor in this discrepancy is the tendency to collapse mental health symptoms into "mixed mood" or "psychological distress," as opposed to examining anxiety independent of depressive symptoms (Bacconnier et al., 2015; El-Miedany & El Rasheed, 2002; Euesden et al., 2017; Matcham et al., 2016b; Michelson et al., 2017). While partially explained by lack of consensus as how to best evaluate anxiety symptomatology in this patient population (Kilic et al., 2016; Scott et al., 2018), this lack of consensus has led to incongruity in the existing literature in terms of anxiety estimates and associated outcomes. As such, there is need to explore anxiety alone in the context of RA, in terms of distribution and associated outcomes, using appropriate assessment tools that can be applied clinically.

There is also a need to better understand the long-term consequences of anxiety on RA outcomes, thereby calling for investigations over time. To date, lack of access to comprehensive, longitudinal data including anxiety measures (Cheon et al., 2018; Machin et al., 2020) has limited existing studies to primarily cross-sectional designs. Further, given recognized heterogeneity in anxiety course (Batelaan et al., 2014), any possible interaction effects between anxiety severity and time need be considered.

Beyond this, a formal evaluation of a psychological intervention targeting anxiety in an RA population had yet to be conducted (Fiest et al., 2017), despite longstanding implementation of CBT strategies among RA patients for other concerns (e.g., pain management; Sharpe et al., 2016). Further, although there is support for the use of online CBT programs with RA patients (e.g., Smarr et al., 2011; Spillekom-van Koulil, 2018), the feasibility of an online mental health intervention that does not involve therapist assistance was unknown. These gaps required addressing given that anxiety is best treated through an anxiety-focused intervention (Boersma et al., 2019; Waller et al., 2013); online interventions are a particularly workable option for widespread implementation across health care systems (Moroz et al., 2020); and treatment of anxiety might mitigate disease outcomes in RA.

Aims

The purpose of this dissertation is to examine anxiety in the context of RA, with the objective of addressing these notable limitations in the literature. There are two sub-studies. The first study addresses anxiety symptom severity over time, in terms of trajectory and impacts on both clinician-assessed and patient-reported outcomes. This study used comprehensive, longitudinal data collected from across the province of Manitoba. The second study tested the feasibility of a targeted, Internet-based CBT intervention for anxiety (and depression) among those with RA and elevated anxiety, and preliminarily explored the impact on mental and physical health outcomes. Together, these studies will address relevant questions in terms of anxiety assessment, impact and treatment in RA, therefore potentially informing the development of a stepped care approach to addressing mental health symptoms in people with RA.

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Chapter 2: Study 1

Trajectories of Anxiety Symptomatology and Their Association to Clinical Indicators in a Rheumatoid Arthritis Sample

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Abstract

Objective: Anxiety is both prevalent and poorly understood in the context of rheumatoid arthritis (RA). Existing investigations of co-occurring anxiety in RA support adverse effects of anxiety on disease outcomes (e.g., functional disability, joint counts, disease activity, pain, and fatigue); however the literature is mixed and lacking in longitudinal studies. To better understand these mixed findings and contribute to the literature, I (1) explored the possibility of distinct anxiety trajectory groups; (2) attempted to characterize these groups by examining cross-sectional associations between groups and patient characteristics, mental health characteristics, and disease characteristics; and (3) examined longitudinal associations between groups and disease outcomes over time.

Methods: The current study sample (n=154) was extracted from a larger study examining mental health comorbidity in immune diseases in Manitoba, Canada, across 3 years. Annual longitudinal data were collected for several disease outcomes (i.e., swollen joint count, tender joint count, composite score of disease activity, functional status, pain, and fatigue). I used group-based trajectory analysis to determine trajectory groups of anxiety symptom severity; descriptive statistics followed by chi-square and analysis of variance (ANOVA) to compare groups at baseline; and mixed model regression analysis to determine whether anxiety trajectory groups uniquely predicted disease outcomes over time.

Results: Three distinct anxiety trajectory groups were identified; 60.4% of the sample fell in the normative range for anxiety, 24.0% of the sample had persistent mild levels of anxiety, and 15.6% of the sample had persistent moderate levels of anxiety. At baseline, anxiety severity was linearly associated with younger age, non-White ethnicity, lower education, and higher BMI. Additionally, baseline anxiety severity was linearly associated with depressive symptom severity, composite scores of disease activity, functional disability, pain, and fatigue (i.e., more severe anxiety was associated with worse outcomes). Mild anxiety did not appear to worsen outcomes over time, whereas moderate anxiety was associated with worsening fatigue only.

Conclusion: This study support routine anxiety screening in the management of RA and anxiety intervention as means of mitigating adverse disease consequences.

Introduction

Mental health comorbidity is an increasingly recognized feature of living with rheumatoid arthritis (RA). Estimates suggest 30-60% of RA patients exhibit symptoms of depression (Beşirli et al., 2020; Covic et al., 2012; Juárez-Rojop et al., 2020; Matcham et al., 2013; Pu et al., 2018) and as many as 70% of RA patients exhibit symptoms of anxiety (Covic et al., 2012; El-Miedany & El-Rasheed, 2002; Juárez-Rojop et al., 2020; Ryan & McGuire, 2016). Cross-sectional and longitudinal correlates of depression in RA include worse/worsened clinician-assessed outcomes, such as joint counts (Matcham et al., 2016a; Ng et al., 2020) and indicators of inflammation (Cheon et al., 2018; Matcham et al., 2018), as well as patient-reported outcomes, such as pain (Jamshidi et al., 2016; Soósová et al., 2017) and fatigue (Feldthusen et al., 2016; Nikolaus et al., 2013). While select studies support similar associations between comorbid anxiety and disease outcomes (Brahem et al., 2017; Cordingley et al., 2014; Kekow et al., 2011; Lapčević et al., 2017; Matcham et al., 2016a; Zhang et al., 2017), findings are highly mixed due to null results (Beșirli et al., 2020; Matcham et al., 2016a; Walter et al., 2018) and certain (e.g., temporal; Machin et al., 2020) hypotheses remain untested; relative to depression in the same patient group, anxiety in RA is poorly understood (Fiest et al., 2017).

Inconsistency across findings is largely explained by measurement approaches. First, there is a tendency across comorbidity studies to collapse symptoms of anxiety and depression into mixed mood symptoms or "psychological distress" (Bacconnier et al., 2015; El-Miedany & El Rasheed, 2002; Euesden et al., 2017; Matcham et al., 2016b; Michelson et al., 2017). Although the majority of individuals with RA present with both depressive and anxiety symptoms (Covic et al., 2012; Isik et al., 2007), a mixed mood construct hinders assessment of anxiety independent of depression. Second, there is a lack of consensus in terms of what constitutes clinically significant anxiety in RA (Kilic et al., 2016; Scott et al., 2018**).** For example, both elevated anxiety symptoms and anxiety disorders have been used in comorbidity investigations, leading to comparisons between measurement approaches that vary in sensitivity and specificity. Third, existing investigations have primarily used a categorical approach to anxiety as an independent variable (e.g., presence versus absence of an anxiety disorder, dichotomizing symptom severity). While common in research, there is growing concern in using a categorical approach to assessing psychological symptoms (Waszczuk et al., 2017). For example, when using the same measure (Hospital Anxiety Depression Scale, or HADS) to create

variables, continuous variables outperform dichotomized variables in predicting functional impairment (Bjelland et al., 2009) i.e., categorical variables appear to increase risk of Type II error.

Untested temporal hypotheses are largely explained by the relative dearth of longitudinal studies on anxiety in RA (Euesden et al., 2017). This dearth can be attributed to a lack of comprehensive, longitudinal datasets including anxiety measures (Cheon et al., 2018; Machin et al., 2020). Reliance on cross-sectional designs has prevented investigating moderation due to anxiety course and anxiety symptom severity in the relationship between anxiety and RA. Although anxiety course has yet to be investigated in this context, anxiety is notoriously dynamic (Batelaan et al., 2014) and distinct anxiety trajectories (i.e., patterns of symptoms over time) have been identified in other populations, with unique functional impacts. For example, among postpartum women, only increasing prenatal anxiety is associated with adverse infant outcomes (Irwin et al., 2020). Additionally, both mixed anxiety/depression trajectory groups and depression trajectory groups uniquely predict outcomes in RA over time; more specifically, low, increasing mixed mood is associated with less pain improvement than low, stable mixed mood (Norton et al., 2011) and chronic depression has higher risk of disability than intermittent depression (Morris et al., 2011). Evaluating the relevance of anxiety symptom severity in the association between anxiety and RA is also supported, as symptom severity appears to moderate correlates of depression in RA (Imran et al., 2015). Relatedly, anxiety severity demonstrates meaningful effects in terms of anxiety correlates in other health populations (e.g., cancer; Omran & Mcmillian, 2018) as well as non-health populations (e.g., mood disorders; Coryell et al., 2012).

Taken altogether, in this study I chose a dimensional approach to evaluating anxiety symptomatology independent of depression, while considering the feasibility of the approach across a range of research contexts (i.e., to support homogeneity of measures). To investigate the relevance of both anxiety course and severity concurrently, I chose to conduct a group-based trajectory analysis of anxiety in RA followed by an examination of longitudinal associations between groups and disease outcomes over time. For my sample, I used a large, longitudinal, comprehensive data set established through a province-wide study conducted in Manitoba. For my anxiety variable, I used a brief, self-report measure of anxiety symptoms (Cella et al., 2010; Schalet et al., 2014; Sunderland et al., 2018), well validated for use in an RA population

(Hitchon et al., 2020) and assessed continuously. My aims in this study were to: (1) explore whether sub-groups in terms of anxiety symptoms over time (i.e., trajectory groups) exist in RA; (2) identify the trajectory groups in terms of baseline patient characteristics, mental health characteristics, and disease characteristics (given the novelty of anxiety trajectory groups in RA); and (3) determine how group membership predicts disease outcomes (i.e., functional disability, tender joint count, swollen joint count, composite score of disease activity, pain, and fatigue) over time (specifically, rates of change).

Methods

Sample and Procedure

This sample was drawn from a larger study examining mental health comorbidity in the context of immune-mediated inflammatory disease in Manitoba, Canada (Marrie et al., 2018a). Recruitment for this larger study was conducted between November 2014 and July 2016. Individuals with inflammatory bowel disease (IBD), multiple sclerosis (MS) and RA were recruited through conversations at scheduled medical appointments, targeted mail, advertisements in hospitals/private medical clinics, and word of mouth (Marrie et al., 2018a). The final study population included 154 participants with RA. The study received ethical approval from the University of Manitoba Health Research Ethics Board as well as the Research Committee of the Winnipeg Regional Health Authority, Winnipeg Health Sciences Centre, St. Boniface Hospital, Seven Oaks Hospital, and Victoria General Hospital.

For the current study, RA patient data was extracted. To be included in the RA cohort, participants had to meet criteria for an RA diagnosis based on the 2010 ACR/EULAR Rheumatoid Arthritis Classification Criteria: 1) confirmed synovitis of at least 1 joint; 2) a score of 6/10 or greater from the addition of four sub-scores: number and site of involved joints (score range: 0-5), serologic abnormality (score range: 0-3), elevated acute-phase response (score range: 0-1), symptom duration (score range: 0-1); and 3) the absence of a more fitting, alternative diagnosis (Aletaha et al., 2010). All participants provided written consent for the use of their data.

Data collection occurred four times: upon recruitment (i.e., baseline) followed by three consecutive collections separated by a year. Time periods were fixed i.e., intervals between data collections were approximately one year apart for every participant. Assessments were completed primarily in-person, although baseline diagnostic assessments were also completed

over the phone. Measures were mailed only if participants were unable to attend in person for that assessment. Graduate students in clinical psychology, nurses, and research coordinators conducted any in-person or phone assessments. Baseline mental health variables included anxiety symptom severity, depressive symptom severity, and presence of an anxiety or depressive disorder. Only the latter (i.e., the presence of mental health disorder diagnoses) were removed from subsequent assessments. Baseline physical health/disease outcome variables included functional disability, tender joint count, swollen joint count, composite score of disease activity, pain, and fatigue; these outcomes were re-assessed annually.

Measures

Mental Health Measures.

National Institutes of Health (NIH) Patient-Reported Outcomes Measurement Information System (PROMIS) Anxiety and Depression Short Forms (Form 8a). PROMIS is a system of self-report outcome measures initially developed and validated in the general population, yet increasing used with health populations (Cella et al., 2010; Marrie et al., 2018b; Quach et al., 2016). The PROMIS instruments were developed to provide a universal assessment approach to core domains of health across patient populations and settings (Witter, 2016). They are comparable to legacy measures (Cella et al., 2010; Schalet et al., 2014; Sunderland et al., 2018) such as the General Anxiety Disorder-7 (GAD-7) for anxiety and the Patient Health Questionnare-9 (PHQ-9) for depression. Advantages to using PROMIS measures in this study include their sensitivity to temporal changes in negative affect (i.e., anxiety, depression; Schalet et al., 2016) and their validation for use in RA specifically (Bartlett et al., 2015; Cella et al., 2010; Hitchon et al., 2020). Each measure has 8 items, with a total of 5 responses: Never, Rarely, Sometimes, Often, and Always. Anxiety and depression measures were summed individually, to capture anxiety symptom severity and depressive symptom severity, respectively. Raw scores were assessed as continuous variables with scores ranging from 8 to 40; this approach is common when using PROMIS short forms (e.g., Kroenke et al., 2014). Total anxiety scores ≤17 are considered in the normal range; scores >17 and ≤ 21 fall in the mild range; scores >21 and ≤31 in the moderate range; and scores ≤ 32 in the severe range. Total depression scores ≤ 15 are considered in the normal range; scores >15 and ≤ 21 fall in the mild range; scores >21 and ≤32 in the moderate range; and scores ≤ 33 in the severe range.

Structured Clinical Interview for Diagnostic and Statistical Manual-Fourth Edition (DSM-IV; SCID). The SCID is a semi-structured clinical interview (First et al., 1997), supported for use with a range of mental health (Lobbestael et al., 2011; Sanchez-Villegas et al., 2008) and health populations, including cancer (Singer et al., 2010) and HIV (Pence et al., 2006). As a legacy measure of psychological disorders (Drill et al., 2015), the SCID was included in this study to compare anxiety rates by assessment approach (i.e., symptoms versus disorders) and enrich characterization of the mental health profiles of each trajectory group. A registered clinical health psychologist, well versed in diagnostics, trained all SCID interviewers as adequate training has been shown to preserve inter-rater reliability (Glasofer et al., 2015); inter-rater reliability is fair to excellent, disorder-dependent (Lobbestael et al., 2011). The interview is in accordance with the Diagnostic and Statistical Manual of Mental Disorders-4th edition (DSM-IV), as this was the primary classification system in use at the onset of study development (Marrie et al., 2018a). The following anxiety disorders were captured: panic disorder, agoraphobia, social anxiety disorder (social phobia), specific phobia, OCD, PTSD, and generalized anxiety disorder (GAD). However, given small cell sizes, data distinguishing OCD and PTSD from other anxiety disorders (Nemeroff et al., 2013), and the subsequent removal of OCD and PTSD from Anxiety Disorders in the DSM-5 (APA, 2013), OCD and PTSD were removed from analyses in the current study. Probable diagnoses were assessed as four dichotomous variables: past-month presence of an anxiety disorder, lifetime presence of an anxiety disorder, past-month depressive episode and lifetime presence of major depressive disorder. Lifetime prevalence estimates included past-month prevalence estimates.

Disease Measures.

Modified Health Assessment Questionnaire (mHAQ): The mHAQ is a shortened version of the Health Assessment Questionnaire (HAQ), a well-supported indicator of functional status in RA patients (Linde et al., 2008). The mHAQ has similar predictive power to the extended HAQ (Maska et al., 2011), considered an optimal predictor in terms of mortality, disability and economic loss (Wolfe, 2002), while allowing for the brevity that best serves out-patient screening settings (Uhlig et al., 2006). Scores were assessed as a continuous variable of functional status: totals > 1.8 have been discussed as severe functional disability; ≤1.8 yet >1.3 moderate functional disability; ≤1.3 yet >0.3 mild functional disability, and ≤0.3 normal function (Maska et al., 2011).

Clinical Disease Activity Index (CDAI): The CDAI is a modified version of the Simplified Disease Activity Index (SDAI), in that it does not require laboratory tests (Aletaha & Smolen, 2005). It is a composite measure, combining tender joint count (TJC), swollen joint count (SJC), patient visual analogue scale (VAS) of disease activity, and physician VAS of disease activity. Joint counts consider 28 joints, and both the patient and physician VAS range from 0-10. The CDAI has strong psychometric support, including correlations with other composite measures of disease activity over time and related RA measures such as the HAQ (Aletaha & Smolen, 2005; Gaujoux-Viala et al., 2012). Scores were assessed two ways: total score was assessed as a continuous variable of disease activity whereas tender and swollen joint counts were extracted and assessed independently as continuous variables of TJC and SJC, respectively. CDAI totals > 22 represent high activity; ≤22 yet >10 moderate activity; ≤10 yet >2.8 low activity; and ≤2.8 remission (Gaujoux-Viala et al., 2012).

Medical Outcomes Study (MOS) Pain Effects Scale (PES). The PES is a modified form of the pain scale within the Medical Outcomes Study Functioning and Well-Being Profile (Stewart & Ware, 1992). It assesses pain and its functional impact on mood, mobility, sleep, work, recreation, and enjoyment. The PES aligns with other measures of pain (Marrie et al., 2005), and has been supported for use with patients endorsing inflammatory disease associated with pain (Marrie & Goldman, 2007). The measure was assessed as a continuous variable of pain interference, with total scores ranging from 6 (low) to 30 (high) (Hadjimichael et al., 2007).

Fatigue Impact Scale for Daily Use (D-FIS): The D-FIS was modified from the original Fatigue Impact Scale to efficiently quantify the impact of fatigue on daily living among those endorsing medical conditions characterized by fatigue (Fisk & Doble, 2002). Convergent validity with other fatigue scales (e.g., the Visual Analogue Scale of Fatigue) is moderate to high (Benito-León et al., 2007). In an inflammatory disease population including RA, the D-FIS appears to align appropriately with outcomes such as pain, work absenteeism, activity impairment, and emotional distress (Enns et al., 2018). The measure was assessed as a continuous variable of fatigue severity, with total scores ranging from 0 (low) to 32 (high; Serrano-Dueñas et al., 2018).

Covariates.

Responses were collected at baseline through self-report questionnaires for: sex (male, female), date of birth, ethnicity (collapsed into White, Other), marital status (collapsed into

single/divorced/widowed, married/common law), highest level of education attained (collapsed into <High school/GED, >High school), annual household income (collapsed into <$50,000, $50,000-$100,000, >$100,000), number of co-occurring physical health conditions, approximate date/incident age of RA diagnosis, and current use of disease-modifying antirheumatic drugs (DMARDs) and/or biologic therapy. Research assistants collected weight and height to calculate body mass index (BMI; kg/m^2). Variables were collapsed for the purpose of power, due to small cell sizes, with decisions informed by previous research using these data (e.g., Reinhorn et al., 2020). Ethnicity was captured using the categories specified by Statistics Canada (Marrie et al., 2018a): Northwest European/White (U.K., France, Germany, etc.), Eastern European/White (Poland, Hungary, etc.), Southern European/White (Greece, Italy, etc.), Scandinavian/White (Norway, Sweden), African/Black, Latin American (Mexico, Latin Caribbean, Central and South America), Chinese, Japanese, Korean, Arab, West Asian (e.g., Afghan, Iranian, etc.), South Asian (e.g., East Indian, Pakistani, Sri Lankan, etc.), Filipino, Southeast Asian (e.g., Cambodian, Indonesian, Laotian, Vietnamese, etc.), Treaty status Aboriginal, non-Treaty status Aboriginal, and other. Co-occurring physical health conditions were assessed through a validated survey (Sangha et al., 2003) of lifetime physician-made diagnoses including: high cholesterol, high blood pressure, heart trouble, disease of arteries in the legs, lung trouble, diabetes, breast cancer, colon/rectum cancer, lung cancer, skin cancer, other cancers, migraine, thyroid disease, lupus, osteoarthritis, osteoporosis, fibromyalgia, kidney disease, peptic ulcer disease, liver problems, irritable bowel syndrome, and epilepsy (seizure disorder) (Marrie et al., 2018a). All endorsed physical health conditions were combined to create a continuous variable of physical health comorbidities, to control for the effects of other health conditions. Details on RA diagnosis were self-reported (i.e., participants were asked for year and month of both symptom onset and year of diagnosis), and then verified with the use of medical records. Current RA therapy was both self-reported and verified using health records. Biologic therapy was assessed as an indicator of greater disease burden, given that biologics are a second-line treatment relative to DMARDs (Majithia & Geraci, 2007). PROMIS Depression (listed above) was used a covariate, to control for effects due to comorbid depression.

Analytic Strategy

Analysis for this study was conducted in three stages. First, I used the semi-parametric group-based trajectory approach (Jones & Nagin, 2007) to determine trajectories of anxiety

symptoms, using the PROMIS Anxiety measure, in this sample. Group-based trajectory modeling is similar to traditional methodological approaches for analyzing trajectories (i.e., hierarchical modeling, latent curve analysis) in that there is inherent recognition of individual-level heterogeneity in a natural sample; however, group-based trajectory modeling relies less on the assumption of normal distribution (Nagin & Tremblay, 2005). The approach identifies distinctive clusters of individuals who demonstrate similar progressions of some outcome over time (i.e., developmental trajectories; Jones & Nagin, 2007), using concurrent estimations of patterns over time and identification of individuals who align with those estimates (Jones et al., 2001). The censored normal distribution was used to model the trajectories to account for floor and ceiling effects of the anxiety scale. Model selection (i.e., number of trajectory groups included) is an ongoing debate among statisticians; there is currently no consensus (Warren et al., 2015). I started with a two-group model and added one group at a time, up to a total of five groups. As the different models (containing different numbers of groups) were not nested, a chi-square difference test (used in structural equation modeling, for example) could not be used to support model selection. Instead, I used statistical criteria (i.e., the Bayesian Information Criterion [BIC], reasonable group sample sizes) and non-statistical, subjective considerations (i.e., clinical implications) to determine the most appropriate trajectory model. BIC is a fit statistic that addresses degree of fit (a preferred characteristic) and degree of complexity (a non-preferred characteristic) simultaneously (Vrieze, 2012). Lower absolute BIC values are indicative of better fit, compared to higher BIC values (Jones et al., 2001). The BIC was chosen as the criterion of fit over the Akaike Information Criterion (AIC) for several reasons, including: general preference in the statistical community; better suitability (compared to AIC) when model selection is data-driven; and greater likelihood of selecting an unnecessarily (and incorrectly) complex model when using AIC (Ken et al., 2014; Vrieze, 2012). A reasonable group sample size was set at 15.

Next, descriptive analyses were used to capture the percentage of the sample that fell into each group and describe the baseline profile of each group (in terms of sociodemographics, physical health variables, and mental health variables). A series of univariate tests were conducted to examine baseline factors associated with membership in each group. For categorical variables (e.g., gender), chi-square was used. For continuous variables (e.g., age), analysis of variance (ANOVA) was used.

Finally, I conducted a series (i.e., each outcome was assessed independently) of mixed model regression analyses to examine anxiety trajectory group differences in disease outcomes (i.e., functional disability, tender joint count, swollen joint count, composite score of disease activity, pain, and fatigue) over time (i.e., rates of change). This approach was chosen over a traditional linear model to enable the inclusion of random intercepts (i.e., between subjects factor) and random slopes (i.e., within-subjects factor). This allowed consideration of both the impact of group membership on clinical status at baseline and slopes (i.e., rates of change over time). Additional advantages of this approach include: (1) allowance of unequal group sizes (Shek & Ma, 2011); (2) robustness in the presence of missing data (Peters et al., 2012); and (3) consideration of circumstances that arise when simultaneously analyzing between-subjects and within-subjects variables (e.g., nested data; Wainwright et al., 2007).

Key assumptions of a mixed-effects model include: (1) linearity between the predictor variable (i.e., group membership) and response (i.e., disease outcome); (2) homogeneity of the residuals/homoscedasticity;(3) independence of data points; (4) normality of residuals; and (5) missing data occurring completely at random (Schielzeth et al., 2020). Fortunately given the nature of real world data, the model is highly robust to violations (Schielzeth et al., 2020). I took additional steps, however, to assess for violations. For the first two assumptions (i.e., linearity, homoscedasticity), I used visual inspection of scatter plots. To test normality of residuals, I used a quantile-quantile (Q-Q) plot. To assess the randomness of missing data, I compared participants with no missing time points versus those with missing time points on baseline characteristics; individuals with missing data did not differ from those without missing data in terms of gender, age, ethnicity, marital status, income, physical health comorbidities, age of RA diagnosis, endorsement of the current use of biologic therapy, and depression symptom severity. Independence of data points was inherent to the data.

I assessed the relationship between group membership and disease outcomes in both unadjusted and adjusted models. Covariates were selected based on theory and the univariate analyses conducted on differences between the three groups at baseline (detailed in Results). Specifically, age, highest level of education attained (reference group= > Highschool), physical health comorbidities, current use of biologic therapy (reference group=current use endorsed), and depressive symptom severity, were entered into the adjusted models. Aside from relevant univariate group differences, age was selected due to its association with anxiety

severity/trajectory (e.g., Penninx et al., 2011); highest level of education attained, as an indication of socioeconomic status, due to its association with anxiety (Bjelland et al., 2008); physical health comorbidities due to correlation with psychological symptoms in RA (Treharne et al., 2005); endorsement of the current use of biologic therapy due to association with anxiety in RA (Oláh et al., 2020); and depressive symptoms due to high comorbidity with anxiety in RA (Covic et al., 2012).

Given how mixed effects models handle missing data, the randomness of the missing data, the risks associated with imputation (Jakobsen et al., 2017), and the proportion of missing data (5%), missing variables was left missing. This decision was made in consultation with a statistician. All differences were considered statistically significant at an alpha level of <0.05. Statistical analyses were conduced in SAS and SPSS.

Results

The sample (n=154) was mostly White women in their late 50s to early 60s, living with RA for almost two decades. There were 55 participants (35.7% of the sample) with clinical anxiety (score >17 on the PROMIS Anxiety measure), 33 participants (21.6% of the sample) who met criteria for a current anxiety disorder at baseline, and 47 participants (30.7% of the sample) who met criteria for a lifetime anxiety disorder at baseline. For current and lifetime estimates, the most common diagnosis was social phobia (11.1% and 17% of the sample, respectively). Of note, 69 participants (44.5% of the sample) had clinical depression (scores >15 on the PROMIS Depression measure), 17 participants met criteria for a past-year depressive episode (11.1% of the sample) and 41 participants (26.8% of the sample met criteria for lifetime depressive disorder. Given the disproportionate gender ratio, I performed a sensitivity analysis for all mixed effect models using females only to assess whether findings were consistent; results were consistent among females only.

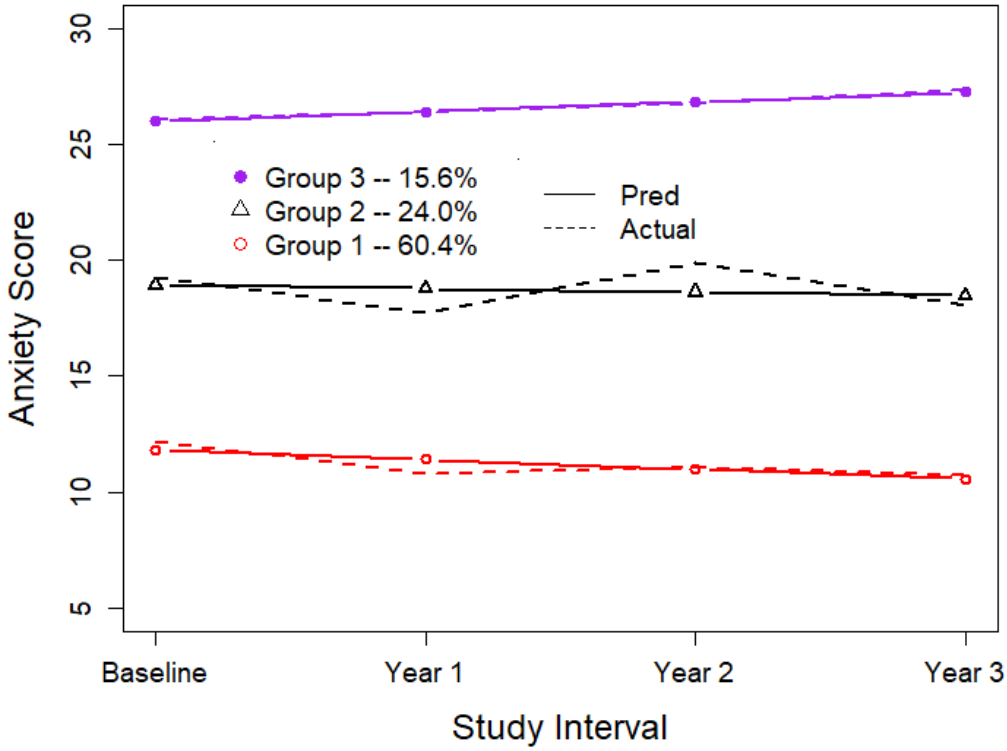
Anxiety Trajectory Groups

I tested two-, three-, four-, and five-group models. The BIC values for the two-, three-, four-, five-group models were -1743.8, -1719.0, -1712.8, and -1720.4, respectively, with the three-group solution being the most efficient when considering goodness of fit (i.e., BIC value) and parsimony. Referencing the latter, the four-group model had two groups consistently in the normal range except one group deviated just slightly above threshold at one time point; the more parsimonious explanation was chance rather than clinical meaningfulness.

Figure 2.1 depicts the distinct trajectories of the three-group model for anxiety. The broken lines represent trajectories of actual symptoms, calculated as mean scores for patients in each group. The solid lines represent predicted anxiety scores and were calculated with the model's coefficient estimates. The first group, consisting of 60.4% of the sample, was characterized by minimal burden (i.e., within the normal range) from baseline to three-year follow-up (Group 1). The second group, consisting of 24.0% of the sample, presented with persistent mild levels of anxiety from baseline to three-year follow-up (Group 2). The third group, 15.6% of the sample, demonstrated persistent moderate levels of anxiety from baseline to three-year follow-up (Group 3).

Figure 2.1

The Three-Class Model of Anxiety Scores According to the PROMIS Anxiety Measure



Characterization of Anxiety Trajectory Groups

In terms of baseline patient characteristics, the groups differed in terms of age ($p<0.05$), ethnicity ($p<0.05$), education ($p<0.01$), and BMI ($p<0.05$). Post-hoc analyses revealed Group 3 was significantly younger, less White, less educated, and higher on the BMI scale than Group 1, yet Groups 1 and 2 and Groups 2 and 3 were not significantly different.

In terms of baseline mental health characteristics, the groups differed in terms anxiety

symptom severity ($p<0.001$), depressive symptom severity ($p<0.001$), and presence of past-year depressive episode ($p<0.001$). Post-hoc analyses revealed a linear trend in terms of anxiety and depressive symptom severity, in that Group 1 had the lowest scores and Group 3 had the highest scores. Group 3 had a higher prevalence of past-month anxiety disorder ($p<0.001$), lifetime anxiety disorder ($p<0.001$), and past-month depressive episode ($p<0.001$) compared to Group 1, yet Groups 2 and 3 were not significantly different.

In terms of baseline disease characteristics, the groups differed in terms of functional disability (<0.001), tender joint count (<0.001), composite score of disease activity (<0.001), pain (<0.001), and fatigue (<0.001). Post-hoc analyses again revealed a seemingly linear relationship across the groups for functional disability, tender joint count, pain, and fatigue, i.e., Group 1 had the lowest scores and Group 3 had the highest scores. For composite score of disease activity, both Groups 2 and 3 had higher activity than Group 1, yet Groups 2 and 3 were not significantly different. All anxiety trajectory group characteristics are presented in Table 2.1.

Functional Relevance of Anxiety Trajectory Groups

Results of the linear mixed models are presented in Table 2.2. Only the adjusted model is presented, as there were no differences in effects. Compared to membership in Group 1, membership in Groups 2 and 3 was significantly associated with worse functional disability, higher tender joint counts, higher composite scores of disease activity, more severe pain, and more severe fatigue at baseline after controlling for age, highest level of education attained physical health comorbidities, current use of biologic therapy, and depressive symptom severity. For most outcomes, there were no significant changes over time and change over time was consistent across anxiety trajectory groups. As indicated by the one significant group by time interaction, however, there was a significant increase over time ($p<0.001$) in fatigue for Group 3 compared to Group 1. This was true in both the unadjusted and adjusted model, and when compared to Group 2.

Table 2.1

Sample Characteristics According to Anxiety Trajectory Group

Variable	Group 1 (n=93; 60.4%)	Group 2 (n=37; 24.0%)	Group 3 (n=24; 15.6%)	p-value
Patient Characteristics				
Gender: *n* (%)				
Female	18 (19.4)	4 (10.8)	1 (4.2)	
Male	75 (80.6)	33 (89.2)	23 (95.8)	
Age (years):				**<0.05**
Mean (SD)	61.4 (11.8)	57.1 (10.9)	55.9 (11.1)	
Ethnicity: *n* (%)				**<0.05**
White	77 (82.8)	25 (67.6)	14 (58.3)	
Other	16 (17.2)	12 (32.4)	10 (41.7)	
Marital status: *n* (%)				
Single/divorced/widowed	31 (33.3)	18 (48.6)	12 (50.0)	
Married/common law	62 (66.7)	19 (51.4)	12 (50.0)	
Education: *n* (valid %)				**<0.01**
≤Highschool/GED	20 (23.3)	17 (45.9)	13 (54.2)	
>Highschool	66 (76.7)	20 (54.1)	11 (45.8)	
Annual income: *n* (%)				
<$50,000	35 (41.2)	22 (61.1)	13 (59.1)	
$50,000-100,000	30 (35.3)	11 (30.6)	7 (31.8)	
>$100,000	20 (23.5)	3 (8.3)	2 (9.1)	
Number of comorbid physical health conditions:				
Mean (SD)	2.2 (1.6)	2.3 (1.8)	3.0 (2.0)	
BMI				**<0.05**
Mean (SD)	27.7 (5.5)	30.2 (8.2)	30.8 (7.7)	
Descriptor	Overweight	Obese	Obese	
Mental Health Characteristics				
Anxiety symptom severity:				**<0.001**
Mean (SD)	12.1 (3.6)	19.5 (4.4)	26.1 (4.5)	
Depressive symptom severity:				**<0.001**
Mean (SD)	11.1 (4.5)	17.9 (7.1)	26.0 (8.2)	

Psychological diagnosis: *n* (valid %)				
Past-month anxiety disorder	12 (12.9)	6 (16.2)	15 (65.2)	**<0.001**
Lifetime anxiety disorder	19 (20.4)	11 (29.7)	17 (73.9)	**<0.001**
Past-month depressive episode	3 (3.2)	4 (10.8)	10 (43.5)	**<0.001**
Lifetime major depressive disorder	22 (23.7)	13 (35.1)	6 (26.1)	
Disease Characteristics				
Age of RA diagnosis (years):				
Mean (SD)	43.8 (14.9)	40.1 (14.8)	41.6 (12.0)	
RA duration (years):				
Mean (SD)	17.8 (13.1)	17.1 (9.6)	14.9 (8.2)	
mHAQ score:				**<0.001**
Mean (SD)	0.4 (0.4)	0.7 (0.4)	1.0 (0.7)	
Descriptor	Moderate	Moderate	Moderate	
SJC:				
Mean (SD)	1.1 (2.5)	1.6 (2.7)	1.7 (2.2)	
TJC:				**<0.001**
Mean (SD)	2.3 (3.4)	6.8 (6.9)	10.7 (11.1)	
CDAI:				**<0.001**
Mean (SD)	6.5 (7.5)	14.4 (10.5)	18.5 (13.9)	
Descriptor	Low	Moderate	Moderate	
MOS PES score:				**<0.001**
Mean (SD)	12.3 (4.8)	17.4 (3.9)	21.2 (5.0)	
DFIS score:				**<0.001**
Mean (SD)	6.6 (5.3)	13.7 (6.8)	19.8 (5.9)	
Disease management approach: *n* (%)				
DMARDs	81 (87.1)	32 (83.8)	21 (87.5)	
Biologics	36 (38.7)	11 (29.7)	6 (25.0)	

Note: RA=rheumatoid arthritis; mHAQ=modified Health Assessment Questionnaire; SJC=swollen joint count; TJC=tender joint count; CDAI=Clinical Disease Activity Index; MOS PES= Medical Outcomes Study (MOS) Pain Effects Scale (PES); DFIS= Fatigue Impact Scale for Daily Use; DMARDs= disease-modifying antirheumatic drugs. Significance is set to $p<0.05$.

Table 2.2

Anxiety Trajectory Group Differences in Disease Outcomes: Results from Mixed Model Analyses

Outcome	Variables	Estimate	SE	*t*	p-value	95% CI
Swollen joint count						
	Intercept	2.48	0.83	3.0	**<0.01**	0.85, 4.12
	Time	0.02	0.12	0.21	0.84	-0.21, 0.26
	Group 2	0.54	0.46	1.18	-0.24	-0.36, 1.44
	Time x Group 2	-0.09	0.22	-0.42	0.68	-0.53, 0.34
	Group 3	0.82	0.61	1.34	0.18	-0.38, 2.01
	Time x Group 3	0.14	0.27	0.51	0.61	-0.39, 0.67
Tender joint count						
	Intercept	5.83	2.20	2.65	**<0.01**	1.47,10.18
	Time	-0.002	0.25	-0.01	0.99	-0.49, 0.49
	Group 2	3.75	1.26	2.98	**<0.01**	1.27, 6.24
	Time x Group 2	-0.70	0.46	-1.52	0.13	-1.61, 0.21
	Group 3	7.74	1.66	4.65	**<0.001**	4.45, 11.02
	Time x Group 3	-0.65	0.56	-1.17	0.24	-1.76, 0.45
Composite score of disease activity						
	Intercept	11.80	3.34	3.53	**<0.001**	5.20, 18.40
	Time	-0.13	0.39	-0.33	0.75	-0.91, 0.65
	Group 2	5.76	1.84	3.14	**<0.01**	2.13, 9.39
	Time x Group 2	-1.04	0.73	-1.41	0.16	-2.49, 0.42
	Group 3	10.21	2.46	4.16	**<0.001**	5.37, 15.06
	Time x Group 3	-0.22	0.90	-0.24	0.81	-2.00, 1.57
Functional status*						
	Intercept	0.16	0.19	0.86	0.39	-0.21, 0.54
	Time	0.01	0.01	0.48	0.63	-0.02, 0.03
	Group 2	0.23	0.09	2.59	**<0.05**	0.06, 0.41
	Time x Group 2	-0.01	0.02	-0.20	0.84	-0.05, 0.04
	Group 3	0.38	0.12	3.10	**<0.01**	0.14, 0.63
	Time x Group 3	-0.02	0.03	-0.51	0.61	-0.07, 0.04
Pain						
	Intercept	7.32	1.72	4.26	**<0.001**	3.93, 10.71
	Time	-0.24	0.17	-1.43	0.16	-0.58, 0.09
	Group 2	4.40	0.90	4.87	**<0.001**	2.61, 6.18
	Time x Group 2	0.07	0.32	0.23	0.82	-0.55, 0.69
	Group 3	6.89	1.22	5.65	**<0.001**	4.48, 9.29
	Time x Group 3	0.35	0.38	0.91	0.37	-0.41, 1.10
Fatigue						
	Intercept	0.24	2.08	0.12	0.91	-3.86, 4.34
	Time	-0.40	0.22	-1.82	0.07	-0.84, 0.04
	Group 2	5.26	1.05	5.03	**<0.001**	3.19, 7.33
	Time x Group 2	0.22	0.41	0.54	0.59	-0.59, 1.03
	Group 3	9.73	1.43	6.81	**<0.001**	6.90, 12.55
	Time x Group 3	1.41	0.50	2.833	**<0.01**	0.42, 2.39

Note: *Covariates include age, highest level of education attained physical health comorbidities, current use of biologic therapy, and depressive symptom severity at baseline. Significance is set to p<0.05. Group 1 is the reference group. *for this outcome, we simplified the model by not treating the slope of time as a random effect, due to difficulty achieving convergence.*

Discussion

To the best of my knowledge, this is the first study to look at distinct anxiety trajectories independent of depressive symptoms in RA; as such, the cross-sectional and longitudinal associations between trajectory groups and disease outcomes are highly novel. My results revealed three distinct trajectories. Approximately 60% of the sample endorsed persistent minimal anxiety burden (i.e., Group 1), 24% endorsed persistent mild anxiety levels (i.e., Group 2), and 16% endorsed persistent moderate anxiety levels (i.e., Group 3). The most anxious individuals (i.e., Group 3) were younger, more ethnically diverse, less educated, higher in terms of BMI, more depressed, and more likely to meet criteria for a past-month anxiety disorder, lifetime anxiety disorder, and past-month depressive episode, than individuals in the normal range for anxiety; on all characteristics by depressive symptom severity, mild and moderate anxiety groups could not be distinguished. The most anxious individuals also demonstrated the worst functional disability, the highest tender joint counts, the most severe pain, and the most Longitudinally, only this most anxious group (i.e., Group 3) was associated with a higher rate of change for a disease outcome (i.e., fatigue) within the sample.

Although anxiety trajectory groups had not yet been identified in RA, the prevalence rates of elevated anxiety symptoms and anxiety disorders were consistent with previous investigations of anxiety levels in RA (Hassan et al., 2019) and mental health disorders in chronic pain (Knaster et al., 2021). The distribution of the sample in terms of anxiety severity also aligns with recent research (Direnzo et al., 2020); using PROMIS measures, their sample indicated 9% of RA patients have ≥ moderate levels of anxiety, 18% have mild anxiety, and the vast majority fall in the normative range. Similar patient characteristics (i.e., younger age, non-White ethnicity, lower education) have also been associated with risk of psychological symptoms, including anxiety, in RA (Evers et al., 2002; Matcham et al., 2016b; Ramjeet et al., 2005). Additionally, the disease-related correlates of anxiety are in accordance with other studies; specifically, anxiety has been correlated with more severe depressive symptom (e.g., VanDyke et al., 2004), worse functional disability (Soósová et al., 2017), higher tender joints counts (Ng et al., 2020), greater pain severity (Zhang et al., 2017), and more severe fatigue

(Lapčević et al., 2017). These correlates are likely due to some combination of shared common pathways (e.g., immune system dsyregulation), shared risk factors (e.g., smoking), and one-directional factors (e.g., illness induced consequences on identity) related to comorbid anxiety (and mood more generally) and RA (Marrie & Bernstein, 2021).

Some findings, however, were more surprising. For example, stable course is uncommon among the limited investigations including anxiety symptoms, in RA over (e.g., Evers et al., 2002; Matcham et al., 2016b; Norton et al., 2011). This finding may be driven by disease duration in this sample (i.e., 17.2 years on average); nearly two decades into living with RA, some disease stability can be expected (e.g., indicators of inflammation have been shown to largely stabilize after the first ten years of disease; Scott & Steer, 2007), particularly among patients willing to engage with a three-year study. Given the cross-sectional associations demonstrated in this study, disease stability can be equated to anxiety stability. Additionally, older age is associated with anxiety symptom decline/stabilization (Ramsawh et al., 2009), and this sample consisted of adults 59.5 years old, on average. Another unique findings was idiosyncrasy between minimal and moderate anxiety in terms of some mental health and disease outcomes. Some research supports differences between minimal and moderate depression in RA (e.g., moderate depression is associated with younger age, relative to minimal; Englbrecht et al., 2019); however, understanding meaningful differences in anxiety severity requires future investigation. A hypothesis worth future investigating is cumulative effects (i.e., from both anxiety and RA), as fatigue can be conceptualized as particularly biopsychosocial in etiology, relative to other disease outcomes (Katz, 2017); perhaps minimal anxiety in RA does not produce the cumulative effects required to impact rates of change. Finally, the unique deleterious effect of anxiety on fatigue over time requires future consideration. This finding might be explained by unique overlap in risk/maintenance factors for both anxiety and fatigue (Pope, 2020), or lack of power due to small (n=24) cell sizes.

Measurement concerns, addressed in the study introduction, were supported. For example, anxiety and depression appeared to be unique in terms of prevalence in this RA sample, which raises concern regarding the “mixed mood construct” approach. Specifically, 35.7% of participants had elevated levels of anxiety and 44.5% had elevated levels of depression. Further, measure-based discrepancy in the determination of “clinical significance” was apparent. While 35.7% of the sample had clinically meaningful anxiety according to the PROMIS Anxiety

measure, 21.6% had clinically meaningful anxiety in accordance with the SCID. More significant still, among the group with the most severe anxiety and most adverse disease outcomes, 9 individuals would not been identified as currently "at-risk" according to the SCID. This might be explained by the nature of the measures (PROMIS evaluates risk, whereas the SCID is a diagnostic tool); or by the nature of anxiety in RA. For example, older adults are particularly prone to health anxiety, particularly when multiple physical health comorbidities are present (El-Gabalawy et al., 2013), and, on average, this sample had approximately three physical health conditions including their RA. Health anxiety, however, was not assessed in this sample, as it is formally recognized as a *somatic symptom and related disorder* in the DSM-5 (APA, 2013). Alternatively, some of the anxiety disorders have a fundamentally intermittent course, due to being episodic or symptomatology being related to a specific trigger (e.g., specific phobia, social phobia). As such, it is possible that individuals might have simply not met criteria during the month their baseline assessment was conducted. This is supported by the lifetime prevalence of anxiety disorders (i.e., 30.7%) aligning more appropriately with the PROMIS-based estimate (i.e., 35.7%).

Overall, the findings of this study support the routine assessment of mental health in RA, in addition to subsequent treatment of mental health in RA. In terms of treatment, findings suggest anxiety interventions might mitigate anxiety-related consequences on fatigue. This was preliminarily confirmed through a feasibility study of an Internet-based cognitive-behavioural therapy (iCBT) program for anxiety; three months after participating in the study, significant reductions in anxiety, depression, and fatigue were evident (Blaney et al., 2021). This effect is worth emphasizing given fatigue is consistently cited as the most problematic feature of the disease for patients (Lwin et al., 2020; Hewlett et al., 2005; Santos et al., 2019) and rheumatologists openly endorse the treatment of fatigue as complicated and beyond their scope (Pope, 2020; Santos et al., 2019). Further, an unmet therapeutic need in terms of psychological distress in RA is commonly reported (Hewlett et al., 2005; Yılmaz et al., 2017). Therefore, advances in assessment and treatment in the management of RA are warranted. Of note, data for this study were collected prior to the COVID-19 global pandemic. A recent investigation supported an increase in anxiety among RA patients in 2020 (Itaya et al., 2021), perhaps associated with greater risk of infection due to immune dysregulation/use of immunosupressants (Lohse et al., 2020). Implementation of anxiety interventions in the management of RA are

especially important within contexts, such as during a pandemic, where normal levels of anxiety associated with RA are likely to be amplified.

Limitations of the study need be considered. The sample lacked diversity in terms of gender, race, and disease duration (of note, RA disproportionately affects females; Tobón et al., 2010). There was also no way of determining which (if any) participants were receiving treatment for their anxiety, in terms of either psychotherapy or pharmacotherapy. Therefore, anxiety course (i.e., stability of symptoms over time) might be explained by ongoing treatment. The sample was derived from one Canadian province exclusively, and participation in a three-year study might have been a deterrent for the most ill patients, both mentally and physically. Sample size, once divided among the trajectory groups, was small; this might have led to Type II error (e.g., missed effects from group membership in terms of rates of change for other disease outcomes).

This study provides meaningful contribution to the RA comorbidity literature. In particular, concerns with measurement approaches to date were brought to light (e.g., equating mental health symptoms and measures), temporal questions were answered, and distinct anxiety trajectory groups were supported. RA patients with moderate anxiety were significantly different than RA patients without anxiety in terms of a number of characteristics (i.e., patient, mental health, and disease-related) and this group was at risk of the most adverse disease outcomes, both cross-sectionally and longitudinally. Assessment (and therefore identification) and treatment of "at-risk" individuals appears warranted.

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Preface to Chapter 3

Chapter 2 demonstrated that anxiety in RA is associated with a host of adverse correlates, including personal (i.e., increased BMI), psychological-based (i.e., mental health symptoms, mental health disorders) and biological-based (i.e., functional disability, tender joint counts, composite score of disease activity, pain, fatigue) outcomes. Additionally, anxiety symptom severity was linearly associated with several disease outcomes (i.e., worse functional disability, higher tender joint counts, greater pain, and more severe fatigue) and depressive symptom severity. These findings suggest that reduction of anxiety symptoms might be associated with disease-related benefits, as well as improved quality of life. This hypothesis was only further supported by the impact of moderate anxiety on fatigue's rate of change; perhaps even small improvement in anxiety (i.e., moderate levels to minimal levels) could avoid accelerated worsening of disease outcomes (at minimum, fatigue) over time.

As I was interested in symptom reduction and supporting homogeneity in mental health assessment in RA, I chose to use the same anxiety symptom measure in Study 2 as I used for my primary outcome in Study 1 (i.e., PROMIS Anxiety). Study 2 serves as an answer to the logical question following the findings of Study 1: How can these adverse outcomes be mitigated or prevented?

Chapter 3: Study 2

Support for a non-therapist assisted, Internet-based cognitive-behavioral therapy (iCBT) intervention for mental health in rheumatoid arthritis patients

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Abstract

Background: Anxiety is common in patients with rheumatoid arthritis (RA) and associated with worse RA outcomes. This study assessed the feasibility and preliminary health impacts (mental and physical) of a non-therapist assisted, online mental health intervention targeting anxiety in this population.

Methods: Participants with confirmed RA and elevated anxiety symptoms were enrolled into the Worry and Sadness program, an Internet-based cognitive-behavioral therapy (iCBT) intervention for anxiety and depression shown to be effective in the general population. Validated self-report measures of anxiety, depression, pain interference, fatigue, physical health-related quality of life, functional status, and patient-reported disease severity were collected at baseline, post-intervention, and at three-month follow-up. Emotional distress scores were tracked between lessons. Participants provided qualitative feedback in writing post-intervention.

Results: We analyzed the responses of 34 participants; the majority was female (86%) and the mean age was 57 (SD=13). Of these, 80% (n=28) completed the study in its entirety. Among these completers, 94.1% described the program as worthwhile. We found statistically significant improvements in anxiety, depression and fatigue from baseline to three-month follow-up, with small to large effect sizes (d=0.39-0.81). Post-hoc analyses revealed that statistically significant change occurred between baseline and post-intervention for anxiety and depression and was maintained at three-month follow-up, whereas statistically significant change occurred between baseline and three-month follow-up for fatigue. Statistically significant reductions in emotional distress occurred across the program, with a large effect size (d=1.16) between the first and last lesson.

Conclusion*:* The Worry and Sadness program shows promise as a feasible resource for improving mental health in RA.

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease producing chronic joint inflammation and pain. For those with this condition, psychological symptoms are frequent (Astin et al., 2002). Approximately 20-40% of RA patients meet criteria for major depressive disorder (Margaretten et al., 2011; Matcham et al., 2013), 25-70% of RA patients present with an anxiety disorder (El-Miedany & Rasheed, 2002; Matcham et al., 2018), and the vast majority exhibit symptoms of both (Covic et al., 2012). Research has consistently supported adverse outcomes, in terms of both disease severity (Kojima et al., 2009) and activity (Edwards et al., 2011) for co-occurring depression and RA, and more recent literature confirms comorbid anxiety is also associated with worsened pain (Jamshidi et al., 2016), fatigue (Geenen & Dures, 2019), functional impairment (Soósová et al., 2017), and quality of life (Beşirli et al., 2020). Yet while interest rises in the use of pharmacotherapy in RA (Vallerand et al., 2019), investment in psychological approaches remains limited (Fiest et al., 2017).

The most widely studied and frequently implemented psychological interventions for anxiety and depression employ cognitive-behavioral therapy (CBT)(Kaczkurkin & Foa, 2015; Thase et al., 2018). CBT refers to a family of effective mental health treatments, which share techniques yet vary depending on target outcomes. CBT interventions demonstrate immediate and sustained effects when targeting both anxiety (Olatunji et al., 2010) and mood symptoms (Driessen & Hollon, 2010) in the general population. Similar effects have been found in samples of patients with chronic diseases, such as inflammatory bowel disease (Evertsz et al., 2017) and multiple sclerosis (Askey-Jones et al., 2013).

CBT has also proven effective in the management of chronic pain (Knoerl et al., 2015). With the explosion of Internet-based CBT (iCBT) and its removal of barriers such as physical accessibility, the number of validated programs for use with pain populations has increased dramatically (Dear et al., 2013). In RA specifically, CBT programs have targeted self-reliance (Trudeau et al., 2015), quality of life (Shigaki et al., 2013), and pain (Sharpe, 2016), with depression and anxiety often framed as peripheral considerations; as such, iCBT programming targeting low mood and anxiety in RA represents an unmet need. An appropriate program candidate would balance feasibility for the patient (e.g., six to 10 total hours over six to 10 weeks; Edhe et al., 2014) and the health care system (e.g., not requiring the costly ongoing engagement of a therapist; Knoerl et al., 2015).

Given the predominance of anxiety relative to depression in RA, my primary outcome of interest for this study was anxiety. My aims were to: (1) assess the feasibility of a non-therapist assisted iCBT intervention for anxiety (i.e., The Worry and Sadness program) in people with RA, as determined by rates of recruitment, treatment adherence and participants' experience during treatment; (2) assess program efficacy for anxiety reduction in people with RA; and (3) assess program efficacy in terms of additional facets of mental health (i.e., depression and emotional distress) and well as physical health (i.e., pain interference, fatigue, physical-health related quality of life, functional status, and patient-reported disease severity).

Methods

Participants

I recruited participants with confirmed RA (Aletaha et al., 2010) through email, letter, or in-person (by a research assistant) from ongoing study cohorts and the Arthritis Centre in Winnipeg, MB. I assessed study eligibility and participants gave verbal consent by phone. Inclusion criteria required: (1) elevated levels of anxiety (as determined by an anxiety screener measure T-score≥56.0); (2) ability to communicate in English; and (3) access to a computer/tablet/smart phone and the Internet. I used anxiety as my screener given that anxiety was my primary outcome. An a priori sample size calculation was not conducted given recommendations and standard practice in the context of feasibility studies (Cocks & Torgerson, 2013; Teare et al., 2014).

Measures

Recruitment and treatment adherence. I recorded the number of participants who were eligible for enrollment, completed baseline measures, enrolled in the program, and completed the program. I also recorded time intervals between data collection points and asked two questions regarding homework completion: (1) did you practice the homework outside of the lessons; and (2) if so, approximately how many hours were dedicated to homework in total (select most appropriate answer between <1 and >6; a total of 7 response options).

Treatment experience. I evaluated treatment experience with the following free text response questions: (1) did you find this program a worthwhile experience; (2) would you recommend the program to a friend with a similar experience as you; (3) did you think the program spoke to your personal experience/if not, how would you have improved it; (4) what

was your favourite aspect of the program; (5) what was your least favourite aspect of the program; and (6) how would you rank the modules (1=favourite, 6=least favourite).

Anxiety and depression. The National Institutes of Health Patient-Reported Outcomes Measurement Information System (PROMIS) is a system of self-report outcome measures proven to be valid and reliable across a range of populations (Cella et al., 2010), with the 4 to 8-item measures found valid and reliable for use in RA (Bartlett et al., 2015; Hitchon et al., 2020). I assessed anxiety symptoms using the 4-item Anxiety Short Form during screening. Study inclusion required a score higher than 8 (T-score≥56.0), indicating anxiety symptoms elevated above the population mean. For treatment response, I assessed anxiety symptoms using the extended 6-item PROMIS Anxiety Short Form. The internal consistency (i.e., Cronbach's alpha) for this Anxiety Short Form at baseline in the current study was α=.88. I also assessed depressive symptoms using the 6-item PROMIS Depression Short Form. The internal consistency for the Depression Short Form at baseline in the current study was α=.94.

Emotional distress. The Kessler Psychological Distress Scale (K-10) is a widely used, 10-item self-report measure of global emotional distress. There is strong psychometric support for its use in the general population (Furuakawa et al., 2003), and evidence for its reliability in RA (Hitchon et al., 2020).

Pain interference. I assessed the functional impact of pain using the 6-item PROMIS Pain Interference Short Form. The internal consistency for the Pain Interference Short Form at baseline was α=.95.

Fatigue. I assessed the experience (frequency, duration, and intensity) and impact of fatigue using the 6-item PROMIS Fatigue Short Form. Construct validity has been established (Bartlett et al., 2018). The internal consistency for the Fatigue Short Form at baseline was α=.94.

Physical health-related quality of life. I assessed physical health-related quality of life using the 2-item PROMIS Global Health-Physical, which demonstrates good internal consistency in other health populations such as stroke (Katzan & Lapin, 2018).

Functional status. I used the 8-item modified Health Assessment Questionnaire (mHAQ) to assess functional status (Maska et al., 2011). The internal consistency for the mHAQ at baseline was α=.90.

Patient-reported disease severity. I used the Patient Global Visual Analogue Scale (PG-VAS) to assess disease severity. Patients were verbally asked: considering all the ways your

condition affects you, how active has your disease been (0=Not active, 10=Severely active). This and several other phrasing variations of the PG-VAS are routinely used in both clinical practice and research (Ferreira et al., 2018).

Treatment

The Worry and Sadness Program is a mixed mental health intervention, targeting anxiety and depressive symptomology in the general adult population (Newby et al., 2013; Newby et al., 2014). The program was originally designed to treat comorbid generalized anxiety disorder and major depressive disorder, as these conditions often co-occur in the general population and this co-occurrence is rarely addressed in CBT protocols (Brown et al., 2001; Newby et al., 2013). Adherence to this treatment was high in a past RCT (89%), with large effect sizes (>0.8) reported in reducing anxiety and depressive symptoms and emotional distress (Newby et al., 2013). Although this program had yet to be investigated in a chronic disease population, a similar intervention developed by the same research group (iCBT for major depressive disorder; iCBT-MDD) improved symptoms of depression, anxiety and emotional distress for people with diabetes (Newby et al., 2017). Aside from program efficacy, I chose this program because it allowed me to target my primary outcome of anxiety without neglecting the high co-occurrence of depression in RA.

The treatment includes six modules (see Table 3.1 for a detailed description). Modules must be completed in order (there is no skip option) and they take approximately 15 minutes to complete. Material is provided in the form of illustrated stories in a slideshow presentation, with both male and female characters overcoming their difficulties with anxiety and depression. Interaction is not required during the lesson; however, a lesson summary is provided at the end that involves responses from the participant. This lesson summary must be downloaded and submitted (i.e., click to submit) to gain access to the next lesson, five days later. The lesson summaries involve tasks that require immediate completion (e.g., provide examples of personal thoughts) as well as optional homework worksheets (e.g., activity planning, thought challenging). The purpose of requiring a submission at the end is to confirm full completion of the lesson; there is no marking/response from a therapist. The purpose of the wait time is to mimic weekly attendance with a live therapist and allow practice of the learned material throughout the week. Additional materials are also provided in the program, including frequently

asked questions about each lesson, patient success stories, and resources on topics such as sleep, medications, and worry stories (i.e., imaginal worry exposure).

Table 3.1
Details of the Worry and Sadness Program

Lesson	Description	Homework Practice Tasks
I: About anxiety and depression	Psychoeducation on anxiety and depression, including the fight or flight response, controlled breathing, and the benefits of physical exercise	Controlled breathing, physical exercise
II: Identifying thoughts and tackling low activity	Cognitive therapy components, including education about the cognitive model and introductions to cognitive distortions and thought monitoring. Activity planning is also introduced.	Thought monitoring, activity planning
III: Tackling thoughts	Thought challenging/cognitive restructuring, including challenging positive and negative meta-cognitive beliefs about repetitive thinking, shifting attention, and hunting for positives	Thought challenging, hunting for positives
IV: Tackling avoidance	Education about avoidance and safety behaviors, as well as graded exposure and structured problem solving	Graded exposure and structured problem solving
V: Mastering your skills	Advanced graded exposure understanding (addressed activities such as imaginal exposure and interoceptive exposure) and troubleshooting difficulties with graded exposure	Graded exposure
VI: Staying well	Relapse prevention	Relapse prevention plan

Note: Adapted from Newby et al., 2013

Procedure

This feasibility study used a single-arm, open-label design i.e., all consenting participants gained access to the iCBT program. At baseline, participants were mailed a package containing a written consent form, a post-marked envelope, and questionnaires, including a demographics form and self-report symptom measures of mental and physical health (i.e., anxiety, depression, pain interference, fatigue, and physical health-related quality of life). Upon receipt of the returned package, I administered measures (i.e., functional status and patient-reported disease severity) by telephone. At this time participants were provided a code to enroll in the online program. Four weeks later, I contacted participants by telephone that received a code for a "check-in," with the primary purpose being troubleshooting any technical difficulties and

reminding participants of the deadline (the intended program duration was 10 weeks, but a two-week "cushion" period was available). Unlike all other measures, the measure of emotional distress was embedded into the program at the start of each lesson, as a means of tracking mental health experience across the duration of treatment.

Upon completion of the program or at the 12-week mark, whichever came first, I administered the measures of functional status and patient-reported disease severity by telephone a second time. The post-intervention package included baseline measures, a post-marked envelope, and qualitative feedback measures (i.e., treatment experience, homework completion). Participants also completed the mailed baseline measures and telephone measures at three-month follow-up (see Figure 3.1 for further details). In summary: measures of anxiety, depression, pain interference, fatigue, physical health-related quality of life, functional status, and patient-reported disease severity were administered are baseline, post-intervention, and three-month follow-up; a measure of emotional distress was administered between lessons; and measures of treatment experience and homework completion were administered at post-intervention. The Health Research Ethics Board approved this study.

Analytic Strategy

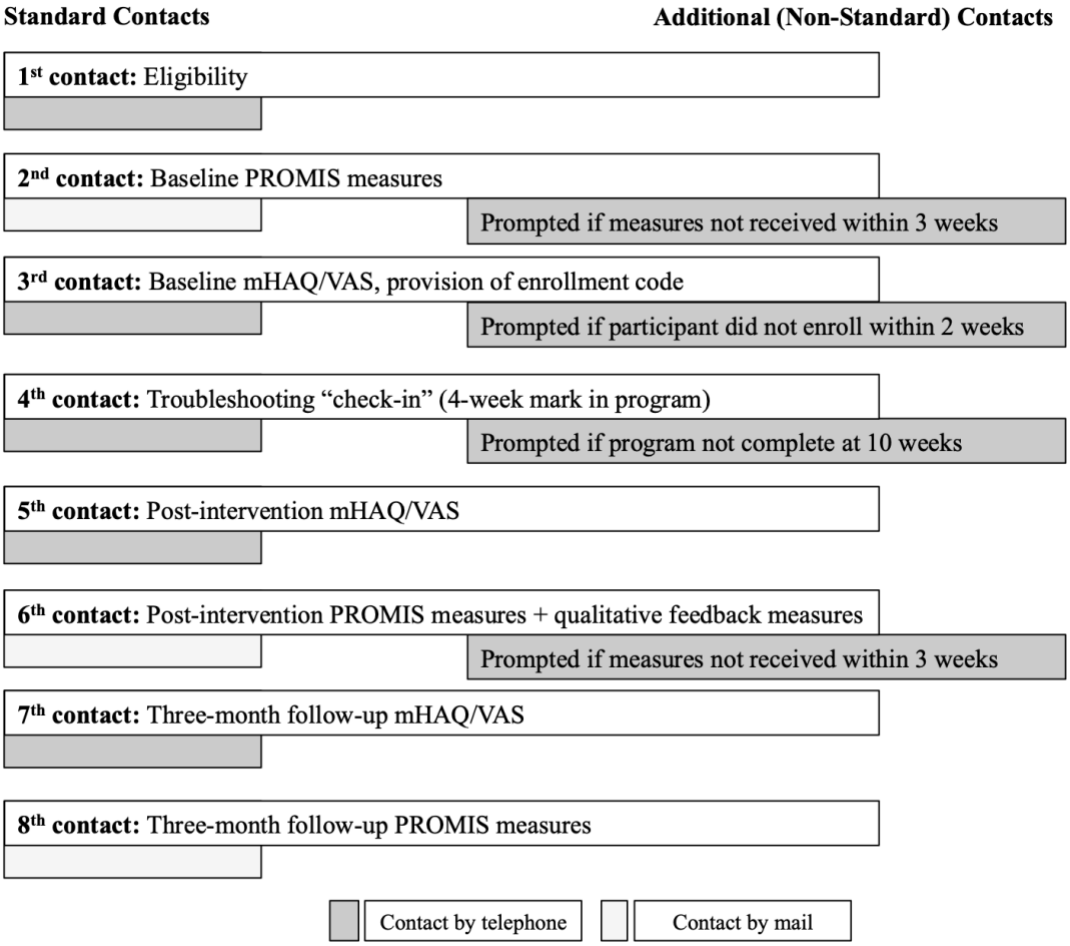
I used descriptive statistics to characterize the sample. I used an intention-to-treat (ITT) approach, complemented by a per-protocol approach for my primary health outcome (i.e., anxiety). Specifically, I used a modified ITT approach (Gupta, 2011), in which one participant was excluded from the ITT analysis because they enrolled in the program then immediately requested removal from the study due to time constraints. An ITT approach was used to capitalize on data given the sample size, and to avoid bias in the estimate of treatment effect; a per-protocol approach was implemented to assess any potential differences between completers and non-completers on the primary health outcome, and to gather a less conservative estimate of treatment effect. To understand the characteristics of those who completed the study for the purpose of future study design, I used chi-squares/one-way ANOVAs to compare the three sub-groups within the sample of participants eligible for enrollment (i.e., per-protocol completers, non-completers, and non-enrollers) on baseline characteristics.

I used descriptive statistics to describe most other facets of feasibility. A summative content qualitative analysis, where the focus is uncovering meanings of content for the purpose of preliminary insight (Hsieh & Shannon, 2005), was performed on appropriate treatment

experience responses. There were two independent coders, and any disagreement in coding was resolved through consensus. Final themes, number/percentage of participants who endorsed each theme, and examples are presented in table format.

All PROMIS summary scores were transformed into T-scores using HealthMeasures Scoring Service powered by Assessment Center^{SM} (Evans et al., 2018). The missing data rate was less than 5%. Missing data in the mailed measures (i.e., anxiety, depression, pain interference, fatigue, and physical health-related quality of life) were managed with imputation, using an expected a priori pattern response scoring method through the HealthMeasures Scoring Service (the Assessment Center^{SM} protocol for scoring PROMIS measures). Missing data in the telephone measures (i.e., functional status, patient-reported disease severity) were managed with the last observation carried forward (LOCF) imputation method, common to small sample ITT analyses (Gupta, 2011). This was only required for one participant, who could not be reached by telephone for three-month follow-up. I used a one-way repeated measures analysis of variance (ANOVA) to assess the effect of time (baseline, post-intervention, and three-month follow-up) on each symptom measure, separately. I also conducted a one-way repeated measures ANOVA to assess the effect of time (pre-lesson one through six) on emotional distress. I used univariate analyses for each mental and physical health outcome given the exploratory nature of this work and to allow comparison of outcomes with the many other feasibility studies using univariate methods (Saccenti et al., 2013). This is appropriate for feasibility studies when the assumption of sphericity is met and there is an overall absence of missing data. Of note, for one of the seven health outcomes (i.e., functional status) that former was not met, and therefore the Greenhouse-Geisser correction was used. Significance was set to $p \leq 0.05$. I did not perform a correction for multiple tests because of the exploratory nature of the study (Armstrong, 2014). I conducted post-hoc analyses on significant results to determine where significant changes occurred. I then used Cohen's *d* comparison of means (T1-T3/pooled standard deviation [SD]; T1-T6/pooled SD in the case of emotional distress) to assess effect sizes as means of better understanding meaningful change. Effect sizes are considered small if $d > 0.20$, medium is $d > 0.5$, and large if $d \geq 0.8$ (Cohen, 1988). Finally, to address clinical significance for our primary mental health outcome (i.e., anxiety), we determined the percentage of participants who completed follow-up measures and no longer demonstrated elevated levels. Analyses were performed using SPSS.

Figure 3.1
The Standard and Additional (Non-Standard) Contacts Participants Received as per Study Protocol



Results

Participant Characteristics

The ITT sample consisted of 34 participants. Of these, 28 (68%) completed the program, producing the per-protocol sample (see Figure 3.2). Baseline participant characteristics are presented in Table 3.2. Most of the ITT sample was female, White, and had moderate (T score ≥60 to <70) levels of anxiety and mild (T -score ≥55 to <60) levels of depression at baseline. Nearly three-quarters of the ITT sample was recruited through email or letter. The per-protocol sample demonstrated similar demographics. At baseline, there were no significant differences between participants eligible for enrollment (i.e., per-protocol completers, non-completers, and

non-enrollers), except for race and recruitment method; specifically the per-protocol completers were more commonly White and recruited through email or mail.

All ITT results from baseline/post-intervention/three-month follow-up comparisons are reported in Table 3.3; the results for changes in anxiety, depression, pain interference, fatigue and physical health-related quality of life are illustrated in Figure 3.2.

Figure 3.2
CONSORT Flowchart

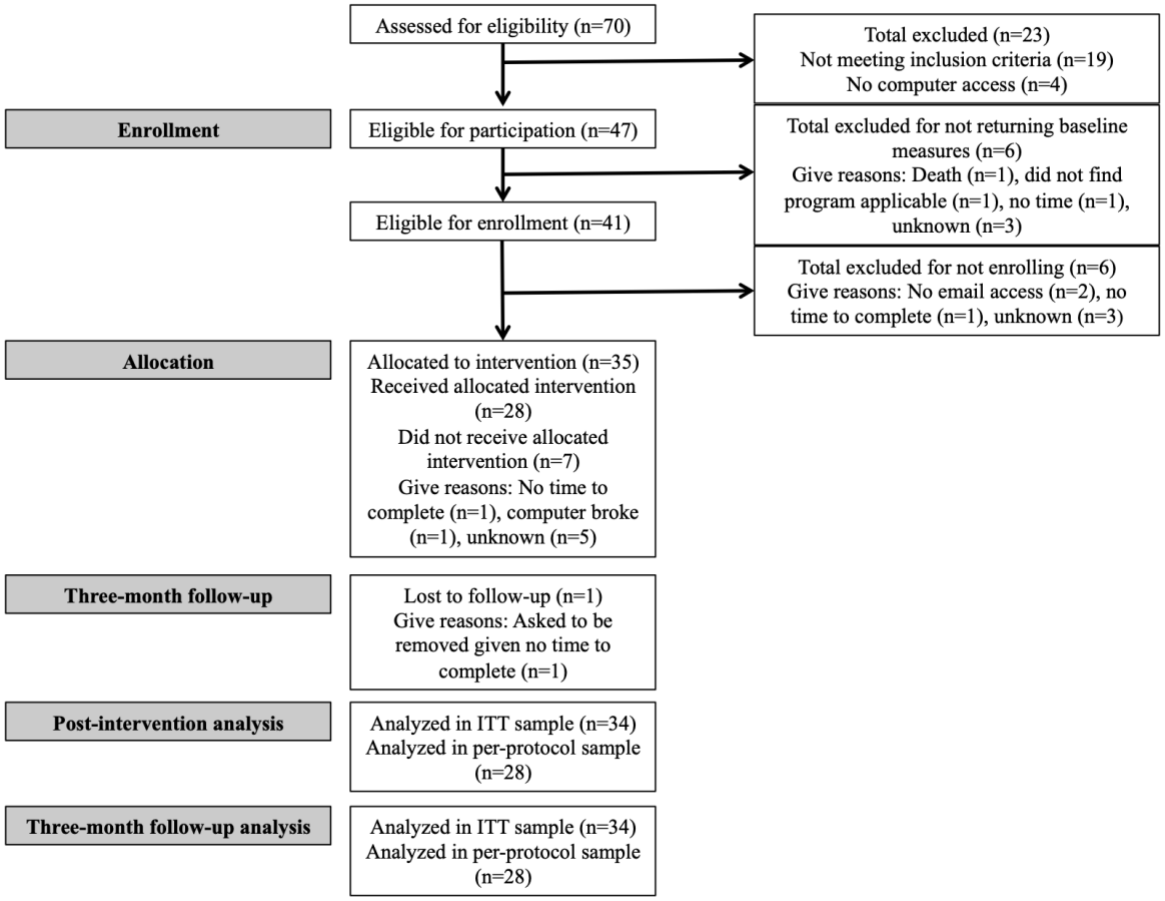


Table 3.2

Characteristics of the Study Sample

	Participants Eligible for Enrollment (n=41)	ITT Sample (n=34)	Per-Protocol Sample (n=28)	Non-Completers (n=7)	Non-Enrollers (n=6)	Chi-square/ ANOVA
Variable						
Gender: *n* (%)						
Female	87.8	85.7	85.7	85.7	100.0	
Male	12.2	14.3	14.3	14.3	0	
Age (years):						
Mean	57.3	57.0	58.4	52.0	58.5	
(SD)	(12.8)	(13.0)	(12.9)	(12.9)	(13.3)	
Race: *n* (%)						**
White	78.0	85.7	89.3	71.4	33.3	
Other	22.0	14.3	10.7	28.6	66.7	
Marital status: *n* (%)						
Married/ Common Law	70.7	71.4	71.4	71.4	66.7	
Divorced/ Separated	14.6	11.4	10.7	14.3	33.3	
Widowed	4.9	5.7	3.6	14.3	0	
Never Married	9.8	11.4	14.3	0	0	
Education: *n* (%)						
<Highschool	19.5	17.1	17.9	14.3	33.3	
Highschool/ GED	17.1	17.1	14.3	28.6	16.7	
College/Tech/ Trade School	39.0	40.0	42.9	28.6	33.3	
Undergraduate degree	17.1	20.0	17.9	28.6	0	
Graduate	7.3	5.7	7.1	0	16.7	

degree						
Annual income: *n* (%)						
<$15,000	23.1	17.6	14.8	28.6	60.0	
$15,000-$29,999	20.5	23.5	25.9	14.3	0	
$30,000-$49,999	17.9	17.6	22.2	0	20.0	
$50,000-$100,000	38.5	41.2	37.0	57.1	20.0	
Anxiety screener:						
Raw Score						
Mean	11.5	11.6	11.7	10.6	11.5	
(SD)	(2.4)	(2.5)	(2.4)	(2.8)	(2.2)	
T-score						
Mean	62.8	63.0	63.2	60.9	63.0	
(SD)	(4.9)	(5.0)	(4.9)	(5.4)	(4.8)	
Baseline anxiety:						
Raw Score						
Mean	16.3	16.0	15.8	17.1	17.7	
(SD)	(4.3)	(4.4)	(4.8)	(1.9)	(3.4)	
T-score						
Mean	61.2	60.8	60.5	62.2	63.2	
(SD)	(5.9)	(6.0)	(6.6)	(2.5)	(4.5)	
Baseline depression:						
Raw Score						
Mean	15.5	15.4	15.0	17.0	15.8	
(SD)	(5.5)	(5.6)	(5.9)	(3.9)	(5.3)	
T-score						
Mean	58.0	58.0	57.4	60.7	57.7	
(SD)	(8.4)	(8.3)	(8.9)	(4.7)	(9.9)	
Recruitment method: (%)						**
Email/mail	73.2	82.9	89.3	57.1	16.7	
Baseline mHAQ score:						

Mean (SD)	0.67 (0.5)	0.64 (0.5)	0.73 (0.5)	0.27 (0.3)	0.83 (0.3)
Descriptor	Mild	Mild	Mild	Normal	Mild
Baseline VAS:					
Mean (SD)	5.0 (2.5)	4.8 (2.4)	5.0 (2.4)	4.1 (2.5)	6.2 (2.6)

Note: $^{**}p \leq 0.01$; ITT=intention to treat, mHAQ=modified health assessment questionnaire, VAS=visual analogue scale

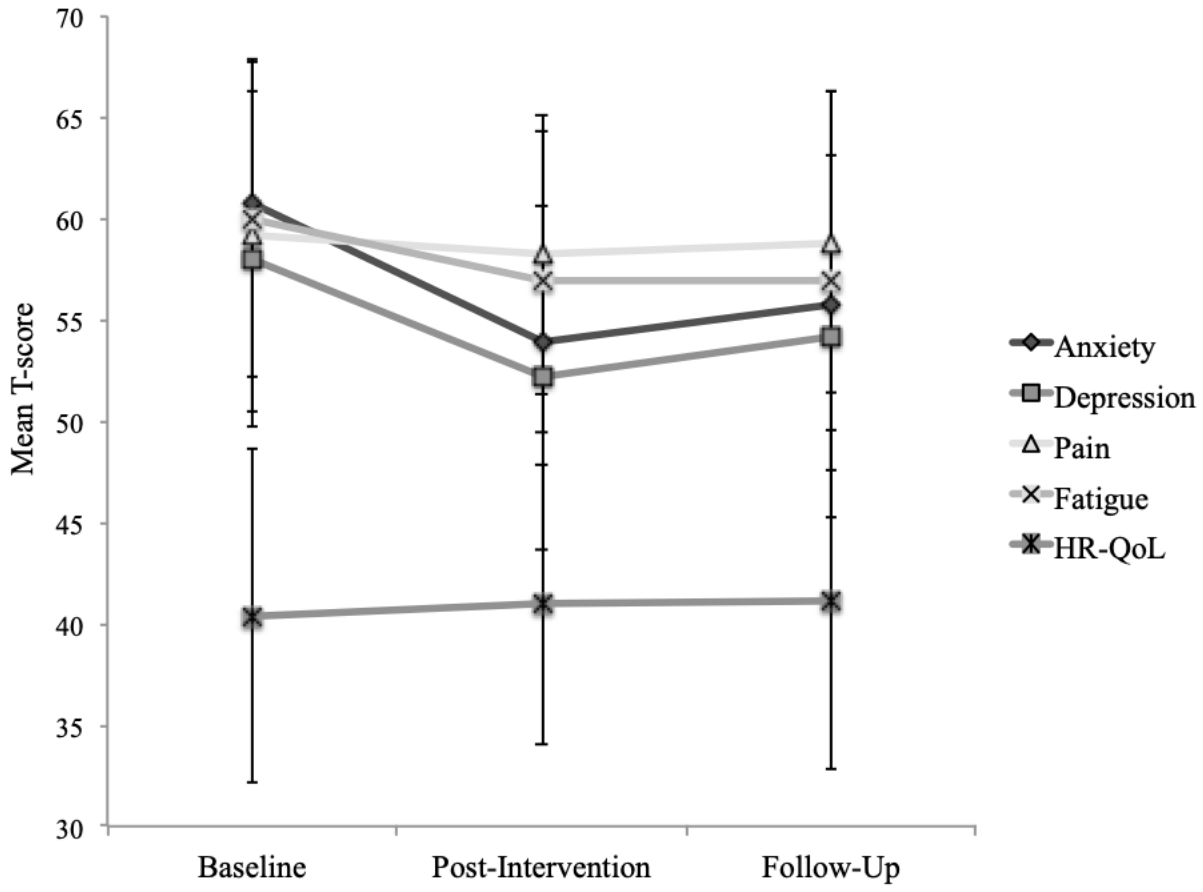
Table 3.3

Results from the ITT Analysis

Outcome	**Baseline** Mean (SD)	**Post-intervention** Mean (SD)	**Three-month follow-up** Mean (SD)	***F*-value**	***p*-value**	**Cohen's *d***
Anxiety	60.82 (6.13)[a]	53.92 (7.65)[b]	55.75 (7.04)[b]	15.74	<0.001	0.77
Depression	58.08 (8.40)[a]	52.17 (8.51)[b]	54.20 (8.94)[b]	10.07	<0.001	0.45
Quality of life	39.91 (7.92)[a]	40.94 (6.89)[a]	41.19 (8.38)[a]	1.47	0.245	0.15
Pain interference	59.67 (8.19)[a]	58.21 (6.87)[a]	58.85 (7.43)[a]	1.16	0.326	0.11
Fatigue	60.29 (7.79)[a]	56.90 (7.44)[ab]	56.91 (9.33)[b]	3.83	<0.05	0.39
Functional impairment	5.26 (4.25)[a]	4.79 (3.81)[a]	4.82 (4.03)[a]	0.73	0.44	0.11
Patient-reported disease severity	4.91 (2.42)[a]	4.65 (2.30)[a]	4.50 (2.35)[a]	0.63	0.538	0.17

Note: Quality of life = physical health-related quality of life. [ab]Means in a row without a common superscript letter differ (p<0.05).

Figure 3.3
Baseline, Post-Intervention, and Three-Month Follow-Up Mean Scores for the Five PROMIS Measures (Anxiety, Depression, Pain Interference, Fatigue and Physical Health-Related Quality of Life; n=34)



Feasibility Outcomes

Recruitment. Of 70 candidates approached, 47 (67%) were eligible for participation. Of those, 41 (87%) returned completed baseline measures and were therefore considered eligible for enrollment. Of this group, 35 (85%) enrolled in the program, 34 (83%) began the program and completed post-intervention measures, and 28 participants (80% of the enrollers) completed the program per-protocol (see Figure 3.2).

Treatment adherence. Baseline measures (n=41) were completed, on average, 42.7 days (SD=18.3; range=4.0-92.0) before engagement with the program. For completers, the average program completion time was 61.3 days (SD=18.7; range=32.0-98.0). Post-intervention measures were completed, on average, 17.4 days (SD=18.9; range=26-83) after program

completion and 83.5 days (SD=26.9; range=41.0-120.0) after last completed lesson for non-completers. Three-month follow-up measures were completed, on average, 115.1 days (SD=25.7; range=93.0-227.0) after program completion and 172.2 (SD=17.3; range=151.0-194.0) days after last completed lesson for non-completers. Of those who completed the full program, 96.4% completed supplementary homework. On average, completers engaged in 2.9 (SD=1.7; range=0-6.0) hours of homework total.

Treatment experience. There had been some confusion among non-completers on how to describe their treatment experience. For that reason, non-completers were excluded from this analysis. Of those who completed the program (n=28), (1) 94.1% described the program as a worthwhile experience; (2) 88.2% would recommend the program to a friend with a similar experience; and (3) 54.8% indicated the program spoke to their personal experience. In contrast, 9.7% felt the program did not speak to their experience, and 35.5% indicated the program needed improvement. Of those who called for improvement, the most common suggestion (15% of responders) was to incorporate disease-relevant content. The provision of self-management tools was cited as the (4) favourite aspect of the program (45% of responders); and the structure of the course (e.g., issues with homework) was cited as the (5) least favourite aspect of the program (39% of responders). Among those who endorsed a favourite/least favourite module (n=19), (6) the most common favourite (37% of responders) was Lesson 1: About anxiety and depression and the two least favourite lessons (26% of responders, respectively) were Lesson 5: Mastering your skills and Lesson 6: Staying well. Full details of the summative content qualitative analysis are presented in Table 3.4. Mean agreement between coders was 84%.

Table 3.4

Results from the Summative Content Qualitative Analysis of Per-Protocol Participants' Feedback on the Intervention

Theme	n (%) Who Endorsed	Quote Support
Question: Did you think the program spoke to your personal experience? If not, how would you have improved it?		
Positive endorsement, no suggestions	23 (70%)	"Yes. It mostly did. Thank you."
Incorporate disease-relevant Content	5 (15%)	"Have incidents that would happen for a person with disabilities and their particular issues."
Incorporate content unrelated to disease experience	3 (9%)	"For me more family situations (with kids, etc.,) would be better."
Logistical issues (no computer involvement, more structure)	2 (6%)	"I would have preferred mailed packages. I have no use for computers. If it was easily accessible, than I would have been a better participant."
Speak to location	2 (6%)	"However, in Canada-weather and inability to go outside (when you have disability and mobility issues and the snow and cold are severe) makes it a difficulty situation…seasonal aspects are more of a challenge for me living in Winnipeg-so that is one thing that stood out to me… (the course) does not speak to our locational aspects of depression here in the cold."
Negative endorsement no suggestions	1 (3%)	"No, I don't really feel the depression and anxiety applied to me."
Question: What was your favourite aspect of the program?		
Provides self-management tools	15 (45%)	"Learning the tools and strategies to recognize and deal with anxiety and depression."
User-friendly/convenient	13 (39%)	"That I could work on it when and where I wanted to. Also, that I have a year to go back and review the program as I need to."
Appealing/interesting platform/content	11 (33%)	"I like how they had two characters who gave examples of how anxiety and depression affected them."

Promotes self-awareness	9 (27%)	"Made me stop and 'think'…your attitude is everything! I am in control of my attitude, no one else. There is no "pill" to fix how you think. I actually have control over quite a bit, which is directly related to how I feel most of the time (I learned that here!)"
Promotes sense of unity with others	3 (9%)	"I am not unique in how I feel."
Question: What was your least favourite aspect of the program?		
Structure of course (length, timing of lessons, amount of content, design/organization of content, issues with homework, no therapist involvement)	13 (39%)	"The homework took considerable time."
Content of course (not easy to understand, not engaging/interesting, issues with specific content)	4 (12%)	"The lessons seemed repetitive sometimes."
Issue unrelated to program/participation	4 (12%)	"Trying to incorporate these lessons in my life- habits are hard to break (old habits)."
Not relatable to a pain population	3 (9%)	"…Another aspect (that) was lacking was the importance of exercise for people with some form of arthritis. Yes, they did say exercise but such exercises as shown would be out of the realm of someone with severe RA. Check (The Arthritis Help Book by Drs. Kate Lorig and James Fries). Pages are devoted to exercise we can do-how encouraging and motivating!.."
Specific timing of study	2 (6%)	"I think for me it was the timing, i.e., the cold and dreary weather, where you stay at home and a million and one thoughts go through your mind (mostly negative). I think that having to redo these exercises (during summer and fall) would (have) had different results. More positive than negative."
Discomfort with	5 (3%)	"Getting onto the computer with (the password) was challenging. Not very user

technology/technological issues	friendly. After having the same problems every time I just gave up and left the program.”

Note: Mean agreement between coders was 84%.

Mental Health Outcomes

Statistical changes from baseline. In the ITT analysis (n=34), there was a statistically significant difference in anxiety and depression scores from baseline to three-month follow-up. Additionally, there was a statistically significant difference in emotional distress across the duration of the program [$F(5,21)=9.78$, $p<0.001$]. Pairwise comparisons determined significant change occurred between baseline and post-intervention for anxiety and depression, and these reductions were maintained at three-month follow-up. For emotional distress, there was a significant reduction across all time points yet pairwise comparisons of means demonstrated some change between consecutive modules was significant and some change was not (see Table 3.3).

Meaningful changes from baseline. From baseline to three-month follow-up, the reduction in anxiety was deemed a medium effect size and the reduction in depression was deemed a small effect size. From lesson one to lesson six, reduction in emotional distress was deemed a large effect size (d=1.16).

Clinical change from baseline. Fifteen participants (44.1%) scored in the normal range (T-score<55) for anxiety at three-month follow-up.

Changes in anxiety for completers only. In the per-protocol analysis (n=28), there was a similar statistically significant difference in anxiety [$F(2,26)=16.13$, $p<0.001$] from baseline to three-month follow-up, evident post-intervention and maintained at three-month follow-up. From baseline to three-month follow-up, reduction in anxiety was deemed a large effect size (d=0.81) and again 15 participants (53.6% of the per-protocol sample) scored in the normal range for anxiety at three-month follow-up.

Physical Health Outcomes

Statistical changes from baseline. In the ITT analysis (n=34), there was only a statistically significant difference in fatigue across the three time points. Pairwise comparisons demonstrated non-significant effects between consecutive time points. There was no significant effect of time for pain interference, physical health-related quality of life, functional status, and patient-reported disease severity (see Table 3.3).

Meaningful changes from baseline. From baseline to three-month follow-up, reduction in fatigue was deemed a small effect size.

Discussion

This project is novel in several respects, given that psychological approaches to mental health are heavily reliant on therapist involvement in chronic pain (Knoerl et al., 2015) and rare to non-existent in RA. I established the feasibility of a non-therapist assisted iCBT program for anxiety among those with RA and provided preliminary evidence of clinical benefit. I had a completion rate of 80%, with an average completion time just under nine weeks. Most participants found the program worthwhile and would recommend it to a friend. Over half indicated that the program spoke directly to their personal experience. I found improvements at three-month follow-up for anxiety, depression, and fatigue, with the improvements in anxiety and depression demonstrating significant change immediately post-treatment. Changes in emotional distress between lessons suggested mental health improvements are greater with greater treatment progression. Effect sizes indicated meaningful change similar to that found in the general population (Newby et al., 2013) and change scores indicated clinically significant reductions in anxiety symptoms.

This study suggests that the Worry and Sadness program is a feasible treatment option for anxiety in RA. Outcomes were largely positive; the completion rate nearly replicated that from the original paper evaluating the Worry and Sadness Program in the general population (Newby et al., 2013) and most participants described the program favourably. This aligns with literature suggesting that most patients desire emotional support when living with RA (Sharpe, 2016). Many hypothesized concerns regarding online psychological treatment with an RA sample, such as difficulty with ongoing computer engagement due to hand deformity and resistance towards psychological approaches to managing illness experience, did not appear to be obstacles to treatment adherence/success. Importantly, the absence of therapist engagement (a treatment factor traditionally associated with online program success; Andersson & Cuijpers, 2008) also did not appear to hinder efficacy.

My results also hinted at a possible explanation for the documented correlation between therapist involvement and online treatment success. In my study, self-identifying mental health difficulties appeared to be a factor in initial engagement and treatment adherence (i.e., almost 90% of completers responded to a received email or letter). This aligns with past research (Newby et al., 2013) where program adherence was better among individuals with expressed interest in iCBT (i.e., those self-seeking supports) versus those from primary care (i.e., those not

self-seeking supports). This suggests that establishing readiness to change might be an important step missing from non-therapist assisted programs. If true, for RA patients specifically, this supports routine psychoeducation (e.g., pamphlets in Rheumatology waiting rooms) as part of any pragmatic mental health initiative, promoting psychological readiness without therapist involvement.

Potential limitations of the program in terms of feasibility for this population were also highlighted. For example, the material in the Worry and Sadness Program is not specific to a disease population and, while only endorsed by 15% of responders, my qualitative analysis revealed the most commonly suggested area for improvement was to add RA-related content. Another factor in adherence might be participants' reactions to homework (cited as the least enjoyed aspect of participation), which might improve with modification of homework materials or advance notice prior to enrollment. The importance of adherence to the program in its entirety was highlighted by the fact that completers experienced greater benefit (e.g., only completers moved into the normal range for anxiety following treatment). The intervention had the largest impact on mental health, with some benefit also seen for fatigue. The largest effect at three-month follow-up was for anxiety, despite elevations for both anxiety and depressive symptoms at baseline. The simplest explanation for this differential is baseline anxiety was higher than baseline depression because it was specifically targeted for inclusion criteria. However, another interpretation of these results is that anxiety in the context of RA is more amenable to online treatment, relative to depression. If true, implementation of anxiety interventions may be particularly worthwhile. The reduction in fatigue may be a result of reducing mental-health contributions to fatigue, or an outcome of common mechanistic pathways (Nerurkar et al., 2019). I did not find a significant impact on pain interference, physical health-related quality of life, functional status, or patient-reported disease severity, which may be because the intervention was not intended to directly target these outcomes. Alternatively, reductions in these aspects may have become evident over a greater length of time.

With this small sample, there was potential for Type II error (e.g., missing characteristic differences between completers, non-completers, and non-enrollers) and the potential for a cohort effect related to the impact of seasonal change (all baseline measures were collected in winter and follow-up measures in spring). Caution in the interpretation of secondary outcomes should be applied. I did not control for changes in medication, other non-pharmacologic

interventions or time engaged with the program. My sample also lacked diversity in terms of gender, race and baseline disease status. Some participants required prompting, and despite no clinical involvement, this may have impacted program outcomes. Additionally, there is potential for bias when using patient-report measures.

The Worry and Sadness program may be an appropriate psychological intervention for RA patients presenting with elevated anxiety symptoms. While randomized controlled trials/RCTs enrolling a larger, more diverse sample are needed, establishing feasibility was a critical starting point. Minor program modifications such as integrating RA specific content may further enhance efficacy. This online iCBT program is a potentially useful initial step in an integrated care approach for addressing mental health symptoms in people with RA, as it appears to combine ease of access and cost-efficiency with efficacy.

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General Discussion

Summary of Findings

Acute need for biopsychosocial considerations in the management of co-occurring anxiety and RA was highlighted with the findings of this dissertation. Prior to these studies, a meaningful relationship between anxiety and RA had been supported and preliminarily characterized (e.g., Machin et al., 2020). As summarized in Chapter 1, individuals with RA and anxiety tend to be female and of lower SES (Watad et al., 2017). These individuals appear to be at greater risk of adverse illness outcomes (i.e., functional impacts, as previously defined), including increased disabilty (Jamshidi et al., 2016) and reduced quality of life (Guerrero-López et al., 2017), as well as adverse disease outcomes (i.e., pathophysiology) in both cross-sectional and longitudinal analyses. Across cross-sectional studies, demonstrated correlates of comorbid RA and anxiety include worse tender joint count (Brahem et al., 2017), serum indicators of inflammation (Cordingley et al., 2014), composite scores of disease activity (Cadena et al., 2003), pain (Jamshidi et al., 2016), fatigue (Mancuso et al., 2006), and functional status (Soósová et al., 2017). Although fewer longitudinal studies have been published, there is evidence to support worsened outcomes in the presence of anxiety in terms of tender joint counts (Matcham et al., 2016), composite scores of disease activity (Kuijper et al., 2018), pain (Ødegård et al., 2007), and fatigue (Mancuso et al., 2006). CBT strategies, targeting outcomes such as pain management, have demonstrated secondary benefits on both depression and anxiety among RA patients, in both offline and online formats (Shen et al., 2020); and yet, questions/gaps in the literature remained.

One unexplained facet of the extant literature is discrepancy across studies; for nearly every disease outcome, associations with anxiety have been both confirmed and disconfirmed. This may relate, in part, to limitations in this prior research including differences in study design, measurement approaches, and population characteristics. Study 1 investigated a potentially pertinent population characteristic i.e., between-subjects differences in anxiety symptom severity over time. This was accomplished through a group-based trajectory analysis of anxiety symptoms in an RA sample, followed by an examination of the cross-sectional and longitudinal associations between those groups and the following disease outcomes: swollen joint count, tender joint count, composite score of disease activity, functional status, pain, and fatigue. Another unclear facet of the extant literature was the possibly unique benefit of anxiety-specific

psychotherapy among RA patients. Prior to this thesis, there had yet to be an investigation of an anxiety-targeted intervention in an RA sample, despite evidence of higher efficacy when a symptom is directly targeted in a given intervention among the general population (Boersma et al., 2019; Sharpe, 2016). As such, a complete understanding of the impact of anxiety reduction on disease outcomes was missing. Given the rise of online programming for RA patients (largely due to removed barriers such as limited accessibility; Dear et al., 2013; Shigaki et al., 2013), Study 2 tested the feasibility of an Internet-based CBT (iCBT) intervention for anxiety (and comorbid depression) in an RA sample. Feasibility outcomes included rates of recruitment, treatment adherence and treatment experience. Pilot post-intervention outcomes included anxiety, depression, emotional distress, pain interference, fatigue, physical-health related quality of life, functional status, and patient-reported disease severity. Together, these studies provide support for innovative health care approaches in RA.

Some results corroborated prior research. Specifically, Study 1 revealed elevated anxiety among RA patients, both in terms of anxiety symptoms (35.7% of the sample exhibited symptoms in the mild to severe anxiety range) and anxiety disorders (past-month prevalence: 21.6% of the sample; lifetime prevalence: 30.7% of the sample). Certain sample characteristics were associated with the highest elevations of anxiety (i.e., younger age, lower level of education, non-White ethnicity, higher BMI). Cross-sectional correlates of anxiety included worse tender joint count, higher composite score of disease activity, poorer functional status, and more severe pain and fatigue. CBT strategies were effective for improving outcomes in the context of RA. Other findings across the two studies, however, were highly novel. Unique anxiety trajectory groups were demonstrated in this RA sample and anxiety severity appeared to positively correlate with outcomes (i.e., in terms of functional disability, tender joint count, pain, and fatigue). Chronic, clinically significant, albeit mild, anxiety did not appear to worsen disease outcomes over time; chronic, moderate anxiety significantly worsened fatigue over time. An iCBT intervention for anxiety appears feasible for RA patients. Therapist involvement did not appear to be necessary for program efficacy, whereas self-referring to the program was associated with treatment adherence. CBT for anxiety demonstrated preliminary evidence of significant improvements in anxiety, depression, emotional distress, and fatigue. Completing the intervention in full had the most advantageous effects for anxiety.

Conceptualizing Findings with Theory

Implementation of evidence-based interventions begins with research and, subsequently, appropriate packaging of said research (Kilbourne et al., 2007). Contextualizing findings in pre-existing theory has been shown to support the translation of research knowledge into health care action (Ward et al., 2009). Given this, I will contextualize findings in content-appropriate theory, beginning with an adaptation of Dekker & Groot's (2018) WHO ICF framework for psychological adjustment to illness, introduced in Chapter 1. Next I will discuss the feasibility findings of my intervention study in accordance with related literature.

Findings Related to Anxiety Characterization and Impact

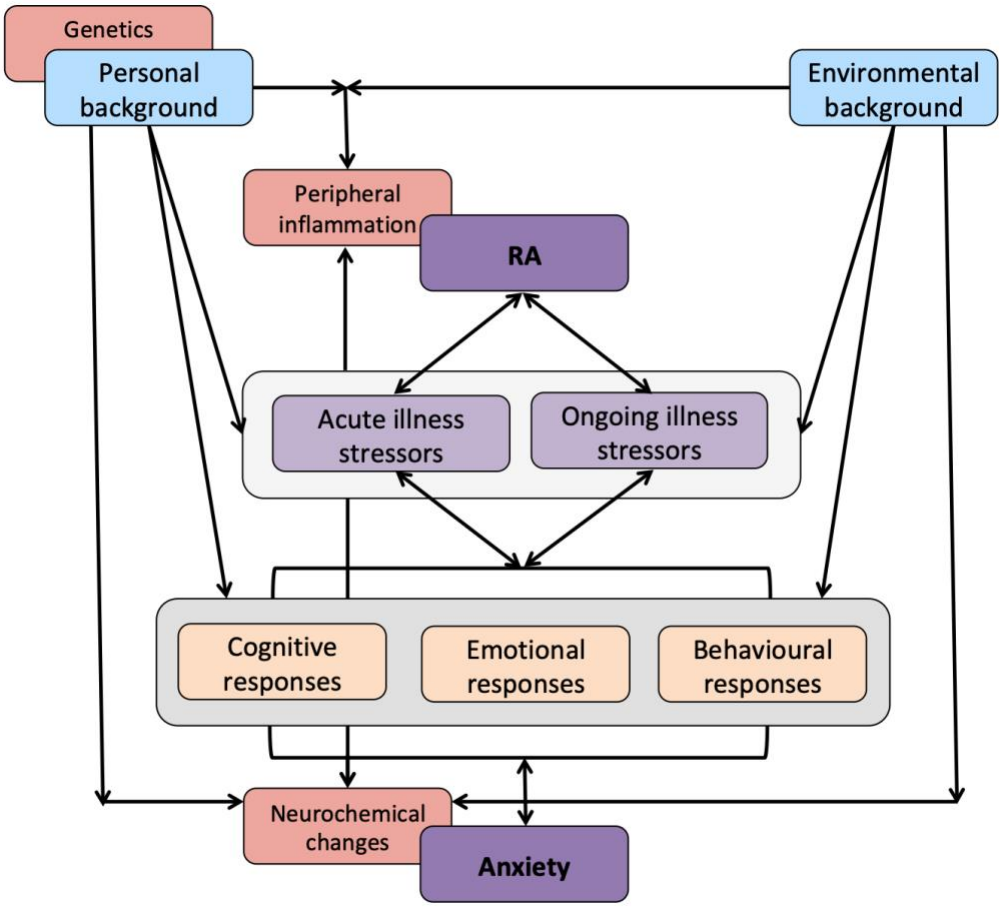
The adaptation of Dekker & Groot's (2018) WHO ICF model incorporates biological theory (highlighted in pink, also introduced in Chapter 1) on mental health comorbidity in RA. With this incorporation, a complete example of a biopsychosocial framework is created. Conceptualizing the findings in this way highlights the interaction of biological and psychological variables, in particular, in the development, severity and maintenance of co-occurring anxiety and RA. I will refer to the model moving forward as the *biological ICF theory of anxiety in RA*.

Results from Study 1 indicated that anxiety was elevated in the RA population relative to estimates previously reported in the general population, and disease outcomes were exacerbated in the presence of anxiety, thereby further supporting the need for comorbidity models such as the biological ICF theory of anxiety in RA. Results from Study 1 also suggested that co-occurrence of (at least moderate) anxiety and RA was associated with younger age, higher BMI, lower education, and ethnic diversity. In the model, age would be considered a facet of *personal background*. Younger age is commonly associated with greater emotional difficulties including anxiety (Charles, 2010), and there are multiple hypotheses for this recurrent finding (e.g., acceptance increases with age; Shallcross et al., 2013). One explanation, however, is particularly interesting in the context of this model. A continuous positive correlation between increasing age and *sense of coherence* has been supported (Silverstein & Heap, 2015). Sense of coherence is an adaptive coping construct capturing the degree to which an individual feels stressors (particularly illness stressors) are comprehensible, manageable and meaningful (i.e., worthy of energetic investment and engagement; Super et al., 2015). Sense of coherence predicts both psychological

improvement and health status in RA (Goulia et al., 2015), likely through mediation of *cognitive*, *emotional*, and *behavioural coping responses*. More explicitly, higher sense of coherence results in more adaptive coping responses, such as better lifestyle choices (Super et al., 2015). Therefore, the personal background variable of age might influence the relationship between anxiety and RA through moderating coping responses. BMI is another facet of *personal background* in this model. High BMI has been previously associated with both elevated inflammation (e.g., plasma IL-6; Balter et al., 2021) and passive coping responses such as self-criticism (*a cognitive response*) and social withdrawal (*a behavioural response*)(Varela et al., 2020); therefore high BMI might moderate both biological and psychological components of the model.

Figure 4.1

The Biological ICF Theory of Anxiety in RA



Contextualizing the role of ethnicity in the model is somewhat problematic given the possible ethnic diversity captured with the descriptor of "other" i.e., non-White in Study 1; of note, ethnicity was collapsed into a dichotomous variable for the purpose of power. However, it would be careless to not include the variable in light of results and the geographical location of the study. The largest non-European ethnic group in Manitoba is Indigenous Canadians (Statistics Canada, 2016) and, as with all ethnic groups, Indigenous ethnicity entails unique social context and life experience. Growing up Indigenous in Canada is linked too often to *environmental background* factors such as adverse childhood social environments (e.g., high rates of intimate partner violence; Brownridge et al., 2017), that have been shown to alter HPA axis activity (Luecken et al., 2009) and worsen anxiety (McLaughlin et al., 2010) in adulthood. Education level is also conceptualized as an *environmental background* factor in this model. Evidence to support this includes: the inverse correlation between highest education achieved and indicators of peripheral inflammation (e.g., ESR; Steinvil et al., 2008); the association between lower education background (e.g., level of mathematical education) and altered neurochemistry (e.g., ϒ-aminobutyric acid, or GABA; Zacharopoulos et al., 2021); and an association between lower education and more passive, non-adaptive coping tendencies (e.g., complaining, denial) following illness stress (Son et al., 2016). Taken together, both ethnicity and education level appear to be *environmental background* factors that moderate the relationship between RA and anxiety through both biological and psychological processes.

Across this dissertation as a whole, one finding related to the impact of anxiety in RA stood out in terms of novelty: across studies, fatigue appeared uniquely related to the co-occurrence of RA and anxiety, compared to other disease outcomes. Results from Study 1 identified (moderate) anxiety as especially problematic for fatigue in RA, i.e., anxiety predicted a higher rate of change for fatigue and fatigue was the only disease outcome temporally impacted. Results from Study 2 indicated that the intervention was uniquely effective for the improvement of fatigue i.e., fatigue was the only disease outcome significantly improved by the intervention. This latter finding is particularly important given that fatigue is consistently reported as a priority concern by RA patients (e.g., Dures et al., 2016) and rheumatologists consider the symptom particularly difficult to manage (Pope, 2020; Santos et al., 2019).

The unique relationship with fatigue and co-occurring RA and anxiety is likely explained by the convergence of risk/maintenance factors for fatigue produced in this comorbidity. This is

illustrated with the biological ICF theory of anxiety in RA. Fatigue is associated with *peripheral inflammation* (e.g., genetic mutations in interleukin-1beta/IL-1b, IL-6 and TNF-α) and *neurochemical changes* (e.g., genetic modifications of the serotonergic system; reviewed by Wang et al., 2017). Fatigue symptoms have been connected to *personal background* variables in the discussed model such as elevated BMI, even when controlling for physical activity levels (Cooper et al., 2019). Fatigue has also been associated with the discussed *environmental background* factors; for example, chronic fatigue is more prevalent in non-White ethnic groups compared to Whites (Bhui et al., 2011) and among those with lower education levels (Jing et al., 2015). Finally, fatigue has been previously correlated with maladaptive coping strategies, specifically *cognitive responses* such as wishful thinking, escape avoidance, and self-blame (Mark & Smith, 2018).

The improvement in fatigue following a CBT intervention for anxiety can be largely attributed to successfully modifying the maladaptive *cognitive*, *emotional*, and *behavioural responses* that maintain the feedback loop in comorbid anxiety and RA. The exclusivity of the improvement (i.e., fatigue scores improved following the intervention, whereas pain interference, physical-health related quality of life, functional status, and patient-reported disease severity did not), however, was surprising; most surprising was the absence of an effect on pain interference, given demonstrated correlation between pain and fatigue (Pollard et al., 2006). Possible explanations for the unique improvement in fatigue include:

(1) The complex etiology of fatigue (Pollard et al., 2006; Pope, 2020). As hinted above, fatigue is particularly multi-faceted in the context of RA, with factors including pain, inflammation, hormonal imbalances, other physical health comorbidities (especially cardiovascular conditions), low physical activity, sleep disturbance, mood difficulties, and constructs such as illness perceptions (Katz, 2017; Pope, 2020). Unlike other RA outcomes, biological and psychological factors appear to contribute equally to the experience of fatigue. In support of this, medical management strategies that benefit disease outcomes such as pain and functional status demonstrate limited effectiveness for fatigue (Katz, 2017). In this study, however, significant improvement might have been made possible by the accumulation of biological and psychological benefits, for example, stabilization of hormones levels due to increased activity (Mohandas et al., 2017) in addition to changes in illness perceptions (e.g., personal control, perceived consequences)

due to more adaptive coping strategies (Liu et al., 2021). Other disease outcomes (e.g., physical-health related quality of life) might have failed to receive both psychological and biological benefits, or at least not to the same degree as fatigue.

(2) Methodological choices might have limited assessment of disease-based improvements. For example, the construct of pain interference (i.e., pain impact) was assessed as opposed to pain severity. Pain interference was selected as the construct of interest, given clinical consensus that a patient's relationship with their pain is a better target for functional improvement than pain severity itself (Vowles et al., 2014); pain interference was used as a proxy measure of that relationship with pain. However, when longitudinal associations between anxiety and pain were previously identified, pain severity was assessed (e.g., with a visual analogue scale of pain severity and the Arthritis Impact Measurement Scales (AIMS) pain scale; Ødegard et al., 2007). Since study development, pain interference has been shown to be less responsive to change (over time and due to treatment) relative to other pain measures (e.g., Brief Pain Inventory) in a sample of mixed musculoskeletal pain conditions (Kean et al., 2016). Additionally, there is now evidence that demonstrated correlations between pain inference and physical function do not persist over time (Karayannis et al., 2017). All things considered, pain interference might have been a less appropriate construct for capturing effects from an anxiety-focused intervention.

(3) Improvement in fatigue could be the consequence of improvement in a third, untested variable, which exerts less impact on other disease outcomes in RA relative to fatigue. For example, physical exercise (addressed in both the primary and supplementary content of the Worry and Sadness program) is discussed as the most effective strategy for the reduction of fatigue (Mohandas et al., 2017), whereas links between physical exercise and the assessed outcomes, including pain interference (Merriwether et al., 2018) and functional status (as identified through activities of daily living; Gu & Conn, 2008), have not been established. These outcomes might be better targeted through another third variable; for example, pain interference appears more closely linked to social isolation (Karayannis et al., 2019).

(4) Other disease outcomes might require a longer surveillance period to demonstrate change.

(5) The feasibility study (n=34) might have been underpowered to capture the full range of effects.

(6) There might have been limited opportunity for improvement in certain disease outcomes (e.g., functional status), as the sample was relatively high functioning in certain domains.

Findings Related to Feasibility of an Online Anxiety Intervention

Results of Study 2 indicate the online intervention (i.e., the Worry and Sadness program) is appropriate for true efficacy testing (i.e., a randomized controlled trial; RCT). Specifically, findings spoke most to practicality (e.g., ability of participants to engage in intervention), acceptability (e.g., satisfaction, perceived appropriateness), and preliminary efficacy (e.g., estimate of intended effects of program), three prominent areas of focus for feasibility studies (Bowen et al., 2009).

Beginning with practicality, initial concerns included program usability with an older population as well as a population with potential physical limitations (e.g., hand deformity). Regarding the former concern, 80% of those who enrolled in the program successfully completed the program; the mean age of this sub-sample was 57.0 years old. Additionally, younger age was not associated with successful completion. However, some participants (n=5) raised a potentially age-related concern: navigating technological issues with enrolment/ adherence. Participant feedback included, “Getting onto the computer with (the password) was challenging. Not very user friendly. After having the same problems every time I just gave up and left the program.” This concern has emerged in other studies of online mental health interventions for older adults as well; for example, one participant in an online behavioral intervention study (mean age of sample: 74.0 years old) noted “I am not a tech-savvy person…you won’t know what the (technology-related) problem (will be) until you have it” (Li et al., 2020). Therefore, while usability in a middle-to-older age group was supported, age-related areas for improvement were noted. Regarding the second concern, difficulties due to RA-related physical limitations were not supported; the completion rate among this RA sample was comparable to that found in other feasibility studies of online mental health interventions for both chronic illness groups (e.g., a 78% completion rate in cancer; Kubo et al., 2019) and the general population (e.g., a 74.2% completion rate; DaPointe et al., 2018).

In terms of acceptability, two initial concerns were related to non-involvement of a therapist and non-inclusion of disease-related content. Regarding the former, effect sizes for the

reduction of anxiety and depression resembled those of therapist-assisted online mental health programs (Saddichha et al., 2014), suggesting therapist involvement might not be as critical among RA patients as it has been framed to be in the literature (e.g., Spillekom-van Koulil et al., 2017). Alternatively, this might have been a particularly motivated group of participants; determination of this will require study replication in a primary care setting. Interest in disease-related content, on the other hand, did appear to be a legitimate concern, as it was referenced several times in the qualitative feedback (e.g., "Have incidents that would happen for a person with disabilities and their particular issues"). It should be noted, however, that 70% of the sample indicated the program sufficiently spoke to their personal experience, and the personal relevancy of online program content is a concern that comes up in non-health populations as well (DaPointe et al., 2018). Additionally, 94.1% of program completers described the program as worthwhile and 88.2% would recommend the program to a friend. Therefore, the program seems to be acceptable for RA patients, but some disease-related modification might be warranted.

As previously mentioned, preliminary efficacy was also supported. Reductions of anxiety and depression mirrored that from investigations of the same iCBT intervention (i.e., The Worry and Sadness program) in the general population (Newby et al., 2013), and RA-related improvement was evident (i.e., in terms of fatigue). As expected from existing literature, full treatment adherence/module completion was associated with the best mental health outcomes (Donkin et al., 2011).

Clinical Implications

The current Canadian health care system serves as important context for determining evidence-based next steps in the management of RA. Canada has a publically funded health care system, better conceptualized as thirteen separate health systems (one for each province and territory). While health care practices are provincially regulated, health services are federally sourced. Despite billions of federal dollars directed at mental health services in recent years, barriers to adequate mental health care remain (Moroz et al., 2020). Evidence of this includes a recent report indicating 2.3 million Canadians describe their mental health needs as unmet (Statistics Canada, 2019). Barriers to met needs include confusion as how to access support, long wait times, shortage of clinicians, mental health stigma, geographical distance to services, and the absence of integration between primary care and community-based psychological supports (Moroz et al., 2020; Slaunwhite, 2015). Of note, Canadians with comorbid psychological

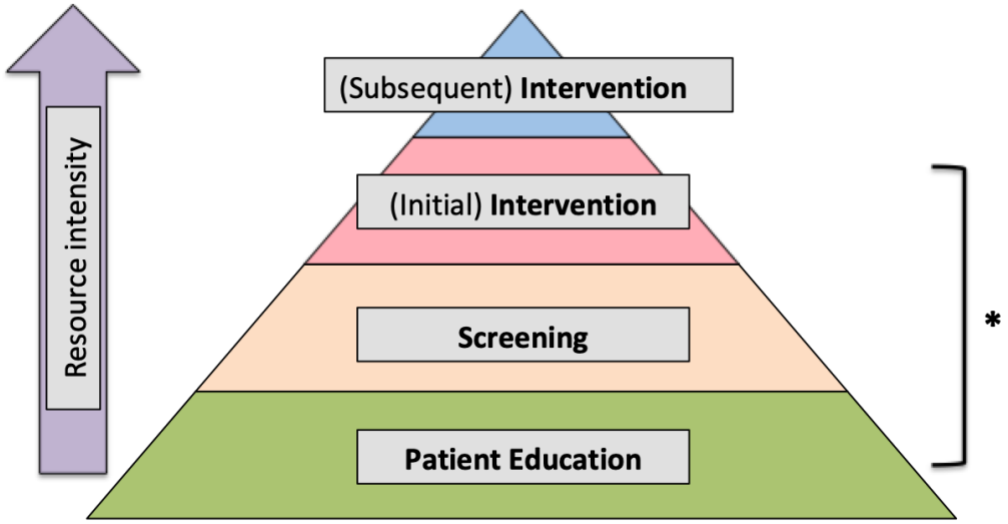
conditions (Wang, 2006) as well as comorbid mental and physical health conditions (Bahm & Forchuk, 2008) are more likely to experience barriers to mental health service use; given demonstrated comorbidity rates, this places patients with RA at particular risk.

The current management of RA is a reflection of the Canadian health care system in terms of gaps in care pertaining to mental health. Routine screening for mental health symptoms in RA, especially via psychological measures, is nonexistent (Sharpe, 2016); although approximately 60% of RA patients endorse need for greater support with managing their emotions, only 1 in 4 RA patients endorse consistent opportunity to discuss their emotional experience with a rheumatology professional (Dures et al., 2016). Relatedly, there is a disconnection between discussion of mental health symptoms with a primary care provider (e.g., rheumatologist, family doctor) and connection to psychological resources.

The most promising option for resolving these gaps in care for RA patients is the implementation of stepped care models (Moroz et al., 2020). A stepped care approach balances effectiveness and efficiency in the delivery of mental health supports. The innovative approach involves a series of initiatives, implemented in a sequential order, until a clinically significant reduction in symptoms is reached. The first intervention initiatives are low-intensity (e.g., self-help programs, single-session treatments, virtual interventions), with later initiatives (e.g., extended programs, face-to-face individual sessions) reserved for those that do not respond to low-intensity interventions. Stepped care models have already demonstrated success in improving the management of mental health in the context of chronic pain e.g., the stepped care approach at the Ottawa Hospital Pain Clinic has substantially reduced wait times for psychological resources and improved patient care (Bell et al., 2020).

Figure 4.2

A Visualization of a Stepped Care Approach to Mental Health Care



Note: *=Discussed directly in relation to my findings.

Patient Education

Patient education, or "learning experiences designed to facilitate voluntary adoption of behaviours conducive to health" (Niedermann et al., 2004), serves several purposes. One purpose is primary prevention i.e., strategies to prevent the onset of symptoms. In primary care, these programs are most effective when targeted (i.e., focused on patients with some combination of risk factors; García-Campayo et al., 2015). According to Study 1, these risk factors would be younger age, non-White ethnicity, a lower level of education, and a higher BMI. Primary prevention might entail providing patients (with >1 of these risk factors) access to bibliotherapy (a self-directed program involving reading material and written exercises related to mental health education and treatment; Sharma et al., 2014). Bibliotherapy has proven advantageous for the reduction of mental health symptoms, including anxiety, in both illness (e.g., cancer; Malibiran et al., 2018) and non-illness populations (Reeves & Stace, 2005; Scogin et al., 2003). Content, printed or virtual, might include curated information about the biopsychosocial factors in RA, self-help reading lists (e.g., "Cognitive behavioral therapy made simple" by Seth J. Gillihan) and information on lifestyle changes (e.g., aerobic exercise, sleep hygiene, smoking cessation).

Given my finding involving BMI from Study 1, the importance of physical exercise might be particularly underscored.

A second purpose of patient education is empowering patients to play an active role in their health status, e.g., through promotion of self-identifying mental health symptoms/concerns. According to the results of Study 2, self-referral (i.e., self-identification of anxiety/depression) appears to predict treatment adherence (and subsequent better treatment outcomes) in an online mental health intervention, relative to those who were recruited. RA patient education has been historically accomplished through in-person groups ranging between 4 and 15 weeks long; significant benefit has been demonstrated from these initiatives in terms of (largely short-term) coping (Niedermann et al., 2004). However, these initiatives were time-consuming, resource-intensive, and limited in terms of psychological considerations. As means of extending education and increasing access given the growing number of Canadians with RA (Safiri et al., 2019), patient education needs to move online and emphasize psychoeducation. High interest in psychoeducation involving a variety of sources has been made apparent among RA patients (Marrie et al., 2019). Aside from disease knowledge, website content might include information about the relationship between anxiety (and depression) and RA, the early signs of anxiety (and depression), and simple adaptive coping strategies (e.g., increasing pleasant activities). An ongoing study, registered with clinicaltrials.gov, is currently developing and testing an online patient education program with newly diagnosed RA patients in Denmark; their estimated study completion date is in 2024. An alternative (and likely easier) option to promote patient education is to adapt online sources of information currently used by RA patients. For example, The Arthritis Society is Canada's primary not-for-profit organization dedicated to arthritis prevention, education, and support. The organization has created a highly user friendly Mental Health page, with tabs including "Understanding Mental Health Care" and "Mental Wellness Self-Assessment Quiz," which contains questions on coping strategies, quality of life, self-actualization, flexibility, social wellness, and balance. This page represents a prime opportunity for increased patient education, such as through the inclusion of the biopsychosocial framework of RA and anxiety (and depression).

Screening

As demonstrated in other health populations (e.g., cancer, diabetes), appropriate screening is essential to a stepped care approach (Halliday et al., 2017; Recklitis & Syrjala,

2017). Screening begins with provider education. At present, health care professionals consistently underreport mental health symptoms in RA relative to their patients' reports (Lwin et al., 2020). Worse still, the presence of mental health symptoms has been shown to result in a lesser quality of care for RA patients (Knaak et al., 2017). This disadvantage can be, in part, explained by provider frustration related to treatment (e.g., RA patients with mental health symptoms perceive their disease to be more severe than their providers do; Challa et al., 2017) as well as increased health care use (e.g., RA patients with comorbid mental health conditions require more physician visits and hospitalizations; Hitchon et al., 2021). An additional factor previously linked to poorer health care for patients with co-occurring mental health problems is provider mental health stigma (Knaak et al., 2017). A promising strategy for improving patient care is virtual seminars for providers. These seminars could promote awareness of mental health presentations in RA (e.g., discussing the prevalence of anxiety, depression, and personality dysfunction; Blaney et al., 2020) and how these presentations impact both interactions with the clinician and disease outcomes. Other topics might include: navigating interpersonal challenges with these patients; broaching mental health with patients; how to amend pre-existing patient history forms to include mental health history; prevention strategies for mental health in RA (e.g., bibliotherapy); and best practices in the assessment of anxiety among RA patients in primary care/speciality clinics. Leveraging primary care provider support is essential for an effective stepped care approach (Scogin et al., 2003), particularly given how essential monitoring patient progress is to this model of care (Franx et al., 2012).

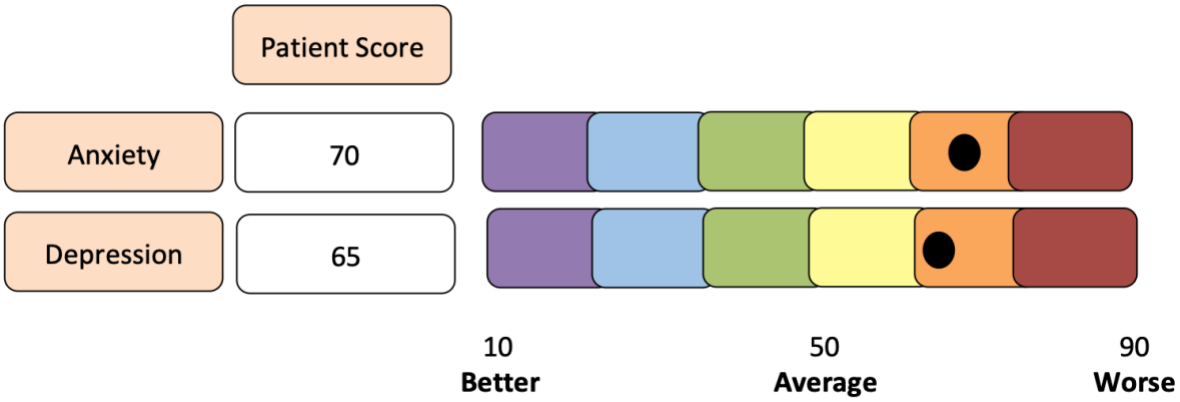
A second initiative related to screening is the determination and implementation of appropriate measures to assess mental health in an RA population. Both my dissertation, and the larger body of literature, supports the use of patient-reported mental health outcome measures for screening. Specifically, Study 2 revealed that over 1/3 of patients at risk of the most severe disease outcomes as well as accelerated worsening of disease outcomes (i.e., fatigue) would not be identified as "at-risk" if screening was based on presence of a current anxiety disorder. In terms of screening options, the PROMIS measures (used in both of my studies) are promising. This promise is due to the unique development of the PROMIS system summarized in Chapter 1 (e.g., test banks with standardized scoring; Bevans et al., 2014), the demonstrated efficacy of measures when identifying mental health symptoms in RA (Bartlett et al., 2015; Hitchon et al., 2020), and feasibility in primary care (Kroenke et al., 2018) given their brevity. The consistency

of anxiety symptom severity over time demonstrated in Study 1 suggests that mental health evaluation timing is a lower priority concern: however, temporal changes in mental health symptoms have been previously demonstrated (Fragoulis et al., 2020) and CBT-treatment effectiveness is thought to be more effective in the earlier stages of disease (Evers et al, 2002). Therefore, mental health screening should be implemented quickly and routinely (i.e., with the same consistency as other disease outcomes) post-diagnosis.

In order for screening to be valuable, there must be some way for physicians (both primary care and speciality doctors) to receive and make sense of the data. A recent investigation addressed both of these concerns in a Rheumatology clinic. In this feasibility study, patients were asked to arrive to their scheduled appointments 30 minutes early and complete a set of PROMIS measures via tablet, including PROMIS Anxiety and PROMIS Depression (Bartlett et al., 2020). Results were immediately transferred to the patients' charts in an easily interpretable format (see Figure 4.3) that allowed for comparison with reports from previous visits. Of note, an electronic charting system is almost essential for this type of initiative. Clinicians were encouraged to review the results with patients, at their discretion. Following these changes, 80% of patients reported improved communication with their physician, while simultaneously physicians endorsed the benefit of added insight. Of note, physicians reported some discomfort discussing emotional results, which reiterates my earlier comment about the need for provider education.

Figure 4.3

An Example, Adapted from the Work of Bartlett and Colleagues (2020), of a Colour-Coded PROMIS Report For Physicians



Treatment

A partial explanation for the lack of mental health screening among RA patients is physician uncertainty about next steps following an elevated symptom score. Currently, options are limited in terms of psychological supports for Canadians with RA. For those who can afford private, individual psychotherapy (rates of a private, registered clinical psychologist range between $170 and $220/hour), there are obstacles such as wait times and ambiguity around who to contact. For those who cannot afford clinicians in the private sector, they are dependent on being deemed appropriate for services at a pain clinic that specializes in chronic pain management (e.g., the Pain Clinic at Health Sciences Centre in Winnipeg and the Ottawa Hospital Pain Clinic in Ottawa). These services require a physician referral (and therefore accurate identification of need); additionally, eligibility criteria mandates the target of psychotherapy remain on pain management as opposed to anxiety or depression.

Study 2 was developed with these limitations in mind. The ultimate goal was to identify a feasible online option for anxiety and depression reduction that was appropriate for RA patients and could be "prescribed" by primary care physicians and rheumatologists. An online program increases feasibility from the patient perspective (e.g., in terms of wait times, transportation and child care concerns during appointments) and the health care system perspective (e.g., in terms of reduced costs and resources such as clinician employment). Related to the latter, I tested a non-therapist assisted program with the purpose of increasing real-world value. Findings from Study 2 support the feasibility of this intervention (i.e., the Worry and Sadness program), or one similar. Were this option to be implemented today, it would cost $55 CA for three months access (of note, in Australia, where the program was developed, the intervention is free with a prescription). A prescription (with the costs covered as part of universal health care or not) would be as simple as physician administration of a 7-letter code. It can be completed in 6 weeks, without need for a clinician, and findings from Study 2 suggest the program will be both appreciated and beneficial among RA patients.

Additional, specific benefits of the Worry and Sadness program include its transdiagnostic targets (particularly appropriate for use with RA patients given high co-occurrence of anxiety and depression; Covic et al., 2012) and its positive impact on fatigue (particularly given difficulties in the medical management of fatigue; Pope, 2020). Program additions, however, do appear warranted; participants expressed interest in RA topics and

previous interventions in pain populations have included detailed explanations of chronic pain physiology and its relation to psychological intervention (Nathan et al., 2017). Therefore, an ideal intervention option would involve some disease-related tailoring (e.g., discussion of the biopsychosocial perspective of mental health in RA), information on the intervention's expected effects, and the likely causal factors in the expected effects. This component of the intervention could be separate from the online program itself, allowing this component to be substituted appropriately in different health contexts. Other potentially beneficial additions to the program include support of computer literacy, a concern that presented itself in Study 2 as well as other discussions on stepped care (Meulddijk et al., 2021). For example, this might include a trouble-shooting/tips forum board, accessible to all participants, and/or supplying detailed instructions for working with the virtual platform. Need for computer literacy support was reinforced by participant feedback in a recent conceptualization study for an online mental health program for older adults (mean age of focus group sample: 61.8 years old; Eichenberg et al., 2018).

Future Directions

As with all research, answers tend to lead to more questions. There are still many things to consider in future studies on anxiety in RA. For example, in term of patient education, mental health-focused bibliotherapy requires development and feasibility testing in the context of RA. This will involve evaluating patient preference in terms of online content or leaflets; recent literature suggests patients see advantages to both (Kumar et al., 2020). Next, comparison with a control group will capture any effects from bibliotherapy on mental health symptom prevalence and mental health symptom self-identification among RA patients. Related studies are needed to understand: (1) who is eligible for this support i.e., what combination of risk factors (e.g., younger age, lower level of education, etc.) predicts anxiety in RA consistently; (2) what constitutes endorsement of a given risk factor (e.g., at what number does BMI become predictive of anxiety); and (3) are there predictors (e.g., patient characteristics, pain severity) associated with success using mental health-focused bibliotherapy in an RA sample.

The most important screening-related future direction is the determination of what constitutes clinically meaningful anxiety, in need of intervention, in RA i.e., at what symptom threshold is a patient considered at-risk of adverse outcomes due to anxiety. Although findings from Study 1 suggested even mild levels of anxiety (i.e., 0.5-1.0 standard deviations/SD above the population mean) were associated with worse disease outcomes, only moderate anxiety (i.e.,

1.0-2.0 SD above the population mean) was associated with accelerated worsening, of fatigue specifically. Therefore, when it comes to determining who should receive a prescription for the online intervention, some thought will need to go towards eligibility. Research that could support this decision includes identifying clinically meaningful changes in disease outcomes in RA (e.g., as has been done with disease activity in systematic lupus erthematosus/SLE; Jesus et al., 2019) and investigating the relevance of meeting criteria for an anxiety disorder, in combination with elevated anxiety, in terms of disease outcomes (i.e., determining the possibility of an interaction effect between an anxiety disorder and anxiety symptom severity). Yet another important consideration will be determining appropriate intervals for screening.

In terms of treatment, the next step following my feasibility study (i.e., Study 2) is the implementation of a randomized controlled trial (RCT) of an online anxiety intervention among RA patients who screen positive for anxiety. In this RCT, it would be important to substantially increase the sample size and sample diversity as well as control for psychological interventions outside of the study protocol (both behavioural and pharmacological). It will be important to initiate this study in primary care as well as pain/rheumatology clinics, as means of furthering diversity. To better understand the mechanisms of change in accordance with the biological ICF theory of anxiety in RA, additional constructs should be assessed as mediators. For example, coping responses, as measured with the Brief COPE (Carver, 1997). The Brief Cope captures 14 coping strategies (active coping, planning, positive reframing, acceptance, humour, religion, using emotional support, using instrument support, self-distraction, denial, venting, substance use, behavioural disengagement, and self-blame), which can be used as indicators of *cognitive*, *emotional*, and *behavioural coping responses*; the measure is well-validated, in both illness populations (Hagan et al., 2017) and the general population (Kimemia et al., 2011). This is an example of one type of mediation/moderation study necessary to comprehensively understand intervention effectiveness (Hofmann & Hayes, 2019); another will include identification of patient characteristics associated with treatment success.

As means of supporting usability for the patient, the intervention could also be modified into an app. This would remove the need to access a website and enter login information. Of note, in the brief phone check-ins during the conduction phase of Study 2, this was the primary difficulty reported by patients. The app could be downloaded in the physician's office, as pre-

loading apps has been identified as an option for improving access to mental health supports for elderly people (specifically during the COVID-19 pandemic; Conroy et al., 2020).

From a systems level, if any of the aforementioned initiatives (i.e., patient education, screening, treatment) are to be instigated on a wider scale (compared to within the context of individual organizations, e.g., provincially), a discussion of costs is needed. Costs include technological resources such as tablets, Web pages, smartphone apps, technical support and website hosting fees. Additionally, options/avenues for subsequent intervention (i.e., intervention following this online option in the absence of symptom reduction) will need to be considered. Finally, there will be need to evaluate the stepped care approach in RA. This might include: a 12-month evaluation of anxiety symptomatology within a primary care environment following implementation of the model; a cost-benefit analysis (e.g., involving the examination of service delivery costs and gains in terms of both reduced health care costs and quality of life; Meulddijk et al., 2021); as well as qualitative interviews with both patients and providers, among other critical investigations.

Conclusions

Anxiety in the context of rheumatoid arthritis is exemplary of the interactions between biological, psychological, and sociological/environmental factors in health. These factors, however, are rarely addressed comprehensively in disease management. My research capitalized on a large, rich, longitudinal data set and engaged cohorts of research participants willing to trial an online mental health program, to address meaningful gaps in the mental health and RA comorbidity literature. Ultimately, the findings of my dissertation contribute to the growing rationale for routinely conceptualizing and treating RA using a biopsychosocial framework, such as the biological ICF theory of anxiety in RA. More broadly, my dissertation supports a biopsychosocial approach to disease management universally, as it grows increasingly apparent there is no mental health condition without biological processes, and there is no physical health condition that does not involve psychological factors.

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